AFIB OPTIMAL TREATMENT EXPERT ROUNDTABLE

Effectively Assessing Stroke and Bleeding Risk In Anticoagulation Decision-Making

January 18th, 2012
Washington, D.C.

This expert roundtable is brought to you by the AFib Optimal Treatment Task Force—a group of patient and professional organizations who are raising awareness of the burden of atrial fibrillation, helping to forge expert consensus on the need for new treatment tools that offer patient-tailored anticoagulation assessments, and advocating for adoption and use of these tools.

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ROUNDTABLE OBJECTIVES & AGENDA

Objectives

Successful use of antithrombotic therapy in atrial fibrillation patients depends on patient-tailored assessments that evaluate both stroke and bleeding risk. However, many experts believe that the available risk assessment tools for both have substantial limitations. Additionally, the changing landscape of available antithrombotics could be shifting the "tipping point" at which atrial fibrillation patients should be treated with anticoagulants.

This roundtable will explore the current risk assessment tools and their limitations, discuss how the tools should be updated to overcome these limitations and to reflect the data on emerging therapies, form consensus on what steps should be taken to address any proposed guideline changes and call for mandates, and consider how best to raise awareness amongst health care professionals on this expert consensus and the need for new best practices.

Detailed Agenda

WELCOME & INTRODUCTIONS

8:30 – 8:40 am
Lindsay Clarke
Alliance for Aging Research

Welcome

8:40 – 9:00 am
Keith Mason
National Forum for Heart Disease & Stroke Prevention

Overview & Introductions

WORKING SESSION
Moderator – Keith Mason

9:00 – 10:00 am
Jonathan L. Halperin, MD
Mount Sinai School of Medicine

Stroke/Thromboembolism Risk Assessment
- What tools/schemes are the most accepted and widely used?
- What limitations do these tools have?

10:00 – 11:00 am
Gregory YH Lip, MD
University of Birmingham

Bleeding/Intracerebral Hemorrhage Risk Assessment
- What tools/schemes are the most accepted and widely used?
- Should bleeding risk be explicitly considered?
- What limitations do these tools have?

11:00 – 11:15 am

Break

11:15– 12:15 pm
Daniel E. Singer, MD
Harvard Medical School

Integration of the Two Evaluations

- How do you incorporate both risk assessments? Should one be given more weight than the other?
- How is the tipping point (balancing point between risk of bleeds and benefits of anticoagulants) currently assessed?
- Has the tipping point shifted? Should it?
- What tool(s) and score(s) should be used to determine anticoagulation?
- Should consideration be given to mechanical interventions (e.g. LAA occlusion)?

12:15 – 12:45 pm **Lunch**

12:45 – 1:45 pm
Samuel Goldhaber, MD
Harvard Medical School

Changing Landscape of Anticoagulation

- How do new/emerging drugs shift the tipping point? Should the threshold be lowered?
- How does this shift alter the need for and effectiveness of risk assessment tools?
- Do the adverse events seen with some of the new drugs make proper assessment of bleeding risk even more critical?
- Do safety concerns keep the numbers who should be anticoagulated from expanding?
- How do we keep the tools effective with this changing landscape?

1:45 – 2:45 pm
Jim Scott, JD
Applied Policy

Changes Needed for Optimal Treatment

- Do new risk assessment tools need to be promoted?
- Do guidelines need to be updated?
- What are the necessary steps beyond guideline changes?
- What should be done to promote and educate about the above?
- What should health care professionals do in the meantime?
- What are other ways to improve the decision to treat and adherence/compliance? Better monitoring, initial and ongoing assessment, other?

CLOSING REMARKS & NEXT STEPS

2:45 – 3:30 pm **Wrap-Up**
Keith Mason & Lindsay Clarke

Participant Biographies

Expert Participants

Mark J. Alberts, MD

Dr. Alberts is Professor of Neurology and Director of the Stroke Program at Northwestern University Feinberg School of Medicine and Northwestern Memorial Hospital in Chicago, Illinois. After earning his medical degree with Alpha Omega Alpha (AOA) honors from Tufts University in Boston, Massachusetts, Dr. Alberts completed a Neurology residency at Duke University in Durham, North Carolina, followed by a National Institutes of Health (NIH) sponsored fellowship in cerebrovascular disease, also at Duke. While on the faculty at Duke, he was Director of the Stroke Unit, Transcranial Doppler laboratory, and the Acute Stroke Team. He is board certified in Neurology and Vascular Neurology. He has received numerous awards including the Affiliate of the Year Award from the American Heart Association (AHA) and the National Brain Resuscitation Award. Many organizations including the AHA and NINDS have provided Dr. Alberts with grant support, and he has been funded by NIH to study the genetics of cerebral aneurysms. Dr. Alberts is a member of various committees and boards including the Brain Attack Coalition, AHA Board of Directors, and the Illinois Stroke Task Force. He has been the chairperson for the AHA Brain/Stroke Study Group and serves on two NIH Study Sections. Dr. Alberts assisted in establishing the Stroke Belt Consortium, a highly successful regional organization to improve stroke education. His current research interests include studying genetic etiologies of stroke, identifying new treatments for acute stroke, and studying new medications and interventions to prevent strokes. He has also been very active in studying aspirin resistance in stroke patients. An author of more than 150 articles and book chapters, Dr. Alberts is the Genetics Section Editor of *Stroke*, the editor of the book *Genetics of Cerebrovascular Disease*, and formerly the editor-in-chief (Neurology) of the *Journal of Neurovascular Disease*. Dr. Alberts has been an invited speaker at numerous national and international meetings and is on the Global Publications Committee for the REACH Registry.

Mary Amatangelo, RN, MS, ACNP-BC, CCRN

Mary Amatangelo is the Senior Stroke Researcher, Nurse Practitioner at Partners Neurology, including Massachusetts General Hospital and Brigham and Women's Hospital. Mary oversees the stroke initiatives throughout the six Partners Hospitals. Mary is a lead on the NIH secondary stroke prevention trial IRIS (Insulin Resistance Intervention after Stroke). In addition, Mary is an adjunct for other ongoing clinical stroke trials. She cares for patients along the stroke continuum. She is a liaison for the MGH telestroke sites, and has an active role on a variety of stroke committees at the hospital level as well as state and local involvement. Mary lectures locally, nationally and internationally on a variety of stroke related topics.

Kenneth A. Bauer, MD

Dr. Bauer is Professor of Medicine, Harvard Medical School. His hospital positions include Director, Thrombosis Clinical Research, Beth Israel Deaconess Medical Center and Chief, Hematology Section, VA Boston Healthcare System. Dr Bauer received his medical degree from Stanford University School of Medicine in Stanford, California. He completed his residency in medicine at the University of Chicago Hospitals and Clinics in Illinois. He was a Fellow in Medical Oncology and a Clinical/Research Fellow in the Division of Thrombosis and Hemostasis at Dana Farber Cancer Institute and was also a Clinical/Research Fellow in the Hematology-Oncology Division at Beth Israel Hospital, Boston, Massachusetts. Dr Bauer's research interests include development and clinical evaluation of sensitive new assays for the detection of hypercoagulable states, definition and elucidation of the mechanisms leading to the development of a prethrombotic state, and clinical evaluation of new antithrombotic drugs. Dr Bauer served as immediate past-Chairman of the Council of the International Society on Thrombosis and Haemostasis (ISTH) and was previously Chairman of the Subcommittee on Predictive Haemostatic Variables in Vascular Diseases of the ISTH. Dr Bauer has published over 200 original reports, reviews, and book chapters.

Lynne T. Braun, PhD, CNP, CLS, FAHA, FPCNA, FAAN

Dr. Braun is a nurse practitioner in the Preventive Cardiology Center and the Heart Center for Women and a Professor in the Department of Adult Health Nursing in the Rush College of Nursing. She completed a PhD in Nursing Science at the University of Illinois at Chicago in 1990, and a post-master's certificate as an Adult Nurse Practitioner from Rush University in 1997. She has been on faculty and has held a practice position at Rush University Medical Center since 1980. Her clinical and research interests include cardiovascular risk reduction, exercise, hyperlipidemia, and hypertension management. She currently serves as co-investigator for a research grant funded by the National Institutes of Health, entitled, "Reducing Health Disparity in African American Women: Adherence to Physical Activity." She is a past president of the Preventive Cardiovascular Nurses Association. Dr. Braun has been an active volunteer for the American Heart Association since 1980 in numerous capacities. Most recently, she serves on the board of directors of the American Heart Association of Metropolitan Chicago, the Medical Leadership Committee for Chicago's Go Red Luncheon and the Illinois Advocacy Committee, and she is the vice chairperson of the Council on Cardiovascular Nursing. Dr. Braun is regular speaker at the AHA Scientific Sessions on topics related to cardiovascular disease prevention. She is a co-author of five AHA/ACC Scientific Statements and Clinical Practice Guidelines, and is a co-author of the ACCF/AHA statement on Performance Measures for the Primary Prevention of Cardiovascular Disease. Dr. Braun is a Fellow of the American Academy of Nursing, the American Heart Association, the Institute of Medicine of Chicago, the National Lipid Association and the Preventive Cardiovascular Nurses Association.

Henry I. Bussey, PharmD

Dr. Bussey was selected in 2008 to receive the GSK Distinguished Scholar in Thrombosis Award for his work to incorporate patient self-testing and online management into a better anticoagulation management system. This three-year award is provided by the Chest Foundation of the American College of Chest Physicians. Dr. Bussey served for a decade on the American College of Chest Physicians Consensus Conference on Antithrombotic Therapy and was recently appointed to the Scientific Advisory Board of the North American Thrombosis Forum (NATF). He is a Fellow of the American College of Clinical Pharmacy, the American College of Chest Physicians, and the American Heart Association and its Council on High Blood Pressure Research. His research is clinically focused and was instrumental in the adoption of the INR for warfarin monitoring in North America. Currently, he is a professor in the College of Pharmacy at the University of Texas at Austin, is president of Genesis Clinical Research in San Antonio, TX, is co-founder of ClotCare, and is a consultant to Genesis Advanced Technologies on the development of the ClotFree system for online anticoagulation management. He has over 100 publications, is on the editorial board for Pharmacotherapy, and is a reviewer for several pharmacy and medical journals. Dr. Bussey obtained his B.S. in Pharmacy from the University of Georgia and his Pharm.D. (with a concurrent clinical pharmacy residency in Internal Medicine) from the University of Texas at Austin and the University of Texas Health Science Center in San Antonio. Dr. Bussey served recently on advisory boards for Canyon Pharmaceuticals and Ortho-McNeil; has received research support from Roche Diagnostics, Inc., Bristol Myers Squibb, Pfizer, Merck, and Novartis; and is not on the speakers' bureau of any pharmaceutical company.

A. John Camm, MD, QHP, FRCP, FACC, FESC, FMedSci, FHRS, CStJ

(Participating via teleconference)

Professor A John Camm graduated from Guy's Hospital, London after which he pursued a career in cardiology at St. Bartholomew's Hospital. Since 1986 Professor Camm has occupied the British Heart Foundation Chair of Clinical Cardiology at St. George's University of London, where he is currently Chairman of the Department of Cardiovascular Sciences and the Division of Cardiological Science. Professor Camm was formerly the Chairman of the European Society of Cardiology Working Group on Cardiac Arrhythmias, past President of the British Pacing & Electrophysiology Group and a past council member of the Royal College of Physicians. He is a former Trustee of the North American Society of Pacing and Electrophysiology, a former Chairman of the Joint Cardiology Committee (Royal College of Physicians) and the past President of the British Cardiac Society.

He is currently Convenor of Medicine, University of London, Trustee of the International Society of Pacing and Electrophysiology and President of the Arrhythmia Alliance. Professor Camm is currently the President of the Arrhythmia Alliance, a trustee of the Atrial Fibrillation Association, the Drug Safety Research Unit, the American College of Cardiology and the Interventional Cardiac Pacing and Electrophysiology Society and Editor of Europace, the only European Journal devoted to cardiac electrophysiology and arrhythmology. Professor Camm is also Editor of the European Society of Cardiology Textbook on Cardiovascular Medicine, Evidence Based Cardiology and Electrophysiology of the Heart. Professor Camm is a worldwide renowned clinical trialist and has held or holds memberships in 30 multicentre study committees and has given over 1,000 lectures to international audiences, written more than 1000 peer review papers, more than 500 book chapters and over 30 books.

David Garcia, MD *(Participating via teleconference)*

Dr. David Garcia completed an undergraduate degree at Duke University and received his medical degree from the University of Alabama. After finishing internship, residency and chief residency at the Johns Hopkins Hospital, Dr. Garcia joined the faculty at the University of New Mexico School of Medicine in 1999 as a hospitalist. He is the co-director of the university's Anticoagulation Management Service and is the Director of Undergraduate Medical Education in the Department of Internal Medicine.

Dr. Garcia has been an investigator in numerous clinical trials of anticoagulant medications for the prevention and treatment of thromboembolic disease. He is the President of the Anticoagulation Forum, a national interest group focused on the prevention and treatment of thromboembolic disease. Dr. Garcia's primary research interests include the treatment of warfarin-associated coagulopathy and peri-procedural anticoagulation for patients with mechanical heart valves. He has authored or co-authored peer-reviewed publications in journals such as the *Archives of Internal Medicine, Chest, Thrombosis and Thrombolysis, Geriatric Clinics of North America, ACP Journal Club, the British Journal of Hematology and the Journal of the American College of Cardiology*. Since 2002, Dr. Garcia has been a member of the editorial board of the journal *Thrombosis Research*.

Samuel Z. Goldhaber, MD

Dr. Goldhaber, Professor of Medicine at Harvard Medical School, is Director of the BWH Venous Thromboembolism Research Group. He has been the Principal Investigator for multiple deep vein thrombosis (DVT) and pulmonary embolism (PE) treatment trials, including 5 multicenter PE thrombolysis trials. He is Chair of the Steering Committee of the NIH-sponsored multicenter ATTRACT Trial, which is studying the optimal method to manage massive DVT. He is especially interested in improving venous thromboembolism prophylaxis of at-risk hospitalized patients. In the March 10, 2005 New England Journal of Medicine, he published a 2,500 patient randomized clinical trial which described a new physician alert strategy to reduce symptomatic DVT and PE by 41%. He is currently conducting another 2,500 patient randomized clinical trial at 26 institutions across the United States to determine whether these positive results are reproducible outside of Brigham and Women's Hospital.

Dr. Goldhaber is Principal Investigator of about a dozen ongoing randomized clinical trials and observational studies related to the prevention, treatment, and epidemiology of PE and DVT. As Founder and Director of the BWH Anticoagulation Service, which cares for more than 2,100 active patients, he is also conducting research on optimal warfarin dosing. He is Chair of the Steering Committee of the ADOPT Trial, which is studying the safety and efficacy of a new oral anticoagulant for prophylaxis of venous thromboembolism in acutely ill medical subjects during and following hospitalization. Dr. Goldhaber is also Principal Investigator of an observational trial exploring new ways to foster venous thromboembolism prophylaxis at the time of hospital discharge. He encourages Vascular Medicine Fellows to participate in these research projects.

Dr. Goldhaber is committed to promoting outreach to other health care professionals as well as to the lay public. He helped found and is President of the North American Thrombosis Forum, a nonprofit organization.

He chairs the Steering Committee of the Venous Disease Coalition, another nonprofit initiative, run by the Vascular Disease Foundation

Jonathan L. Halperin, MD

Dr. Halperin, is the Robert and Harriet Heilbrunn Professor of Medicine at Mount Sinai School of Medicine, Director of Clinical Cardiology Services in the Zena and Michael A. Wiener Cardiovascular Institute at The Mount Sinai Medical Center. Educated at Columbia University and Boston University School of Medicine, Dr. Halperin joined the Mount Sinai faculty in 1980. He played a key role in the formation of the Cardiovascular Institute, one of the nation's leading centers for integrated cardiovascular research, education and patient care, and has served as Associate Director since its inception. He was instrumental in the evolution of the Joseph H. Hazen cardiology clinics as a model of ambulatory care, preventive medicine and professional education, and the Cardiac Care Center, which integrates and unifies inpatient cardiovascular services. He serves as Director of Mount Sinai's Urban Community Cardiology Fellowship Program, an educational initiative linked with Mount Sinai's principal municipal hospital affiliate, the City Hospital Center at Elmhurst, Queens, serving one of the nation's most ethnically diverse populations. On the 150th Anniversary of The Mount Sinai Hospital in 2002, Dr. Halperin was the recipient of the Jacobi Medallion, awarded by the alumni in recognition of distinguished achievement in the field of medicine and extraordinary service to the institution.

Widely recognized as an academic clinician, Dr. Halperin has served as a role model for resident and fellow trainees in internal medicine and cardiology and been the recipient of two of Mount Sinai's most distinguished teaching awards, the Simon Dack Award, presented by the Fellows of the Division of Cardiology and the Solomon R. Berson Award, presented by the House Staff of the Department of Medicine. His skills as an educator were crystallized with the publication of *BYPASS* (Times Books-Random House, 1986), critically acclaimed as the most comprehensive treatment of the subject of coronary artery bypass graft surgery -- addressed to the layman but suitable for medical professionals as well. He has been identified repeatedly in both regional and national publications for providing high quality patient care, and engages in an active clinical practice, emphasizing traditional bedside skills and judicious application of modern cardiovascular technology. He is Past-President of the Society for Vascular Medicine and Biology and the New York City Affiliate of the American Heart Association. Dr. Halperin serves on numerous consensus and writing panels that issue clinical practice guidelines for management of patients with various cardiovascular disorders, including atrial fibrillation, peripheral arterial disease, cerebrovascular disease and stroke, and is a member of the ACC/AHA Task Force on Practice Guidelines.

The son of a physician, Dr. Halperin has maintained a stream of clinical investigation, beginning with studies of cardiovascular hemodynamics that contributed to the development of angiotensin converting enzyme inhibition for patients with chronic congestive heart failure and studies of regional circulation that impact the management of patients with Raynaud's Disease, mitral valve disease, and intermittent claudication. He was the principal cardiologist responsible for the design and execution of the Stroke Prevention in Atrial Fibrillation (SPAF) clinical trials, which received over $25 million in grant support from the National Institutes of Health. These multicenter studies, which involved 3,600 patients and over 100 investigators, helped develop antithrombotic strategies to prevent stroke among the estimated 2.5 million Americans with atrial fibrillation. Hailed as the most important advance in medical stroke prevention over that decade, the results of this research prevent tens of thousands of strokes each year, saving hundreds of millions of dollars in the cost of stroke care, and an inestimable toll in human terms. Subsequently, he directed the SPORTIF clinical trials, which evaluated the first oral direct thrombin inhibitor for prevention of stroke in patients with atrial fibrillation. These international trials, involving over 7,000 patients randomized at over 700 clinical centers, in 25 nations, represented the most aggressive effort ever mounted against embolic stroke and tested the first new oral anticoagulant in over half a century. The results were cited by the American Heart Association as among the most important research advances of the year. He is currently engaged in a number of clinical trials aimed at developing improved therapeutic agents for prevention of ischemic events in an array of cardiovascular disease states.

Alan K. Jacobson, MD

Alan K. Jacobson, MD, is a staff cardiologist and the Associate Chief of Staff for Research at the Loma Linda VA Medical Center in Southern California. A native of Canada, Dr. Jacobson has been at Loma Linda since heading south in 1977 for medical school. In addition to practicing noninvasive cardiology, Dr. Jacobson has a special interest in antithrombotic therapy. His research includes pivotal trials such as CHARISMA, RE-LY, RE-MOBILIZE, ACTIVE & THINRS. He has been the medical director of the Cardiology Anticoagulation Clinic since 1988 and has overseen the initiation of both Point-of-Care testing and Patient self-testing for the monitoring of patients on warfarin. Dr. Jacobson has also been active in research relating to standardization of laboratory methods for PT determinations, clinical use of antithrombotic therapy in atrial fibrillation, evaluation of novel antithrombotic therapies and development of anticoagulant monitoring methodologies. Antiarrhythmic therapy in atrial fibrillation has also been an interest and Dr. Jacobson has been involved in multiple studies of amiodarone (including the SAFE-T trial comparing amiodarone, sotalol, and placebo) as well as the AFFIRM trial and trials with amiodarone derivatives, such as ATHENA.

Craig Kessler, MD

Dr. Kessler is professor of Medicine and Pathology and Section Chief of Hematology. He is also Director of the Coagulation Laboratory at Georgetown. A graduate of Tulane School of Medicine, Dr. Kessler received his specialty training in hematology and oncology at The Johns Hopkins Hospital. An international expert in the area of disorders of coagulation, Dr. Kessler has a particular interest in hemophilia. He also has expertise in the treatment of hematologic malignancies.

Gregory YH Lip, MD, FRCP, DFM, FACC, FESC *(Participating via teleconference)*

Professor Lip, MD, is an academic clinical cardiologist based in a busy city centre teaching hospital and leads a large, multidisciplinary research group (including clinical and laboratory-based components). He is also Visiting Professor of Haemostasis Thrombosis and Vascular Sciences in the School of Life & Health Sciences at the University of Aston in Birmingham, England. Half of his time is spent as a clinician, and he practices the full range of cardiovascular medicine, including outpatient clinics, with large atrial fibrillation and hypertension specialist clinics, and coronary care units. He also undertakes coronary intervention and assists in a 24/7 primary angioplasty rota for ST elevation MIs.

As an academic, Professor Lip provides strategy and research direction for his group, with many local, national, and international collaborations in progress. He has had a major interest into the epidemiology of AF, as well as the pathophysiology of thromboembolism in this arrhythmia. Furthermore, he has been researching stroke and bleeding risk factors, and improvements in clinical risk stratification. The CHA_2DS_2-VASc and HAS-BLED scores for assessing stroke and bleeding risk, respectively – were first proposed and independently validated following his research, and are now incorporated into major international management guidelines.

Keith Mason

Keith Mason is the Executive Director of the National Forum on Heart Disease and Stroke Prevention. He brings more than 10 years of experience in the health care field to his new post as the National Forum's first Executive Director. Prior to joining the National Forum in 2009, Mason was with Eli Lilly and Company where he worked to encourage collaboration between professional organizations and consumer groups to improve outcomes for patients with cardiovascular disease.

In addition to his work with the National Forum, Keith also currently serves on the board of HealthNet, an Indianapolis-based federally qualified health center, the Indianapolis affiliate of the American Heart Association, and the National Quality Forum's Population Health Steering Committee. He received a BA in political science from Wabash College and a MS in secondary education from Indiana University, Bloomington.

Edith A. Nutescu, PharmD, FCCP

Edith A. Nutescu is Clinical Associate Professor of Pharmacy Practice at the University of Illinois at Chicago College of Pharmacy and Director of the Antithrombosis Center at the University of Illinois at Chicago Medical Center. Dr. Nutescu is also an Affiliate Faculty at the University of Illinois at Chicago, Center for Pharmacoeconomic Research. She earned her Pharm.D. degree with high honors at the University of Illinois at Chicago College of Pharmacy. After graduation, Dr Nutescu went on to complete an American Society of Health-System Pharmacists (ASHP)–accredited Pharmacy Practice Residency at Lutheran General Hospital–Advocate Health Care and a Primary Care Specialty Residency at the University of Illinois at Chicago Medical Center. As a clinician and educator, Dr. Nutescu has contributed extensively to the care of patients and the education of students and health care providers on topics related to cardiovascular therapeutics. The Antithombosis Center at the University of Illinois at Chicago Medical Center, which Dr. Nutescu directs, has served as a training site and model for pharmacists and other health care providers throughout the US and various other countries such as Thailand, Hong-Kong, Japan, and Singapore.

Dr. Nutescu maintains an active clinical practice and research program. Her research and practice interests are in the areas of thrombosis, antithrombotic therapy, cardiovascular diseases, and stroke. Dr Nutescu has authored or co-authored over 100 scientific articles, book chapters, and abstracts published in the science and medical literature and has served as a reviewer for the literature in her field. She serves on the Editorial Boards for Annals of Pharmacotherapy and the American Journal of Health-System Pharmacy. She has lectured extensively both nationally and internationally on topics related to hyperlipidemia, thrombosis, stroke, and cardiovascular diseases. Dr. Nutescu serves as the Vice-President and on the Board of Directors of the Anticoagulation Forum, and has served on the National Consumers League Senior Outpatient Medication Safety Coalition - Oral Anticoagulant National Advisory Board. Dr. Nutescu was the only pharmacist member nominated to serve on the Steering Committee for the National Quality Forum and the Joint Commission on the Accreditation of Healthcare Organizations - National Consensus Standards for the Prevention and Care of Venous Thrombosis.

James G. Scott, JD

James G. Scott, President & CEO of Applied Policy, founded the company to apply his in-depth and insider knowledge of federal health policy to help health care providers and companies succeed. As a member of the Washington, D.C. health policy community for over a dozen years, he has gained valuable experience and contacts in both the government and private industry.

Immediately prior to founding Applied Policy, Mr. Scott was charged with obtaining optimal Medicare coding, coverage and payment for all pharmaceutical products manufactured by Hoffmann-La Roche Inc., (Roche, now Genentech). While at Roche, he also worked to resolve Medicare and Medicaid reimbursement issues at the federal level and served as the company's principal point of contact with the Centers for Medicare & Medicaid Services (CMS).

Mr. Scott served as the Senior Legislative Advisor at CMS, advising the CMS Administrator on congressional intent in implementing the Medicare Modernization Act of 2003 and engaging Members of Congress in the implementation of the Act. Mr. Scott received agency-wide awards in 2005 for his work with Congress on the successful implementation of the new Medicare prescription drug benefit and for his work with congressional appropriators on the Fiscal Year 2006 President's Budget request.

Prior to his service with CMS, Mr. Scott was an Assistant Counsel with the Office of the Legislative Counsel of the U.S. Senate, where he was a principal drafter of the Medicare Prescription Drug, Improvement and Modernization Act of 2003 and other Medicare legislation. Mr. Scott and his work were recognized through the unanimous passage of a Senate Resolution and in numerous statements by Senators and Representatives printed in the Congressional Record.

Mr. Scott received a Bachelor of Science in Political Science from James Madison University in Harrisonburg, Virginia and received his Juris Doctor, Magna Cum Laude, from the Catholic University of America, Columbus School of Law, in Washington, D.C.

Daniel Singer, MD

Dr. Singer is Professor of Medicine at Harvard Medical School and Professor in the Department of Epidemiology at Harvard School of Public Health. He is a graduate of Yale College, Oxford University (as a Rhodes Scholar), and Harvard Medical School. He is Chief of the Clinical Epidemiology Unit in the General Medicine Division at Massachusetts General Hospital (MGH) and Director of the MGH General Internal Medicine Research Fellowship. Dr. Singer was HMS Associate Dean for Clinical Programs from 2005-2007, during which time he led Harvard's efforts developing its ultimately successful application for an NIH Clinical and Translational Science Award.

Dr. Singer is internationally recognized for his research on prevention of stroke in atrial fibrillation (AF). His work has demonstrated the dramatic efficacy of warfarin anticoagulation, established risk factors for stroke in AF, demonstrated that INR 2-3 is the optimal anticoagulation intensity for AF, and demonstrated the effectiveness of warfarin for AF in usual clinical care. He was lead author for the 2004 and 2008 American College of Chest Physicians Consensus Conference on Antithrombotic Therapy guidelines for AF.

Dr. Singer has received multiple awards for his academic efforts, including the 1993 Nellie Westerman Prize on Clinical Research Ethics from the American Federation of Clinical Research, the 2003 John Eisenberg Award from the National Society for General Internal Medicine for Career Achievements in Research, the 2008 C. Miller Fisher Award from the Massachusetts chapter of the American Stroke Association/American Heart Association for his contributions to stroke research, and the Harvard Medical School 2007-2008 William Silen Award (one of three awardees) for career achievement in mentoring.

Mellanie True Hills

Mellanie True Hills is an atrial fibrillation patient and the CEO and Founder of the American Foundation for Women's Health and StopAfib.org, a non-profit patient advocacy organization. StopAfib.org is dedicated to providing information, education, and support for those living with atrial fibrillation. Her goals are to raise awareness of afib, encourage diagnosis and treatment, improve the quality of life for patients and families, support doctor-patient communication, and decrease afib-related strokes. Since having a surgical procedure, Mellanie has been afib-free for the past 6 years.

Before atrial fibrillation changed her life, she was a corporate executive. She led one of the first corporate web sites, JCPenney.com, and one of the first corporate intranets. She was a high tech executive at Dell, an executive strategist at Cisco, and a world-renowned Internet strategy consultant. She is a best-selling author, including of the award-winning book, *A Woman's Guide to Saving Her Own Life: The HEART Program for Health and Longevity*, and has been featured by hundreds of media around the globe, including CNBC Asia, Reuters, *Newsweek*, *Better Homes and Gardens*, PBS, Fox, ABC, NBC, and CBS. Her story and the mission of the American Foundation for Women's Health have recently been profiled in *USA Weekend*, *More*, *Success*, and *Heart-Healthy Living.*

Albert Waldo, MD, FACC

Dr. Waldo is The Walter H. Pritchard Professor of Cardiology, Professor of Medicine, and Professor of Biomedical Engineering at Case Western Reserve University School of Medicine, Cleveland, Ohio. Dr. Waldo has published more than 600 works in the field of cardiac electrophysiology, in which he has worked and helped to advance since its inception several decades ago. In addition to serving on the editorial boards of *Journal of the American College of Cardiology, Circulation, Heart Rhythm,* and the *American Journal of Cardiology*, he is also a member of the Arrhythmia Disorders section of the *Cardiology Today* editorial board. He is a fellow of the ACC, a fellow of the American Heart Association, and a fellow of the American College of Physicians.

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CURRENT PRACTICE GUIDELINES

Clinical practice guidelines play a critical role in guiding decisions made by health care professionals during diagnosis, management, and treatment. A number of professional organizations issue guidelines that deal with anticoagulation in atrial fibrillation; however, there are currently inconsistencies and ambiguities amongst them that can lead to confusion and reluctance to treat. Some of this variation may stem from over-generalizing research that does not properly emphasize subgroup variations—like age, sex, and ethnicity. Guidelines that fail to properly account for risk factors are not universally applicable and will lead to variability amongst guidelines and in patient outcomes. Optimal treatment and anticoagulation in AFib patients depends on consistency amongst guidelines that allow for personalization of care according to individual risk factors and subpopulation differences.

ACC/AHA/ESC Practice Guidelines

This guideline contains hyperlinks to recommendations and supporting text that have been updated by the "2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Updating the 2006 Guideline)" (*Circulation.* 2011;123:104–123; doi:10.1161/CIR.0b013e3181fa3cf4) and the "2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Update on Dabigatran)" (*Circulation.* 2011;123:1161–1167; doi:10.1161/CIR.0b013e31820f14c0). Updated sections are indicated in the Table of Contents and text.

2011 ACCF/AHA/HRS Focused Updates Incorporated Into the ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

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Developed in partnership with the Heart Rhythm Society

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The 2011 focused updates to this document were approved by the leadership of the American College of Cardiology Foundation, American Heart Association, and the Heart Rhythm Society, and the sections that have been updated are indicated with hyperlinks to the focused updates where applicable.

The American Heart Association requests that this document be cited as follows: Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Kay GN, Le Heuzey J-Y, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann LS. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2011;123:e269–e367.

This article has been copublished in the *Journal of the American College of Cardiology.*

(*Circulation.* 2011;123:e269–e367.)

***Circulation* is available at http://circ.ahajournals.org** **DOI: 10.1161/CIR.0b013e318214876d**

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Preamble (UPDATED)

For new or updated text, view the 2011 Focused Update and the 2011 Focused Update on Dabigatran. Text supporting unchanged recommendations has not been updated.

It is important that the medical profession play a significant role in critically evaluating the use of diagnostic procedures and therapies as they are introduced and tested in the detection, management, or prevention of disease states. Rigorous and expert analysis of the available data documenting absolute and relative benefits and risks of those procedures and therapies can produce helpful guidelines that improve the effectiveness of care, optimize patient outcomes, and favorably affect the overall cost of care by focusing resources on the most effective strategies.

The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) have jointly engaged in the production of such guidelines in the area of cardiovascular disease since 1980. The ACC/AHA Task Force on Practice Guidelines, whose charge is to develop, update, or revise practice guidelines for important cardiovascular diseases and procedures, directs this effort. The Task Force is pleased to have this guideline developed in conjunction with the European Society of Cardiology (ESC). Writing committees are charged with the task of performing an assessment of the evidence and acting as an independent group of authors to develop or update written recommendations for clinical practice.

Experts in the subject under consideration have been selected from all 3 organizations to examine subject-specific data and write guidelines. The process includes additional representatives from other medical practitioner and specialty groups when appropriate. Writing committees are specifically charged to perform a formal literature review, weigh the strength of evidence for or against a particular treatment or procedure, and include estimates of expected health outcomes where data exist. Patient-specific modifiers, comorbidities, and issues of patient preference that might influence the choice of particular tests or therapies are considered as well as frequency of follow-up and cost-effectiveness. When available, information from studies on cost will be considered; however, review of data on efficacy and clinical outcomes will constitute the primary basis for preparing recommendations in these guidelines.

The ACC/AHA Task Force on Practice Guidelines and the ESC Committee for Practice Guidelines make every effort to avoid any actual, potential, or perceived conflict of interest that might arise as a result of an outside relationship or personal interest of the writing committee. Specifically, all members of the Writing Committee and peer reviewers of the document are asked to provide disclosure statements of all such relationships that might be perceived as real or potential conflicts of interest. Writing committee members are also strongly encouraged to declare a previous relationship with industry that might be perceived as relevant to guideline development. If a writing committee member develops a new relationship with industry during their tenure, they are required to notify guideline staff in writing. The continued participation of the writing committee member will be reviewed. These statements are reviewed by the parent Task Force, reported orally to all members of the writing committee at each meeting, and updated and reviewed by the writing committee as changes occur. Please refer to the methodology manuals for further description of the policies used in guideline development, including relationships with industry, available online at the ACC, AHA, and ESC World Wide Web sites (http://www.acc.org/clinical/manual/manual_introltr.htm, http://circ.ahajournals.org/manual/, and http://www.escardio.org/knowledge/guidelines/Rules/). Please see Appendix I for author relationships with industry and Appendix II for peer reviewer relationships with industry that are pertinent to these guidelines.

These practice guidelines are intended to assist healthcare providers in clinical decision making by describing a range of generally acceptable approaches for the diagnosis, management, and prevention of specific diseases and conditions. These guidelines attempt to define practices that meet the needs of most patients in most circumstances. These guideline recommendations reflect a consensus of expert opinion after a thorough review of the available, current scientific evidence and are intended to improve patient care. If these guidelines are used as the basis for regulatory/payer decisions, the ultimate goal is quality of care and serving the patient's best interests. The ultimate judgment regarding care of a particular patient must be made by the healthcare provider and the patient in light of all of the circumstances presented by that patient. There are circumstances in which deviations from these guidelines are appropriate.

The guidelines will be reviewed annually by the ACC/AHA Task Force on Practice Guidelines and the ESC Committee for Practice Guidelines and will be considered current unless they are updated, revised, or sunsetted and withdrawn from distribution. The executive summary and recommendations are published in the August 15, 2006, issues of the *Journal of the American College of Cardiology* and *Circulation* and the August 16, 2006, issue of the *European Heart Journal*. The full-text guidelines are published in the August 15, 2006, issues of the *Journal of the American College of Cardiology* and *Circulation* and the September 2006 issue of *Europace*, as well as posted on the ACC (www.acc.org), AHA (www.americanheart.org), and ESC (www.escardio.org) World Wide Web sites. Copies of the full-text guidelines and the executive summary are available from all 3 organizations.

Sidney C. Smith Jr, MD, FACC, FAHA, FESC, Chair, ACC/AHA Task Force on Practice Guidelines

Silvia G. Priori, MD, PhD, FESC, Chair, ESC Committee for Practice Guidelines

1. Introduction

1.1. Organization of Committee and Evidence Review (UPDATED)

For new or updated text, view the 2011 Focused Update and the 2011 Focused Update on Dabigatran. Text supporting unchanged recommendations has not been updated.

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disturbance, increasing in prevalence with age. AF is often associated with structural heart disease, although a substantial proportion of patients with AF have no detectable heart disease. Hemodynamic impairment and thromboembolic events related to AF result in significant morbidity, mortality, and cost. Accordingly, the American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC) created a committee to establish guidelines for optimum management of this frequent and complex arrhythmia.

The committee was composed of members representing the ACC, AHA, and ESC, as well as the European Heart Rhythm Association (EHRA) and the Heart Rhythm Society (HRS). This document was reviewed by 2 official reviewers nominated by the ACC, 2 official reviewers nominated by the AHA, and 2 official reviewers nominated by the ESC, as well as by the ACCF Clinical Electrophysiology Committee, the AHA ECG and Arrhythmias Committee, the AHA Stroke Review Committee, EHRA, HRS, and numerous additional content reviewers nominated by the writing committee. The document was approved for publication by the governing bodies of the ACC, AHA, and ESC and officially endorsed by the EHRA and the HRS.

The ACC/AHA/ESC Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation conducted a comprehensive review of the relevant literature from 2001 to 2006. Literature searches were conducted in the following databases: PubMed/MEDLINE and the Cochrane Library (including the Cochrane Database of Systematic Reviews and the Cochrane Controlled Trials Registry). Searches focused on English-language sources and studies in human subjects. Articles related to animal experimentation were cited when the information was important to understanding pathophysiological concepts pertinent to patient management and comparable data were not available from human studies. Major search terms included *atrial fibrillation, age, atrial remodeling, atrioventricular conduction, atrioventricular node, cardioversion, classification, clinical trial, complications, concealed conduction, cost-effectiveness, defibrillator, demographics, epidemiology, experimental, heart failure (HF), hemodynamics, human, hyperthyroidism, hypothyroidism, meta-analysis, myocardial infarction, pharmacology, postoperative, pregnancy, pulmonary disease, quality of life, rate control, rhythm control, risks, sinus rhythm, symptoms*, and *tachycardia-mediated cardiomyopathy*. The complete list of search terms is beyond the scope of this section.

Classification of Recommendations and Level of Evidence are expressed in the ACC/AHA/ESC format as follows and described in Table 1. Recommendations are evidence based and derived primarily from published data.

Classification of Recommendations

- Class I: Conditions for which there is evidence and/or general agreement that a given procedure/therapy is beneficial, useful, and effective.
- Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of performing the procedure/therapy.
  - Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.
  - Class IIb: Usefulness/efficacy is less well established by evidence/opinion.
- Class III: Conditions for which there is evidence and/or general agreement that a procedure/therapy is not useful or effective and in some cases may be harmful.

Level of Evidence

The weight of evidence was ranked from highest (A) to lowest (C), as follows:

- Level of Evidence A: Data derived from multiple randomized clinical trials or meta-analyses.
- Level of Evidence B: Data derived from a single randomized trial, or nonrandomized studies.
- Level of Evidence C: Only consensus opinion of experts, case studies, or standard-of-care.

1.2. Contents of These Guidelines

These guidelines first present a comprehensive review of the latest information about the definition, classification, epidemiology, pathophysiological mechanisms, and clinical characteristics of AF. The management of this complex and potentially dangerous arrhythmia is then reviewed. This includes prevention of AF, control of heart rate, prevention of thromboembolism, and conversion to and maintenance of sinus rhythm. The treatment algorithms include pharmacological and nonpharmacological antiarrhythmic approaches, as well as antithrombotic strategies most appropriate for particular clinical conditions. Overall, this

Table 1. Applying Classification of Recommendations and Level of Evidence† (UPDATED) (see the 2011 Focused Update and the 2011 Focused Update on Dabigatran)

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT →			
	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	**CLASS IIa** *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	**CLASS IIb** *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	**CLASS III** *No Benefit* or **CLASS III** *Harm* Procedure/ Test / Treatment COR III: No Benefit: Not Helpful / No Proven Benefit COR III: Harm: Excess Cost w/o Benefit or Harmful / Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations‡	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended / is not indicated / should not be done / is not useful/ beneficial/ effective COR III: Harm: potentially harmful / causes harm / associated with excess morbidity/mortality / should not be done
Comparative effectiveness phrases‡	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as gender, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use. A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

†In 2003, the ACC/AHA Task Force on Practice Guidelines developed a list of suggested phrases to use when writing recommendations. All guideline recommendations have been written in full sentences that express a complete thought, such that a recommendation, even if separated and presented apart from the rest of the document (including headings above sets of recommendations), would still convey the full intent of the recommendation. It is hoped that this will increase readers' comprehension of the guidelines and will allow queries at the individual recommendation level.

is a consensus document that attempts to reconcile evidence and opinion from both sides of the Atlantic Ocean. The pharmacological and nonpharmacological antiarrhythmic approaches may include some drugs and devices that do not have the approval of all government regulatory agencies. Additional informa-tion may be obtained from the package inserts when the drug or device has been approved for the stated indication.

Because atrial flutter can precede or coexist with AF, special consideration is given to this arrhythmia in each section. There are important differences in the mechanisms of AF and atrial flutter, and the body of evidence available to support therapeutic recommendations is distinct for the 2 arrhythmias. Atrial flutter is not addressed comprehensively in these guidelines but is addressed in the ACC/AHA/ESC Guidelines on the Management of Patients with Supraventricular Arrhythmias.[1]

1.3. Changes Since the Initial Publication of These Guidelines in 2001

In developing this revision of the guidelines, the Writing Committee considered evidence published since 2001 and drafted revised recommendations where appropriate to incorporate results from major clinical trials such as those that compared rhythm-control and rate-control approaches to long-term management. The text has been reorganized to reflect the implications for patient care, beginning with recognition of AF and its pathogenesis and the general

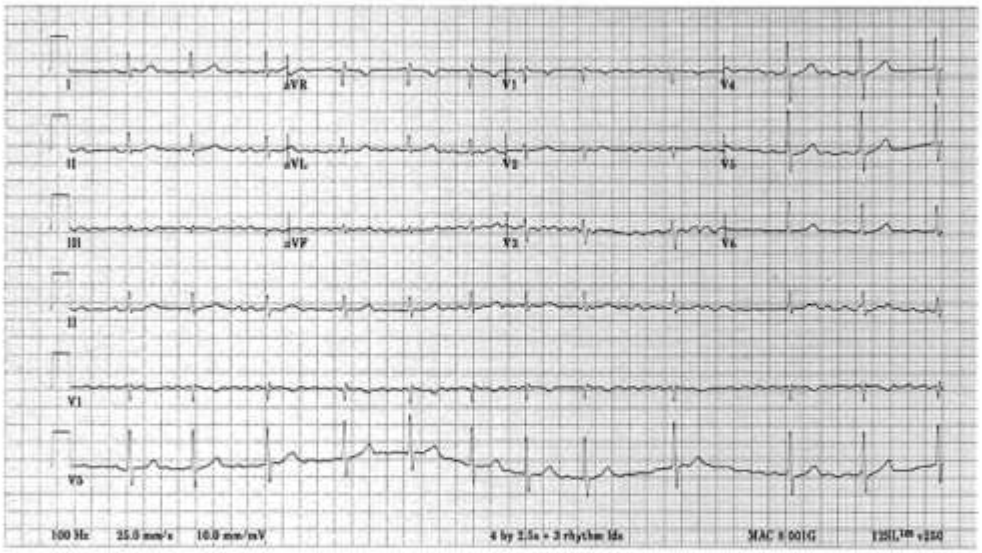

Figure 1. Electrocardiogram showing atrial fibrillation with a controlled rate of ventricular response. P waves are replaced by fibrillatory waves and the ventricular response is completely irregular.

priorities of rate control, prevention of thromboembolism, and methods available for use in selected patients to correct the arrhythmia and maintain normal sinus rhythm. Advances in catheter-based ablation technologies have been incorporated into expanded sections and recommendations, with the recognition that that such vital details as patient selection, optimum catheter positioning, absolute rates of treatment success, and the frequency of complications remain incompletely defined. Sections on drug therapy have been condensed and confined to human studies with compounds that have been approved for clinical use in North America and/or Europe. Accumulating evidence from clinical studies on the emerging role of angiotensin inhibition to reduce the occur-rence and complications of AF and information on approaches to the primary prevention of AF are addressed comprehensively in the text, as these may evolve further in the years ahead to form the basis for recommendations affecting patient care. Finally, data on specific aspects of management of patients who are prone to develop AF in special circumstances have become more robust, allowing formulation of recommendations based on a higher level of evidence than in the first edition of these guidelines. An example is the completion of a relatively large randomized trial addressing prophylactic administration of antiarrhythmic medication for patients undergoing cardiac surgery. In developing the updated recommendations, every effort was made to maintain consistency with other ACC/AHA and ESC practice guidelines addressing, for example, the management of patients undergoing myocardial revascularization procedures.

2. Definition

2.1. Atrial Fibrillation

AF is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function. On the electrocardiogram (ECG), AF is characterized by the replacement of consistent P waves by rapid oscillations or fibrillatory waves that vary in amplitude, shape, and timing, associated with an irregular, frequently rapid ventricular response when atrioventricular (AV) conduction is intact[2] (Fig. 1). The ventricular response to AF depends on electrophysiological (EP) properties of the AV node and other conducting tissues, the level of vagal and sympathetic tone, the presence or absence of accessory conduction pathways, and the action of drugs.[3] Regular cardiac cycles (R-R intervals) are possible in the presence of AV block or ventricular or AV junctional tachycardia. In patients with implanted pacemakers, diagnosis of AF may require temporary inhibition of the pacemaker to expose atrial fibrillatory activity.[4] A rapid, irregular, sustained, wide-QRS-complex tachycardia strongly suggests AF with conduction over an accessory pathway or AF with underlying bundle-branch block. Extremely rapid rates (over 200 beats per minute) suggest the presence of an accessory pathway or ventricular tachycardia.

2.2. Related Arrhythmias

AF may occur in isolation or in association with other arrhythmias, most commonly atrial flutter or atrial tachycardia. Atrial flutter may arise during treatment with antiarrhythmic agents prescribed to prevent recurrent AF. Atrial flutter in the typical form is characterized by a saw-tooth pattern of regular atrial activation called flutter (f) waves on the ECG, particularly visible in leads II, III, aVF, and V_1 (Fig. 2). In the untreated state, the atrial rate in atrial flutter typically ranges from 240 to 320 beats per minute, with f waves inverted in ECG leads II, III, and aVF and upright in lead V_1. The direction of activation in the right atrium (RA) may be reversed, resulting in f waves that are upright in leads II, III, and aVF and inverted in lead V_1. Atrial flutter commonly occurs with 2:1 AV block, resulting in a regular or irregular ventricular rate of 120 to 160 beats per minute (most

agulation, loss of AV synchrony, and lifelong pacemaker dependency. There is also a finite risk of sudden death due to torsades de pointes or ventricular fibrillation.[396] Patients with abnormalities of diastolic ventricular compliance who depend on AV synchrony to maintain cardiac output, such as those with hypertrophic cardiomyopathy or hypertensive heart disease, may experience persistent symptoms after AV nodal ablation and pacemaker implantation. Hence, patients should be counseled regarding each of these considerations before proceeding with this irreversible measure.

The adverse hemodynamic effects of RV apical pacing following AV nodal ablation have been a source of concern. Compared with RV apical pacing, LV pacing significantly improves indices of both LV systolic function (pressure-volume loop, stroke work, ejection fraction, and dP/dt) and diastolic filling.[397] Acutely, LV pacing was associated with a 6% increase in ejection fraction and a 17% decrease in mitral regurgitation.[398] The Post AV Node Ablation Evaluation (PAVE) randomized 184 patients undergoing AV nodal ablation because of permanent AF to standard RV apical pacing or biventricular pacing.[399] After 6 mo, the biventricular pacing group walked 25.6 meters farther in 6 min ($P=0.03$), had greater peak oxygen consumption, and had higher scores in 9 of 10 quality-of-life domains than the RV pacing group. While there was no difference in LV ejection fraction between the groups at baseline, the LV ejection fraction remained stable in the biventricular pacing group while it declined in the RV pacing group (46% vs. 41%, respectively; $P=0.03$). There was no significant difference in mortality. A subgroup analysis suggested that functional improvements were confined to patients with LV ejection fraction below 35% before ablation.

Patients with normal LV function or reversible LV dysfunction undergoing AV nodal ablation are most likely to benefit from standard AV nodal ablation and pacemaker implantation. For those with impaired LV function not due to tachycardia, a biventricular pacemaker with or without defibrillator capability should be considered. Upgrading to a biventricular device should be considered for patients with HF and an RV pacing system who have undergone AV node ablation.[400]

8.1.4. Preventing Thromboembolism

For recommendations regarding antithrombotic therapy in patients with AF undergoing cardioversion, see Section 8.2.7.

RECOMMENDATIONS

CLASS I

1. **Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except those with lone AF or contraindications.** *(Level of Evidence: A)*
2. **The selection of the antithrombotic agent should be based upon the absolute risks of stroke and bleeding and the relative risk and benefit for a given patient.** *(Level of Evidence: A)*
3. **For patients without mechanical heart valves at high risk of stroke, chronic oral anticoagulant therapy with a vitamin K antagonist is recommended in a dose adjusted to achieve the target intensity INR of 2.0 to 3.0, unless contraindicated. Factors associated with highest risk for stroke in patients with AF are prior thromboembolism (stroke, TIA, or systemic embolism) and rheumatic mitral stenosis.** *(Level of Evidence: A)*
4. **Anticoagulation with a vitamin K antagonist is recommended for patients with more than 1 moderate risk factor. Such factors include age 75 y or greater, hypertension, HF, impaired LV systolic function (ejection fraction 35% or less or fractional shortening less than 25%), and diabetes mellitus.** *(Level of Evidence: A)*
5. **INR should be determined at least weekly during initiation of therapy and monthly when anticoagulation is stable.** *(Level of Evidence: A)*
6. **Aspirin, 81–325 mg daily, is recommended as an alternative to vitamin K antagonists in low-risk patients or in those with contraindications to oral anticoagulation.** *(Level of Evidence: A)*
7. **For patients with AF who have mechanical heart valves, the target intensity of anticoagulation should be based on the type of prosthesis, maintaining an INR of at least 2.5.** *(Level of Evidence: B)*
8. **Antithrombotic therapy is recommended for patients with atrial flutter as for those with AF.** *(Level of Evidence: C)*

CLASS IIa

1. **For primary prevention of thromboembolism in patients with nonvalvular AF who have just 1 of the following validated risk factors, antithrombotic therapy with either aspirin or a vitamin K antagonist is reasonable, based upon an assessment of the risk of bleeding complications, ability to safely sustain adjusted chronic anticoagulation, and patient preferences: age greater than or equal to 75 y (especially in female patients), hypertension, HF, impaired LV function, or diabetes mellitus.** *(Level of Evidence: A)*
2. **For patients with nonvalvular AF who have 1 or more of the following less well-validated risk factors, antithrombotic therapy with either aspirin or a vitamin K antagonist is reasonable for prevention of thromboembolism: age 65 to 74 y, female gender, or CAD. The choice of agent should be based upon the risk of bleeding complications, ability to safely sustain adjusted chronic anticoagulation, and patient preferences.** *(Level of Evidence: B)*
3. **It is reasonable to select antithrombotic therapy using the same criteria irrespective of the pattern (ie, paroxysmal, persistent, or permanent) of AF.** *(Level of Evidence: B)*
4. **In patients with AF who do not have mechanical prosthetic heart valves, it is reasonable to interrupt anticoagulation for up to 1 wk without substituting heparin for surgical or diagnostic procedures that carry a risk of bleeding.** *(Level of Evidence: C)*
5. **It is reasonable to reevaluate the need for anticoagulation at regular intervals.** *(Level of Evidence: C)*

CLASS IIb

1. **In patients 75 y of age and older at increased risk of bleeding but without frank contraindications to oral anticoagulant therapy, and in other patients with moderate risk factors for thromboembolism who are unable to safely tolerate anticoagulation at the standard intensity of INR 2.0 to 3.0, a lower INR target of 2.0 (range 1.6 to 2.5) may be considered for primary prevention of ischemic stroke and systemic embolism.** *(Level of Evidence: C)*
2. **When surgical procedures require interruption of oral anticoagulant therapy for longer than 1 wk in high-risk patients, unfractionated heparin may be administered or low-molecular-weight heparin given by subcutaneous injection, although the efficacy of these alternatives in this situation is uncertain.** *(Level of Evidence: C)*
3. **Following percutaneous coronary intervention or revascularization surgery in patients with AF, low-dose aspirin (less than 100 mg per d) and/or clopidogrel (75 mg per d) may be given concurrently with anticoagulation to prevent myocardial ischemic events, but these strategies have not been thoroughly evaluated and are associated with an increased risk of bleeding.** *(Level of Evidence: C)*
4. **In patients undergoing percutaneous coronary intervention, anticoagulation may be interrupted to prevent bleeding at the site of peripheral arterial puncture, but the vitamin K antagonist should be resumed as soon as possible after the procedure and the dose adjusted to achieve an INR in the therapeutic range. Aspirin may be given temporarily during the hiatus, but the maintenance regimen should then consist of the combination of clopidogrel, 75 mg daily, plus warfarin (INR 2.0 to 3.0). Clopidogrel should be given for a minimum of 1 mo after implantation of a bare metal stent, at least 3 mo for a sirolimus-eluting stent, at least 6 mo for a paclitaxel-eluting stent, and 12 mo or longer in selected patients, following which warfarin may be continued as monotherapy in the absence of a subsequent coronary event. When warfarin is given in combination with clopidogrel or low-dose aspirin, the dose intensity must be carefully regulated.** *(Level of Evidence: C)*
5. **In patients with AF younger than 60 y without heart disease or risk factors for thromboembolism (lone AF), the risk of thromboembolism is low without treatment and the effectiveness of aspirin for primary prevention of stroke relative to the risk of bleeding has not been established.** *(Level of Evidence: C)*
6. **In patients with AF who sustain ischemic stroke or systemic embolism during treatment with low-intensity anticoagulation (INR 2.0 to 3.0), rather than add an antiplatelet agent, it may be reasonable to raise the intensity of anticoagulation to a maximum target INR of 3.0 to 3.5.** *(Level of Evidence: C)*

CLASS III

Long-term anticoagulation with a vitamin K antagonist is not recommended for primary prevention of stroke in patients below the age of 60 y without heart disease (lone AF) or any risk factors for thromboembolism. *(Level of Evidence: C)*

Table 11. Risk Factors for Ischemic Stroke and Systemic Embolism in Patients With Nonvalvular Atrial Fibrillation

Risk Factors	Relative Risk
Previous stroke or TIA	2.5
Diabetes mellitus	1.7
History of hypertension	1.6
Heart failure	1.4
Advanced age (continuous, per decade)	1.4

Data derived from collaborative analysis of 5 untreated control groups in primary prevention trials.[47] As a group, patients with nonvalvular atrial fibrillation (AF) carry about a 6-fold increased risk of thromboembolism compared with patients in sinus rhythm. Relative risk refers to comparison of patients with AF to patients without these risk factors.

TIA indicates transient ischemic attack.

8.1.4.1. Risk Stratification

8.1.4.1.1. Epidemiological Data. In a small, retrospective, population-based study in Olmsted County, Minnesota, over 3 decades, the 15-y cumulative stroke rate in people with lone AF (defined as those younger than 60 y with no clinical history or echocardiographic signs of cardiopulmonary disease) was 1.3%.[11] Conversely, in the Framingham Study,[28] the age-adjusted stroke rate over a mean follow-up period of 11 y was 28.2% in those with lone AF, more liberally defined to include patients with a history of hyper-tension or cardiomegaly on chest roentgenography, compared with 6.8% in normal controls.[28] In the SPAF study, the annualized rate of ischemic stroke during aspirin treatment was similar in those with paroxysmal (3.2%) and permanent (3.3%) AF.[404] Those with prior stroke or TIA have a rate of subsequent stroke of 10% to 12% per year when treated with aspirin, and these patients benefit substantially from adjusted-dose oral anticoagulation.[402,403] In addition to prior thromboembolism, HF, hypertension, increasing age, and diabetes mellitus have consistently emerged as independent risk factors for ischemic stroke associated with nonvalvular AF.[47,261,264,382,405] Other factors, such as female gender, systolic blood pressure over 160 mm Hg, and LV dysfunction, have been variably linked to stroke.[261,266,406] The relative risk for ischemic stroke associated with specific clinical features, derived from a collaborative analysis of participants given no antithrombotic therapy in the control groups of 5 randomized trials, is displayed in Table 11.

In patients with nonvalvular AF, prior stroke or TIA is the strongest independent predictor of stroke, significantly associated with stroke in all 6 studies in which it was evaluated, with incremental relative risk between 1.9 and 3.7 (averaging approximately 3.0). Attempts to identify patients with prior stroke or TIA who have relatively low stroke risks by virtue of the absence of other risk factors did not identify any reliable predictors.[261,407–409] The pathogenic constructs of stroke in AF are incomplete, but available data indicate that all patients with prior stroke or TIA are at high risk of recurrent thromboembolism and require anticoagulation unless there are firm contraindications in a given patient. Efforts to enhance risk stratification should remove such patients from consideration and focus instead on the predictive value of pertinent risk factors and absolute stroke rates for primary

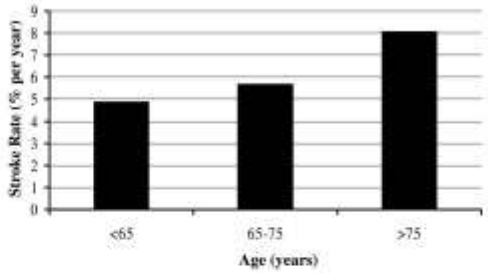

Figure 8. Stroke rates in relation to age among patients in untreated control groups of randomized trials of antithrombotic therapy. Data are from the Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994;154:1449–57.[47]

prevention. Patient age is a consistent independent predictor of stroke (Fig. 8). In 7 studies in which the variable was assessed, hazard ratios averaged 1.5 per decade. Nearly half of AF-associated strokes occur in patients over 75 y, and AF is the most frequent cause of disabling stroke in elderly women.[21,405,406] Older people are also at increased risk for anticoagulant-related bleeding[410] and are less likely to be treated with oral anticoagulation, even in situations for which it has been proved efficacious, in part because of concern about the risk of bleeding.[411] Special consideration of these older patients is therefore a critical aspect of effective stroke prophylaxis.[405]

Female gender has emerged as an independent predictor of stroke in 3 cohort studies of patients with AF but not in several others.[47,268,404] The relative increase was 1.6 in the largest study of the ATRIA cohort.[262] In the SPAF analyses of aspirin-treated patients, gender interacted with age such that women over 75 y old were at particularly high risk, but this interaction was not apparent in the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) cohort.[262,412]

Similarly, hypertension is a consistent, powerful predictor of stroke, with a history of hypertension independently predictive in 5 studies (median relative risk approximately 2.0) and systolic blood pressure significant in 2 others (mean relative risk approximately 2.0). A history of hypertension and systolic blood pressure over 160 mm Hg were independently predictive of stroke in the SPAF aspirin-treated cohorts.

Diabetes was a significant independent predictor in 4 studies, associated with an average relative risk of 1.8, but not in 2 other studies. The strength of diabetes as a predictor may be greater in lower-risk patients with AF, prompting speculation that it may be associated with noncardioembolic strokes. Diabetes is a less powerful independent predictor than prior stroke/TIA, hypertension, or age, but analysis of the type, duration, or control of diabetes has not been undertaken to refine its predictive value for thromboembolism in patients with AF. The reduction in stroke among warfarin-treated patients with diabetes was below average in 2 studies.[413,414]

In 2 studies, CAD was a univariate predictor of stroke in otherwise low-risk patients;[47,415] it has not been shown to have independent predictive value for stroke in patients with AF.

Clinical HF has not been conclusively shown to have independent predictive value for stroke in any study of AF patients. In the SPAF I and II studies,[412] recent (within 3 mo) HF or impaired LV systolic function (defined as M-mode echocardiographic fractional shortening less than 25%) was a significant independent predictor, as was LV systolic dysfunction by 2-dimensional echocardiography in placebo-treated patients in some studies[266] but not in others.[261,268] Clinical diagnosis of HF may be difficult in elderly patients with AF, and misclassification could blunt the power of association. In short, while it seems logical based on pathophysiological concepts and echocardiographic correlates that HF should be an independent predictor of stroke in patients with nonvalvular AF, available data do not provide strong support.

8.1.4.1.2. Echocardiography and Risk Stratification. Echocardiography is valuable to define the origin of AF (eg, detecting rheumatic mitral valve disease or HCM) and may add information useful in stratifying thromboembolic risk. Among high-risk AF patients, impaired LV systolic function on transthoracic echocardiography, thrombus, dense SEC or reduced velocity of blood flow in the LAA, and complex atheromatous plaque in the thoracic aorta on TEE have been associated with thromboembolism, and oral anticoagulation effectively lowers the risk of stroke in AF patients with these features. LA diameter and fibrocalcific endocardial abnormalities have been less consistently associated with thromboembolism. Whether the absence of these echocardiographic abnormalities identifies a low-risk group of patients who could safely avoid anticoagulation has not been established, limiting the value of echocardiography as a prime determinant of the need for chronic anticoagulation in patients with AF.

TRANSTHORACIC ECHOCARDIOGRAPHY. Correlations in placebo-assigned participants in randomized trials of antithrombotic therapy provide information about the independent predictive value of transthoracic echocardiography for thromboembolic events in patients with nonvalvular AF.[265,416] Meta-analysis of 3 trials found moderate to severe LV dysfunction to be the only independent echocardiographic predictor of stroke in patients with AF after adjustment for clinical features; the diameter of the LA was less useful.[266] Secondary analyses of aspirin-assigned patients in multicenter trials yield variable results regarding the role of transthoracic echocardiography for predicting thromboembolic risk.[54,203] In the SPAF I and II studies, LV fractional shortening less than 25% (estimated by M-mode echocardiography) was the only independent echocardiographic predictor of stroke. Among 2012 aspirin-assigned patients in the SPAF trials (including 290 in SPAF-III assigned to a relatively ineffective fixed-dose combination of aspirin plus warfarin), no transthoracic echocardiographic parameter independently predicted thromboembolism when clinical risk factors were considered. Similarly, no independent predictors of thromboembolism were identified by transthoracic echocardiography and TEE at entry in the Embolism in the Left Atrial Thrombi (ELAT) study of 409 patients with nonvalvular AF taking aspirin, 160 mg daily.[268]

TRANSESOPHAGEAL ECHOCARDIOGRAPHY. TEE is a sensitive and specific technique for detection of LA and LAA thrombus, far surpassing transthoracic echocardiography.[203] This modality also permits superior evaluation for other causes of cardiogenic embolism,[320] as well as a means of measuring LAA function.[319] Several TEE features have been associated with thromboembolism, includ-

ing thrombus, reduced flow velocity, and SEC in the LA or LAA and atheromatous disease of the aorta.[252,417]

Detection of LA/LAA thrombus stands as a contraindication to elective cardioversion of AF. Unfortunately, the absence of a detectable thrombus does not preclude stroke after cardioversion in the absence of anticoagulation therapy.[324,418] A TEE-guided strategy for elective cardioversion of AF yielded comparable outcomes for thromboembolism and death compared with conventional anticoagulation for 3 wk before and 4 wk after cardioversion.[320]

8.1.4.1.3. Therapeutic Implications. The efficacy and safety of oral anticoagulation and platelet inhibitor therapy with aspirin for prevention of stroke in patients with AF have been well characterized.[420] The selection of appropriate antithrombotic therapy is discussed below in the context of thromboembolic risk (see Section 8.1.6, Pharmacological Agents to Maintain Sinus Rhythm, and Section 8.1.7, Outof-Hospital Initiation of Antiarrhythmic Drugs in Patients With Atrial Fibrillation). Patients with AF who have low rates of stroke when treated with aspirin may not gain sufficient benefit from anticoagulation to outweigh the attendant risks and the need for close medical monitoring.[421,422] Estimating the risk of stroke for individual AF patients is crucial for the decision to provide anticoagulation therapy to individual patients with AF,[54] but the threshold risk that warrants anticoagulation is controversial. Patients with a stroke risk of 2% per year or less do not benefit substantially from oral anticoagulation, which would require treating 100 or more patients for 1 y to prevent a single stroke.[420] For high-risk AF patients with stroke rates of 6% per year or greater, the comparable number needed-to-treat is 25 or fewer, strongly favoring anticoagulation. Opinion remains divided about routine anticoagulation for patients at intermediate stroke risk (annual rate 3% to 5%).

To stratify the risk of ischemic stroke in patients with AF, several clinical schemes have been proposed based on analyses of prospectively monitored cohorts of participants in clinical trials in which antithrombotic therapy was controlled.[391,421,423] One set of criteria (Atrial Fibrillation Investigators [AFI]) is based on multivariate pooled analysis of 1593 participants assigned to the control or placebo groups of 5 randomized primary prevention trials in which 106 ischemic strokes occurred over a mean follow-up of 1.4 y.[47] Patients were divided into 2 strata, distinguishing low-risk patients from those at intermediate or high risk. Although echocardiographic features were not considered initially, a subsequent analysis of 3 of the trials identified abnormal LV systolic function as an independent predictor of stroke.[421] The SPAF study criteria were based on multivariate analysis of 854 patients assigned to aspirin and followed for a mean of 2.3 y, during which 68 ischemic strokes were observed. These criteria were subsequently used to select a low-risk cohort for treatment with aspirin in the SPAF III study. Over a mean follow-up of 2 y, the rate of ischemic stroke was 2.0% per year (95% CI 1.5% to 2.8%) and the rate of disabling ischemic stroke was 0.8% per year (95% CI 0.5% to 1.3%). Patients with a history of hypertension had a higher rate of thromboembolism (3.6% per year) than those without hypertension (1.1% per year; *P* less than 0.001). Other criteria have been developed by expert consensus[423,424] based on consideration of the foregoing schemes to classify patients into low-, intermediate-, and high-risk groups. Still others have employed recursive partitioning and other techniques to identify low-risk patients.

Nine schemes that included more than 30 stroke events have been promulgated based on multivariate analysis of clinical and/or echocardiographic predictors. Three were derived from overlapping patient cohorts, while 6 were derived from entirely independent cohorts.[47,261,266,412,415] Of the 6 studies with distinct patient cohorts, 2 involved participants in randomized trials, 2 were based on clinical case series, one was a population-based epidemiological study, and the other was a hospital-based case-control study. The largest study[262] was limited to analysis of female gender as an independent predictor.

A multivariate analysis from the Framingham Heart Study examined risk factors for stroke among 705 patients with recently detected AF, excluding those who had sustained ischemic stroke, TIA, or death within 30 d of diagnosis.[423] The only significant predictors of ischemic stroke were age (RR=1.3 per decade), female gender (RR=1.9), prior stroke or TIA (RR=1.9), and diabetes mellitus (RR=1.8), consistent with earlier studies. Systolic blood pressure became a significant predictor of stroke when warfarin was included in a time-dependent Cox proportional hazards model. With a scoring system based on age, gender, systolic hypertension, diabetes, and prior stroke or TIA, the proportion of patients classified as low risk varied from 14.3% to 30.6% depending upon whether stroke rate thresholds were less than 1.5% per year or less than 2% per year. Observed stroke rates were 1.1% to 1.5% per year based on 88 validated events. In the future, it may be possible to consider other characteristics that may contribute to stroke risk, including genetic abnormalities of hemostatic factors and endothelial dysfunction, but none have yet been identified that have sufficient predictive value for clinical use in risk stratification.[230,413]

Another stroke risk classification scheme, known as $CHADS_2$ (Cardiac Failure, Hypertension, Age, Diabetes, Stroke [Doubled]) integrates elements from several of the foregoing schemes. The $CHADS_2$ risk index is based on a point system in which 2 points are assigned for a history of stroke or TIA and 1 point each is assigned for age over 75 y, a history of hypertension, diabetes, or recent HF (Table 12).[415,426] The predictive value of this scoring system was evaluated in 1733 Medicare beneficiaries with nonvalvular AF between the ages of 65 and 95 y who were not given warfarin at hospital discharge. Although high scores were associated with an increased stroke rate in this elderly cohort, few patients had a score of 5 or more or a score of 0. In the same cohort, the modified AFI scheme had high-risk (prior stroke or TIA, hypertension, or diabetes) and moderate-risk (age greater than 65 y without other high-risk features) categories, corresponding to stroke rates of 5.4% per year (95% CI 4.2% to 6.5% per year) for high-risk and 2.2% per year (95% CI 1.1% to 3.5% per year) for moderate-risk patients. Patients with high-risk features according to the SPAF criteria (prior stroke or TIA, women older than 75 y, or recent HF) had a stroke rate of 5.7% per year (95% CI 4.4% to 7.0% per year); moderate-risk patients (history of hyper-tension with no other high-risk features) had a rate of 3.3% per year (95% CI 1.7% to 5.2% per year); and low-risk patients (without risk factors) had a stroke rate of 1.5% per year (95% CI 0.5% to 2.8% per year).

Although the schemes for stratification of stroke risk identify patients who benefit most and least from anticoagu- lation, the threshold for use of anticoagulation is controversial. Opinion is particularly divided about

Table 12. Stroke Risk in Patients With Nonvalvular AF Not Treated With Anticoagulation According to the $CHADS_2$ Index

$CHADS_2$ Risk Criteria	Score
Prior stroke or TIA	2
Age >75 y	1
Hypertension	1
Diabetes mellitus	1
Heart failure	1

Patients (N=1733)	Adjusted Stroke Rate (%/y)* (95% CI)	$CHADS_2$ Score
120	1.9 (1.2 to 3.0)	0
463	2.8 (2.0 to 3.8)	1
523	4.0 (3.1 to 5.1)	2
337	5.9 (4.6 to 7.3)	3
220	8.5 (6.3 to11.1)	4
65	12.5 (8.2 to17.5)	5
5	18.2 (10.5to27.4)	6

*The adjusted stroke rate was derived from multivariate analysis assuming no aspirin usage. Data are from van Walraven WC, Hart RG, Wells GA, et al. A clinical prediction rule to identify patients with atrial fibrillation and a low risk for stroke while taking aspirin. *Arch Intern Med* 2003;163:936–43;[415] and Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;285:2864–70.[416]

AF indicates atrial fibrillation; $CHADS_2$, Cardiac Failure, Hypertension, Age, Diabetes, and Stroke (Doubled); CI, confidence interval; and TIA, transient ischemic attack.

anticoagulation for those at intermediate risk (stroke rate 3% to 5% per year). Some advocate the routine use of anticoagulation for those with stroke rates in this range,[427] whereas others favor selective anticoagulation of patients at intermediate risk, with weight given to individual bleeding risks and patient preferences.[34,428] The threshold of benefit at which AF patients choose anticoagulation varies; some at intermediate risk elect anticoagulation, whereas others do not.[429] Our recommendations for antithrombotic therapy in patients with AF are summarized in Table 13.

Atrial flutter is uncommon as a chronic arrhythmia, and the risk of thromboembolism is not as well established as it is for AF but is generally estimated as higher than that for patients with sinus rhythm and less than that for those with persistent or permanent AF. On the basis of multivariate analysis, Wood et al[430] reported hypertension as the only significant correlate of previous thromboembolism for patients with chronic atrial flutter. From a review of 8 y of retrospective data from 749 988 hospitalized older patients, including 17 413 with atrial flutter and 337 428 with AF, 3 of 4 patients with atrial flutter also had or developed AF. The overall stroke risk ratio for patients with atrial flutter was 1.406, and for those with AF, it was 1.642 compared with the control group. Coexisting HF, rheumatic heart disease, and hypertension predicted an episode of AF in patients with atrial flutter. Risk ratios for patients with these comorbid conditions were 1.243, 1.464, and 1.333, respectively.[431]

Although the overall thromboembolic risk associated with atrial flutter may be somewhat lower than with AF, it seems prudent to estimate risk by the use of similar stratification criteria for both arrhythmias until more robust data become available (Tables 13 and 14).

8.1.4.2. Antithrombotic Strategies for Prevention of Ischemic Stroke and Systemic Embolism

Before 1990, antithrombotic therapy for prevention of ischemic stroke and systemic embolism in patients with AF was limited mainly to those with rheumatic heart disease or prosthetic heart valves.[21] Anticoagulation was also accepted therapy for patients who had sustained ischemic stroke to prevent recurrence but was often delayed to avoid hemorrhagic transformation. Some advocated anticoagulation of patients with thyrotoxicosis or other conditions associated with cardiomyopathy. Since then, 24 randomized trials involving patients with nonvalvular AF have been published, including 20 012 participants with an average follow-up of 1.6 y, a total exposure of about 32 800 patient-y (Table 15). In these studies, patient age averaged 71 y; 36% were women. Most trials originated in Europe (14 trials, 7273 participants) or North America (7 trials, 8349 participants). Most studied oral vitamin K inhibitors or aspirin in varying dosages/intensities, but other anticoagulants (low-molecular-weight heparin, ximelagatran) and other antiplatelet agents (dipyridamole, indobufen, trifulsal) have also been tested. Nine trials

Table 13. Antithrombotic Therapy for Patients With Atrial Fibrillation

Risk Category	Recommended Therapy
No risk factors	Aspirin, 81 to 325 mg daily
One moderate-risk factor	Aspirin, 81 to 325 mg daily, or warfarin (INR 2.0 to 3.0, target 2.5)
Any high-risk factor or more than 1 moderate-risk factor	Warfarin (INR 2.0 to 3.0, target 2.5)*

Less Validated or Weaker Risk Factors	Moderate-Risk Factors	High-Risk Factors
Female gender	Age greater than or equal to 75 y	Previous stroke, TIA or embolism
Age 65 to 74 y	Hypertension	Mitral stenosis
Coronary artery disease	Heart failure	Prosthetic heart valve*
Thyrotoxicosis	LV ejection fraction 35% or less	
	Diabetes mellitus	

*If mechanical valve, target international normalized ratio (INR) greater than 2.5.

INR indicates international normalized ratio; LV, left ventricular; and TIA, transient ischemic attack.

Table 14. Risk-Based Approach to Antithrombotic Therapy in Patients With Atrial Fibrillation

Patient Features	Antithrombotic Therapy	Class of Recommendation
Age less than 60 y, no heart disease (lone AF)	Aspirin (81 to 325 mg per day) or no therapy	I
Age less than 60 y, heart disease but no risk factors*	Aspirin (81 to 325 mg per day)	I
Age 60 to 74 y, no risk factors*	Aspirin (81 to 325 mg per day)	I
Age 65 to 74 y with diabetes mellitus or CAD	Oral anticoagulation (INR 2.0 to 3.0)	I
Age 75 y or older, women	Oral anticoagulation (INR 2.0 to 3.0)	I
Age 75 y or older, men, no other risk factors	Oral anticoagulation (INR 2.0 to 3.0) or aspirin (81 to 325 mg per day)	I
Age 65 or older, heart failure	Oral anticoagulation (INR 2.0 to 3.0)	I
LV ejection fraction less than 35% or fractional shortening less than 25%, and hypertension	Oral anticoagulation (INR 2.0 to 3.0)	I
Rheumatic heart disease (mitral stenosis)	Oral anticoagulation (INR 2.0 to 3.0)	I
Prosthetic heart valves	Oral anticoagulation (INR 2.0 to 3.0 or higher)	I
Prior thromboembolism	Oral anticoagulation (INR 2.0 to 3.0 or higher)	I
Persistent atrial thrombus on TEE	Oral anticoagulation (INR 2.0 to 3.0 or higher)	IIa

*Risk factors for thromboembolism include heart failure (HF), left ventricular (LV) ejection fraction less than 35%, and history of hypertension.
AF indicates atrial fibrillation; CAD, coronary artery disease; INR, international normalized ratio; and TEE, transesophageal echocardiography.

had double-blind designs for antiplatelet[57,405,432–435] or anticoagulation[436–438] comparisons.

8.1.4.2.1. Anticoagulation With Vitamin K Antagonist Agents. Five large randomized trials published between 1989 and 1992 evaluated oral anticoagulation mainly for primary prevention of thromboembolism in patients with nonvalvular AF[57,428,432,436,437] (Fig. 9, Table 15). A sixth trial focused on secondary prevention among patients who had survived nondisabling stroke or TIA.[403] Meta-analysis according to the principle of intention to treat showed that adjusted-dose oral anticoagulation is highly efficacious for prevention of all stroke (both ischemic and hemorrhagic), with a risk reduction of 62% (95% CI 48% to 72%) versus placebo[420] (Fig. 9). This reduction was similar for both primary and secondary prevention and for both disabling and nondisabling strokes. By on-treatment analysis (excluding patients not undergoing oral anticoagulation at the time of stroke), the preventive efficacy of oral anticoagulation exceeded 80%. Four of these trials were placebo controlled; of the 2 that were double blinded with regard to anticoagulation,[437] one was stopped early because of external evidence that oral anticoagulation was superior to placebo, and the other included no female subjects. In 3 of the trials, oral anticoagulant dosing was regulated according to the prothrombin time ratio; 2 used INR target ranges of 2.5 to 4.0 and 2.0 to 3.0. These trials are summarized in Table 15. The duration of follow-up was generally between 1 and 2 y; the longest was 2.2 y, whereas in clinical practice, the need for antithrombotic therapy in patients with AF typically extends over much longer periods.

All reported trials excluded patients considered at high risk of bleeding. Patient age and the intensity of anticoagulation are the most powerful predictors of major bleeding.[449–454] Trial participants, at an average age of 69 y, were carefully selected and managed, however, and it is unclear whether the relatively low observed rates of major hemorrhage also apply to patients with AF in clinical practice, who have a mean age of about 75 y and less closely regulated anticoagulation therapy.[19,431,455]

The target intensity of anticoagulation involves a balance between prevention of ischemic stroke and avoidance of hemorrhagic complications (Fig. 10). Targeting the lowest adequate intensity of anticoagulation to minimize the risk of bleeding is particularly important for elderly AF patients. Maximum protection against ischemic stroke in AF is probably achieved at an INR range of 2.0 to 3.0,[456] whereas an INR range of 1.6 to 2.5 is associated with incomplete efficacy, estimated at approximately 80% of that achieved with higher-intensity anticoagulation.[432,449] Two randomized trials with a target INR of 1.4 to 2.8 (estimated mean achieved INR 2.0 to 2.1) found the largest relative risk reductions for ischemic stroke. A trial in which AF patients with prior stroke or TIA were randomly assigned to target INR ranges of 2.2 to 3.5 versus 1.5 to 2.1 found a greater rate of major hemorrhage with the higher intensity.[450] For patients with nonvalvular AF, an INR of 1.6 to 3.0 is efficacious and relatively safe. For primary prevention in most AF patients under age 75 y and for secondary prevention, an INR of 2.5 (target range 2.0 to 3.0) is recommended. A target INR of 2.0 (target range 1.6 to 2.5) seems reasonable for primary prevention in patients older than 75 y who are considered at high risk of bleeding. In clinical trials, INRs achieved during follow-up were more often below than above the target range. Low-intensity anticoagulation requires special efforts to minimize time spent below the target range, during which stroke protection is sharply reduced. The major bleeding rate for 5 randomized clinical trials was 1.2% per year[202] (Fig. 11).

Despite anticoagulation of more elderly patients with AF, rates of intracerebral hemorrhage are considerably lower than in the past, typically between 0.1% and 0.6% in contemporary reports. This may reflect lower anticoagulation intensity, more careful dose regulation, or better control of hypertension.[438,457] In 2 time-dependent INR analyses of anticoagulation in elderly AF cohorts, intracranial bleeding increased with INR values over 3.5 to 4.0, and there was no increment

Table 15. Randomized Trials of Antithrombotic Therapy in Patients With Nonvalvular AF

Trials	Reference	Year Published	No. of Patients	Interventions
Large published trials				
Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation I (AFASAK I)	432	1989	1007	VK A, ASA, placebo
Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation II (AFASAK II)	439	1998	677	VKA, ASA, LDA + ASA, LDA
Stroke Prevention in Atrial Fibrillation I (SPAF I)	57	1991	1330	VKA, ASA, placebo
Stroke Prevention in Atrial Fibrillation II (SPAF II)	440	1994	1100	VKA, ASA
Stroke Prevention in Atrial Fibrillation III (SPAF III)	402	1996	1044	VKA, LDA + ASA
Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF)	428	1990	420	VKA, control
Canadian Atrial Fibrillation Anticoagulation (CAFA)	436	1991	378	VKA, placebo
Stroke Prevention in Nonrheumatic Atrial Fibrillation (SPINAF)	437	1992	571	VKA, placebo
European Atrial Fibrillation Trial (EAFT)	403	1993	1007	VKA, ASA, placebo
Studio Italiano Fibrillazione Atriale (SIFA)	441	1997	916	VKA, indobufen
Minidose Warfarin in Nonrheumatic Atrial Fibrillation	442	1998	303	VKA, LDA*
Prevention of Arterial Thromboembolism in Atrial Fibrillation (PATAF)	443	1999	729	VKA, LDA,* ASA
Stroke Prevention using an Oral Direct Thrombin Inhibitor In Patients with Atrial Fibrillation (SPORTIF-III)	477	2003	3407	DTI, VKA
Stroke Prevention using an Oral Direct Thrombin Inhibitor In Patients With Atrial Fibrillation (SPORTIF-V)	438	2005	3922	DTI, VKA
National Study for Prevention of Embolism in Atrial Fibrillation (NASPEAF)	445	2004	1209	VKA, triflusal, VKA + triflusal
Small or pilot trials				
Harenberg et al.	446	1993	75	LMW heparin, control
Low-dose Aspirin, Stroke, Atrial Fibrillation (LASAF)	447	1996	285	ASA, placebo
Subgroups with AF in other trials				
European Stroke Prevention Study II (ESPS II)	404	1997	429	ASA, dipyridamole, placebo

Adapted with permission from Hart RG, Benavente O, McBride R, et al. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999;131:492–501.[420]

AF, atrial fibrillation; ASA, aspirin; DTI, direct thrombin inhibitor; LDA, low-dose aspirin; LMW, low-molecular-weight; and VKA, vitamin K antagonist.

with values between 2.0 and 3.0 compared with lower INR levels.[454,456] Pooled results of randomized trials and a large cohort comparison, however, suggest a doubling of intracranial hemorrhages with mean INR values between 2.0 and 2.5.[458] Other than dose intensity, advanced age, and hypertension, factors associated with higher rates of intracerebral hemorrhage during anticoagulant therapy include associated cerebrovascular disease and possibly concomitant antiplatelet therapy, tobacco or alcohol consumption, ethnicity, genotype, and certain vascular abnormalities detected by brain imaging, such as amyloid angiopathy, leukoaraiosis, or microbleeds.[457] No stratification scheme for prediction of intracerebral hemorrhage during anticoagulant therapy has been prospectively evaluated.

8.1.4.2.2. Aspirin for Antithrombotic Therapy in Patients With Atrial Fibrillation. Aspirin offers only modest protection against stroke for patients with AF[246,57,403,432,439,440,443,447,448] (Fig. 12). Meta-analysis of 5 randomized trials showed a stroke reduction of 19% (95% CI 2% to 34%).[420] The effect of aspirin on stroke in these trials was less consistent than that of oral anticoagulation,[420,459] but differences in patient features may have influenced aspirin efficacy. For example, aspirin reduced stroke occurrence by 33% in primary prevention studies (in which the stroke rate with placebo averaged 5% per year) versus 11% for secondary prevention trials (in which the stroke rate with placebo averaged 14% per year).[420] Aspirin may be more efficacious for AF patients with hypertension or diabetes[459] and for reduction of noncardioembolic versus cardioembolic ischemic strokes in AF patients.[200] Cardioembolic strokes are, on average, more disabling than noncardioembolic strokes.[250] Aspirin appears to prevent nondisabling strokes more than disabling strokes.[420] Thus, the greater the risk of disabling cardioembolic stroke in a population of patients with AF, the less protection is afforded by aspirin.[250]

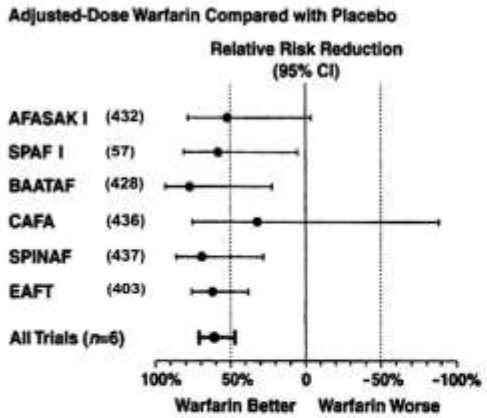

Figure 9. Effects on all stroke (ischemic and hemorrhagic) of therapies for patients with atrial fibrillation. Adjusted-dose warfarin compared with placebo (six random trials. Adapted with permission from Hart RG, Benavente O, McBride R, et al. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999;131:492–501.[420] AFASAK indicates Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation Anticoagulation; CI, confidence interval; EAFT, European Atrial Fibrillation Trial; SPAF, Stroke Prevention in Atrial Fibrillation; and SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation.

Additional information about event rates on aspirin or no antithrombotic therapy can be extracted from contemporary databases such as the ATRIA cohort of 13 428 ambulatory patients with AF enrolled in the Kaiser Permanente Medical Care Program in North Carolina during the period 1996 through 1999.[262,456,458,461] In the 11 526 patients without apparent contraindications to anticoagulation,[458] 6320 patients were treated with warfarin. Among the 5089 patients not treated with warfarin, the absolute rate of thromboembolism was 2.0% per year.[461] There was a history of stroke or TIA in only 4% of the patients not treated with anticoagulation, making this mainly a primary prevention cohort.[458]

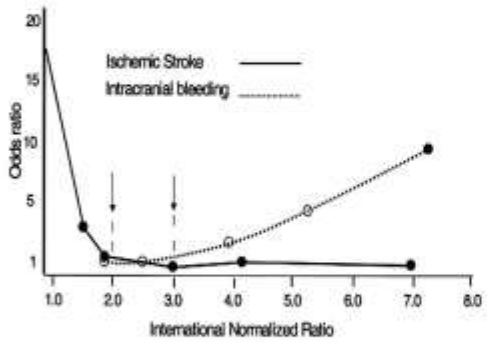

Figure 10. Adjusted odds ratios for ischemic stroke and intracranial bleeding in relation to intensity of anticoagulation. Modified with permission from Hylek EM, Singer DE. Risk factors for intracranial hemorrhage in outpatients taking warfarin. *Ann Intern Med* 1994;120:897–902.[451] Data from Odén A, Fahlén M and Hart RG. Optimal INR for prevention of stroke and death in atrial fibrillation: a critical appraisal. *Thromb Res* 2006;117:493–9.[452]

During a mean follow-up of 2.2 y (median 2.35 y), 249 thromboembolic events (231 ischemic strokes and 18 systemic embolic events outside the central nervous system) occurred among the patients who were not anticoagulated (2.0% per year [95% CI 1.8% to 2.3%]). From a nested case-control study of 294 patients, it was estimated that about 45% were using aspirin. When those from the larger cohort with contraindications to warfarin (who were older and more often had prior stroke or TIA) were included, the rate of thromboembolism was 2.5% per year.

While the use of administrative and claims-based data from a managed care organization may have been prone to underdetection of stroke events, these rates were not very different from those in other reported populations. By comparison, among 1853 patients without prior thromboembolic events assigned to aspirin in the SPAF I, II, and III trials, the rate of ischemic stroke was 2.7% per year.[261] In the AFI cohort of 2732 patients from 6 randomized trials (about half from the SPAF trials), without prior stroke or TIA, the rate of ischemic stroke was 2.1% per year with aspirin therapy. Among 210 patients in the population-based Cardiovascular Health Study (mean age 74 y) followed without anticoagulation, the stroke rate was 2.6% per year.[462] When stratified according to the $CHADS_2$ stroke risk scheme,[426] patients in the ATRIA cohort with a single stroke risk factor (32% of the cohort) who were not anticoagulated had a rate of stroke and systemic embolism of 1.5% per year (95% CI 1.2% to 1.9%).[458] Of 670 patients treated with aspirin in 6 clinical trials, the stroke rate was 2.2% per year for those with a $CHADS_2$ score of 1 (95% CI 1.6% to 3.1% per year).[463]

In summary, adjusted-dose oral anticoagulation is more efficacious than aspirin for prevention of stroke in patients with AF, as suggested by indirect comparisons and by a 33% risk reduction (95% CI 13% to 49%) in a meta-analysis of 5 trials.[420] Randomized trials involving high-risk AF patients (stroke rates greater than 6% per year) show larger relative risk reductions by adjusted-dose oral anticoagulation relative to aspirin (Fig. 12), whereas the relative risk reductions are consistently smaller in trials of AF patients with lower stroke rates. Accordingly, oral anticoagulation may be most beneficial for AF patients at higher intrinsic thromboembolic risk, offering only modest reductions over aspirin in both the relative risk and absolute rates of stroke for patients at low risk. Individual risk varies over time, so the need for anticoagulation must be reevaluated periodically in all patients with AF.

8.1.4.2.3. Other Antiplatelet Agents for Antithrombotic Therapy in Patients With Atrial Fibrillation. Anticoagulation with oral vitamin K antagonists has been compared with platelet cyclooxygenase inhibitors other than aspirin in 2 trials involving 1395 participants. In the Italian Studio Italiano Fibrillazione Atriale (SIFA) study,[441] indobufen, 100 to 200 mg twice daily, was compared with warfarin (INR 2.0 to 3.5) in 916 patients with recent cerebral ischemic events. Incidences of the combined endpoint of nonfatal stroke, intracerebral bleeding, pulmonary or systemic embolism, MI, and vascular death were not significantly different between treatment groups, but more ische-

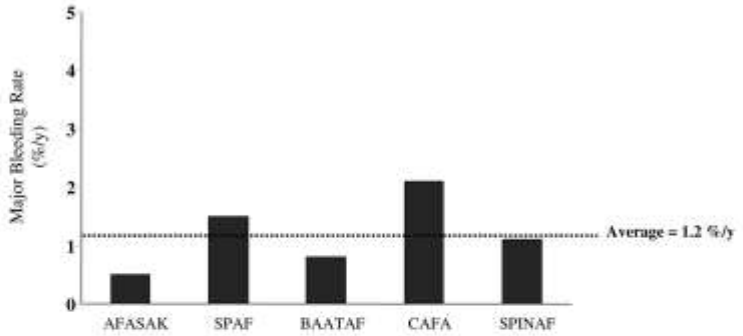

Figure 11. Annual rates of major hemorrhage during anticoagulation in primary prevention trials involving patients with nonvalvular atrial fibrillation. The mean age of participants was 69 years. Major hemorrhage was variously defined but typically involved bleeding severe enough to require hospitalization, transfusion or surgical intervention, involved a critical anatomical site, or was permanently disabling or fatal. Data adapted from Hart RG, Benavente O, McBride R, et al. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999;131:492–501.[420] AFASAK indicates Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation Anticoagulation; SPAF, Stroke Prevention in Atrial Fibrillation; and SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation.

mic strokes occurred in the indobufen group[18] than in the warfarin group.[10] In the primary prevention cohort of the Spanish National Study for Prevention of Embolism in Atrial Fibrillation (NASPEAF) trial,[445] the rate of the composite of thromboembolism plus cardiovascular death was lower with acenocoumarol than with triflusal. There was no significant difference in rates of ischemic stroke and systemic embolism. Neither indobufen nor trifusal is widely available; these agents have not been compared with aspirin for efficacy and safety, nor do they offer advantages over anticoagulation with a vitamin K antagonist in patients with AF at high risk of thromboembolism.

In the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-W), which was stopped on the recommendation of the Data Safety and Monitoring Board before planned follow-up was completed, the combination of the thienopyridine antiplatelet agent clopidogrel (75 mg daily) plus aspirin (75 to 100 mg daily) proved inferior to warfarin (target INR 2.0 to 3.0) in patients with an average of 2 stroke risk factors in addition to AF.[464] Additional studies are ongoing to assess the impact of this therapy for patients unable or unwilling to take warfarin.

8.1.4.2.4. Combining Anticoagulant and Platelet-Inhibitor Therapy (UPDATED). **For new or updated text, view the 2011 Focused Update. Text supporting unchanged recommendations has not been updated.** Combinations of oral anticoagulants plus antiplatelet agents to reduce the risk of hemorrhage by allowing lower intensities of anticoagulation or to augment efficacy for selected patients at particularly high risk of thromboembolism, such as those with prior stroke, have been evaluated in several trials. Such a strategy

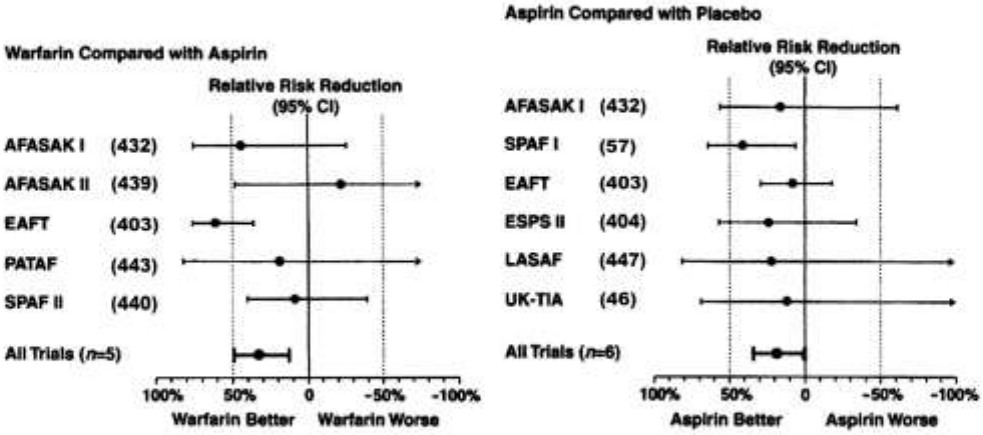

Figure 12. Effects on all stroke (ischemic and hemorrhagic) of therapies for patients with atrial fibrillation: warfarin compared with aspirin and aspirin compared with placebo. Modified with permission from Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999;131:492–501.[420] AFASAK indicates Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation; CI, confidence interval; EAFT, European Atrial Fibrillation Trial; ESPS, European Stroke Prevention Study; LASAF, Low-dose Aspirin, Stroke, Atrial Fibrillation; UK-TIA, The United Kingdom transient ischaemic attack aspirin trial; PATAF, Prevention of Arterial Thromboembolism in Atrial Fibrillation; SPAF, Stroke Prevention in Atrial Fibrillation; and SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation.

has been successful in reducing the risk of thromboembolism in patients with mechanical heart valves.[465] Still another objective of combination therapy is to enhance protection against ischemic cardiac events in patients with AF who have established coronary atherosclerosis or diabetes. In 2 trials, SPAF III and Copenhagen Atrial FIbrillation, Aspirin, and Anticoagulation (AFASAK) 2, the combination of low-dose oral anticoagulation (INR less than 1.5) with aspirin added little protection against stroke compared with aspirin alone in patients with AF.[402,439]

In 2 other trials, substantially higher intensities of anticoagulation combined with platelet inhibitor agents were evaluated in patients with AF. The French Fluindione-Aspirin Combination in High Risk Patients With AF (FFAACS) study compared the oral anticoagulant fluindione (target INR 2.0 to 2.6) plus placebo or in combination with aspirin, 100 mg daily, versus fluindione alone in patients at high risk of stroke. The trial was stopped with only 157 patients enrolled (mean follow-up 0.84 y) because of excessive hemorrhage in the group receiving the combination therapy.[433]

In the larger Spanish National Study for Primary Prevention of Embolism in Nonrheumatic Atrial Fibrillation (NASPEAF) study, patients were stratified into a high-risk group (n=495) with AF and rheumatic mitral stenosis or AF and a history of stroke, TIA, or systemic embolism, and a lower-risk group (n=714) with AF and age greater than 60 y, hypertension, or HF.[445] The higher-risk patients were randomized to anticoagulation with acenocoumrarol (target INR 2.0 to 3.0) or to acenocoumarol (INR 1.4 to 2.4) combined with the platelet cyclooxygenase inhibitor triflusal (600 mg daily). The lower-risk patients were randomized to triflusal alone, acenocoumarol alone (INR 2.0 to 3.0), or the combination of triflusal plus acenocoumarol (INR 1.25 to 2.0). The achieved anticoagulation intensities in the anticoagulation and combination therapy arms were closer to one another than intended, however (mean INR 2.5 with acenocoumarol alone in both risk strata versus 1.96 and 2.18 for the combination arms in the lower- and higher-risk groups during median follow-up of 2.6 and 2.9 y, respectively). The primary outcome was a composite of thromboembolism plus cardiovascular death (sudden death or death due to thromboembolism, stroke, bleeding, or HF but not MI). Patients in both risk categories had a lower risk of primary events with the combination therapy than with acenocoumarol alone. These observations suggest that a combination of platelet inhibitor and anticoagulant therapy might be effective and relatively protective if targeted INR levels are closer to the standard range, but the superiority of combination therapy over mono-therapy with a vitamin K antagonist for prevention of ischemic stroke and MI has not been convincingly established.

Combining aspirin with an oral anticoagulant at higher intensities may accentuate intracranial hemorrhage, particularly in elderly AF patients.[466] In a retrospective analysis of 10 093 patients with AF after hospital discharge (mean age 77 y), platelet inhibitor medication was associated with a higher rate of intracerebral hemorrhage (relative risk 3.0, 95% CI 1.6% to 5.5%),[467] but 2 case-control studies yielded conflicting results.[454,468]

The superior efficacy of anticoagulation over aspirin for prevention of recurrent stroke in patients with AF was demonstrated in the European Atrial Fibrillation Trial.[403] Therefore, unless a clear contraindication exists, AF patients with a recent stroke or TIA should be treated with long-term anticoagulation rather than antiplatelet therapy. There is no evidence that combining anticoagulation with an antiplatelet agent reduces the risk of stroke compared with anticoagulant therapy alone. Hence, pending further data for AF patients who sustain cardioembolic events while receiving low-intensity anticoagulation, anticoagulation intensity should be increased to a maximum target INR of 3.0 to 3.5 rather than routinely adding antiplatelet agents.

Several studies have evaluated anticoagulation in combination with aspirin for prevention of ischemic cardiac events in patients with CAD. From these it may be possible to draw inferences regarding management of antithrombotic therapy in patients who have both CAD and AF. A meta-analysis of 31 randomized trials of oral anticoagulant therapy published between 1960 and 1999 involving patients with CAD treated for at least 3 mo and stratified by the intensities of anticoagulation and aspirin therapy came to the following conclusions.[469] High-intensity (INR 2.8 to 4.8) and moderate-intensity (INR 2.0 to 3.0) oral anticoagulation regimens reduced rates of MI and stroke but increased the risk of bleeding 6.0- to 7.7-fold. Combining aspirin with low-intensity anticoagulation (INR less than 2.0) was not superior to aspirin alone. While the combination of moderate- to high-intensity oral anticoagulation plus aspirin appeared promising compared with aspirin alone, the combination was associated with increased bleeding.

From the results of more contemporary trials involving long-term treatment of patients with acute myocardial ischemia[470–473] and the Combined Hemotherapy and Mortality Prevention Study (CHAMP),[474] it appears that high-intensity oral anticoagulation (INR 3.0 to 4.0) is more effective than aspirin but increases the risk of bleeding. The combination of aspirin and moderate-intensity warfarin (INR 2.0 to 3.0) is more effective than aspirin alone but is associated with a greater risk of bleeding. The combination of aspirin and moderate-intensity warfarin (INR 2.0 to 3.0) is as effective as high-intensity warfarin and associated with a similar risk of bleeding. The contemporary trials, however, have not addressed the effectiveness of moderate-intensity warfarin (INR 2.0 to 3.0) alone. In the absence of direct evidence, it cannot be assumed that moderate-intensity warfarin is superior to aspirin in preventing death or reinfarction. The choice for long-term management of patients with CAD and AF therefore involves aspirin alone, aspirin plus moderate-intensity warfarin (INR 2.0 to 3.0), or warfarin alone (INR 2.0 to 3.0). For those with risk factors for stroke, the latter 2 regimens are more effective than aspirin alone but are associated with more bleeding and inconvenience. Further, without close INR control, the combination regimen may be associated with a greater risk of bleeding. For most patients with AF who have stable CAD, warfarin anticoagulation alone (target INR 2.0 to 3.0) should provide satisfactory antithrombotic prophylaxis against both cerebral and myocardial ischemic events.

The importance of platelet-inhibitor drugs for prevention of recurrent myocardial ischemia is enhanced in patients undergoing percutaneous coronary intervention, but no adequate studies have been published that specifically address this issue in patients who also require chronic anticoagulation because of AF. It is the consensus of the authors of these guidelines that the most important agent for the maintenance of coronary and stent

patency is the thienopyridine derivative clopidogrel and that the addition of aspirin to the chronic anticoagulant regimen contributes more risk than benefit. Although it is usually necessary to interrupt or reduce anticoagulation to prevent bleeding at the site of peripheral arterial puncture, the vitamin K antagonist should be resumed as soon as possible after the procedure and the dose adjusted to achieve an INR in the therapeutic range. Aspirin may be given temporarily during the hiatus, but the maintenance regimen should then consist of the combination of clopidogrel, 75 mg daily, plus warfarin (INR 2.0 to 3.0) for 9 to 12 mo, following which warfarin may be continued as mono-therapy in the absence of a subsequent coronary event.

8.1.4.2.5. Emerging and Investigational Antithrombotic Agents (UPDATED). **For new or updated text, view the 2011 Focused Update and 2011 Focused Update on Dabigatran. Text supporting unchanged recommendations has not been updated.** While clearly efficacious against stroke in patients with AF, warfarin carries a substantial risk of hemorrhage, a narrow therapeutic margin necessitating frequent monitoring of the INR level, and interactions with numerous drugs and foods that may cause a need for dose adjustments. These limitations result in undertreatment of a considerable proportion of the AF population at risk, particularly the elderly, for whom numerous concomitant medications are typically prescribed,[455,475] engendering a quest for safer, more convenient alternatives.

Because of its central role in thrombogenesis, thrombin (factor IIa) represents an attractive target for specific inhibition. Direct thrombin inhibitors bind to the active site of thrombin and prevent it from cleaving fibrinogen to form fibrin. These compounds also suppress thrombin-mediated activation of platelets and coagulation factors V, VIII, XI, and XIII. Ximelagatran is administered orally and converted after absorption to the active direct thrombin inhibitor melagatran. The compound appears to have stable pharmacokinetics independent of the hepatic P450 enzyme system and a low potential for food or drug interactions.[476] Two long-term phase III studies compared ximelagatran with warfarin in patients with AF, SPORTIF (Stroke Prevention using an Oral Thrombin Inhibitor in patients with atrial Fibrillation) -III and -V, with a combined population of more than 7000.[444] In these trials, ximelagatran was administered without dose titration or coagulation monitoring and was compared with warfarin (INR 2.0 to 3.0) for the primary endpoint of all stroke (ischemic and hemorrhagic) and systemic embolism.

SPORTIF-III involved an open-label design[444] and careful regulation of dosing among patients assigned to warfarin, with INR values within the therapeutic range for 66% of the duration of exposure. The relative risk reduction of 29% and absolute risk reduction of 0.7% per year according to intention-to-treat confirmed the noninferiority of ximelagatran to warfarin. By on-treatment analysis, the relative risk reduction with ximelagatran was 41% ($P=0.018$. There was no significant difference between treatments in rates of hemorrhagic stroke, fatal bleeding, or other major bleeding, but when minor hemorrhages are considered as well, ximelagatran caused significantly less bleeding (25.5% vs. 29.5% per year, $P=0.007$).

The results of the SPORTIF-V trial, in which treatment was administered in a double-blind manner, were similar to those of SPORTIF-III.[434] The primary event rates were 1.6% per year with ximelagatran and 1.2% per year with warfarin (absolute difference 0.45% per year, 95% CI 0.13% to 1.03% per year, P less than 0.001 for the noninferiority hypothesis), and there was no difference between treatment groups in rates of major bleeding, but as in the SPORTIF-III study, total bleeding (major plus minor) was lower with ximelagatran.

In both the SPORTIF-III and V trials, serum alanine aminotransferase levels rose to greater than 3 times the upper limit of normal in about 6% of patients treated with ximelagatran. Hence, despite evidence of efficacy comparable to carefully adjusted warfarin and some advantage in terms of bleeding risk, ximelagatran will not be marketed for clinical use as an anticoagulant, mainly because of concerns about hepatic toxicity.[478] Trials of a variety of investigational oral anticoagulant compounds that directly inhibit thrombin, antagonize factor Xa, or inactivate prothrombin are ongoing or planned, but there are no currently available alternatives to vitamin K antagonists.

8.1.4.2.6. Interruption of Anticoagulation for Diagnostic or Therapeutic Procedures. From time to time, it may be necessary to interrupt oral anticoagulant therapy in preparation for elective surgical procedures. In patients with mechanical prosthetic heart valves, it is generally appropriate to substitute unfractionated or low-molecular-weight heparin to prevent thrombosis.[479,480] In patients with AF who do not have mechanical valves, however, based on extrapolation from the annual rate of thromboembolism in patients with nonvalvular AF, it is the consensus of the Writing Committee that anticoagulation may be interrupted for a period of up to 1 wk for surgical or diagnostic procedures that carry a risk of bleeding without substituting heparin. In high-risk patients (particularly those with prior stroke, TIA, or systemic embolism) or when a series of procedures requires interruption of oral anticoagulant therapy for longer periods, unfractionated or low-molecular-weight heparin may be administered intravenously or subcutaneously.

The use of low-molecular-weight heparin instead of unfractionated heparin in patients with AF is based largely on extrapolation from venous thromboembolic disease states and from limited observational studies.[481] In general, low-molecular-weight heparins have several pharmacological advantages over unfractionated heparin. These include a longer half-life, more predictable bioavailability (greater than 90% after subcutaneous injection), predictable clearance (enabling once- or twice-daily subcutaneous administration), and a predictable antithrombotic response based on body weight, which permits fixed-dose treatment without laboratory monitoring except under special circumstances such as obesity, renal insufficiency, or pregnancy.[482] Treatment with low-molecular-weight heparin is associated with a lower risk of heparin-induced thrombocytopenia than unfractionated heparin.[483] The favorable properties of low-molecular-weight heparins may simplify the treatment of AF in acute situations and shorten or eliminate the need for hospitalization to initiate anticoagulation. Self-administration of low-molecular-weight heparins out of hospital by patients with

AF undergoing elective cardioversion is a promising approach that may result in cost savings.[484]

8.1.4.3. Nonpharmacological Approaches to Prevention of Thromboembolism (UPDATED). **For new or updated text, view the 2011 Focused Update. Text supporting unchanged recommendations has not been updated.** An emerging option for patients with AF who cannot safely undergo anticoagulation, which is not yet sufficiently investigated to allow general clinical application, is obliteration of the LAA to remove a principal nidus of thrombus formation.[485,486] In addition to direct surgical amputation or truncation of appendage, several methods are under development to achieve this with intravascular catheters or transpericardial approaches.[487] The efficacy of these techniques is presumably related to the completeness and permanence of elimination of blood flow into and out of the LAA. This has been demonstrated by TEE at the time of intervention, but the durability of the effect has not been confirmed by subsequent examinations over several years. Whether mechanical measures intended to prevent embolism from thrombotic material in the LAA will prove to be comparably effective and safer than anticoagulation for some patients remains to be established.[488] These must presently be considered investigational, and indications for this type of intervention have not been convincingly established.

8.1.5. Cardioversion of Atrial Fibrillation

RECOMMENDATIONS

Recommendations for Pharmacological Cardioversion of Atrial Fibrillation

CLASS I

Administration of flecainide, dofetilide, propafenone, or ibutilide is recommended for pharmacological cardioversion of AF. *(Level of Evidence: A)*

CLASS IIa

1. **Administration of amiodarone is a reasonable option for pharmacological cardioversion of AF.** *(Level of Evidence: A)*
2. **A single oral bolus dose of propafenone or flecainide ("pill-inthe-pocket") can be administered to terminate persistent AF outside the hospital once treatment has proved safe in hospital for selected patients without sinus or AV node dysfunction, bundle-branch block, QT-interval prolongation, the Brugada syndrome, or structural heart disease. Before antiarrhythmic medication is initiated, a beta blocker or nondihydropyridine calcium channel antagonist should be given to prevent rapid AV conduction in the event atrial flutter occurs.** *(Level of Evidence: C)*
3. **Administration of amiodarone can be beneficial on an outpatient basis in patients with paroxysmal or persistent AF when rapid restoration of sinus rhythm is not deemed necessary.** *(Level of Evidence: C)*

CLASS IIb

Administration of quinidine or procainamide might be considered for pharmacological cardioversion of AF, but the usefulness of these agents is not well established. *(Level of Evidence: C)*

CLASS III

1. **Digoxin and sotalol may be harmful when used for pharmacological cardioversion of AF and are not recommended.** *(Level of Evidence: A)*
2. **Quinidine, procainamide, disopyramide, and dofetilide should not be started out of hospital for conversion of AF to sinus rhythm.** *(Level of Evidence: B)*

8.1.5.1. Basis for Cardioversion of Atrial Fibrillation

Cardioversion may be performed electively to restore sinus rhythm in patients with persistent AF. The need for cardio-version may be immediate when the arrhythmia is the main factor responsible for acute HF, hypotension, or worsening of angina pectoris in a patient with CAD. Nevertheless, cardio-version carries a risk of thromboembolism unless anticoagulation prophylaxis is initiated before the procedure, and this risk is greatest when the arrhythmia has been present for longer than 48 h.

8.1.5.2. Methods of Cardioversion

Cardioversion may be achieved by means of drugs or electrical shocks. Drugs were commonly used before direct-current cardioversion became a standard procedure. The development of new drugs has increased the popularity of pharmacological cardioversion, but the disadvantages include the risk of drug-induced torsades de pointes or other serious arrhythmias. Moreover, pharmacological cardioversion is less effective than direct-current cardioversion when biphasic shocks are used. The disadvantage of electrical cardioversion is that it requires conscious sedation or anesthesia, which pharmacological cardioversion does not.

There is no evidence that the risk of thromboembolism or stroke differs between pharmacological and electrical methods of cardioversion. The recommendations for anticoagulation are therefore the same for both methods, as outlined in Section 8.1.4 (Preventing Thromboembolism. Cardioversion in patients with AF following recent heart surgery or MI is addressed later (see Section 8.4, Special Considerations).

8.1.5.3. Pharmacological Cardioversion

The quality of evidence available to gauge the effectiveness of pharmacological cardioversion is limited by small samples, lack of standard inclusion criteria (many studies include both patients with AF and those with atrial flutter), variable intervals from drug administration to assessment of outcome, and arbitrary dose selection. Although pharmacological and direct-current cardioversion have not been compared directly, pharmacological approaches appear simpler but are less efficacious. The major risk is related to the toxicity of antiarrhythmic drugs. In developing these guidelines, placebo-controlled trials of pharmacological cardioversion in which drugs were administered over short periods of time specifically to restore sinus rhythm have been emphasized. Trials in which the control group was given another antiarrhythmic drug have, however, been considered as well.

Pharmacological cardioversion seems most effective when initiated within 7 d after the onset of an episode of AF.[489–492]

AHA/ASA Guideline

Guidelines for the Primary Prevention of Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.

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Background and Purpose—This guideline provides an overview of the evidence on established and emerging risk factors for stroke to provide evidence-based recommendations for the reduction of risk of a first stroke.

Methods—Writing group members were nominated by the committee chair on the basis of their previous work in relevant topic areas and were approved by the American Heart Association (AHA) Stroke Council Scientific Statement Oversight Committee and the AHA Manuscript Oversight Committee. The writing group used systematic literature reviews (covering the time since the last review was published in 2006 up to April 2009), reference to previously published guidelines, personal files, and expert opinion to summarize existing evidence, indicate gaps in current knowledge, and when appropriate, formulate recommendations using standard AHA criteria (Tables 1 and 2). All members of the writing group had the opportunity to comment on the recommendations and approved the final version of this document. The guideline underwent extensive peer review by the Stroke Council leadership and the AHA scientific statements oversight committees before consideration and approval by the AHA Science Advisory and Coordinating Committee.

Results—Schemes for assessing a person's risk of a first stroke were evaluated. Risk factors or risk markers for a first stroke were classified according to potential for modification (nonmodifiable, modifiable, or potentially modifiable) and strength of evidence (well documented or less well documented). Nonmodifiable risk factors include age, sex, low birth weight, race/ethnicity, and genetic predisposition. Well-documented and modifiable risk factors include hypertension, exposure to cigarette smoke, diabetes, atrial fibrillation and certain other cardiac conditions, dyslipidemia, carotid artery stenosis, sickle cell disease, postmenopausal hormone therapy, poor diet, physical inactivity, and obesity and body fat

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The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on August 18, 2010. A copy of the statement is available at http://www.americanheart.org/presenter.jhtml?identifier=3003999 by selecting either the "topic list" link or the "chronological list" link (No. KB-0080). To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

The online-only Data Supplement is available at http://stroke.ahajournals.org/cgi/content/full/10.1161/STR.0b013e3181fcb238.

The American Heart Association requests that this document be cited as follows: Goldstein LB, Bushnell CD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, Creager MA, Culebras A, Eckel RH, Hart RG, Hinchey JA, Howard VJ, Jauch EC, Levine SR, Meschia JF, Moore WS, Nixon JV, Pearson TA; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Epidemiology and Prevention, Council for High Blood Pressure Research, Council on Peripheral Vascular Disease, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42:517–584.

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***Stroke* is available at http://stroke.ahajournals.org** **DOI: 10.1161/STR.0b013e3181fcb238**

distribution. Less well-documented or potentially modifiable risk factors include the metabolic syndrome, excessive alcohol consumption, drug abuse, use of oral contraceptives, sleep-disordered breathing, migraine, hyperhomocysteinemia, elevated lipoprotein(a), hypercoagulability, inflammation, and infection. Data on the use of aspirin for primary stroke prevention are reviewed.

Conclusion—Extensive evidence identifies a variety of specific factors that increase the risk of a first stroke and that provide strategies for reducing that risk. **(*Stroke*. 2011;42:517-584.)**

Key Words: AHA Scientific Statements ■ stroke ■ risk factors ■ primary prevention

Stroke remains a major healthcare problem. Its human and economic toll is staggering. Approximately 795 000 people in the United States have a stroke each year, of which about 610 000 are a first attack; and 6.4 million Americans are stroke survivors.[1] Stroke is also estimated to result in 134 000 deaths annually and is the third leading cause of death in the nation behind heart disease and cancer.[1] Progress has been made in reducing deaths from stroke. Along with other healthcare organizations, the American Heart Association (AHA) set the goal of decreasing cardiovascular and stroke mortality by 25% over 10 years.[1] Between 1996 and 2006 the death rate for stroke fell by 33.5%, with the total number of stroke deaths declining by 18.4%.[1] The goal of a 25% reduction was exceeded in 2008. The declines in stroke death rates, however, were greater in men than in women (age-adjusted male-to-female ratio decreasing from 1.11 to 1.03).[1] Despite overall declines in stroke deaths, stroke incidence may be increasing.[2] From 1988 to 1997 the age-adjusted stroke hospitalization rate grew 18.6% (from 560 to 664 per 10 000), while the total number of stroke hospitalizations increased 38.6% (from 592 811 to 821 760 annually).[3] In 2010, the cost of stroke is estimated at $73.7 billion (direct and indirect costs),[1] with a mean lifetime cost estimated at $140 048.[1]

Stroke is also a leading cause of functional impairments, with 20% of survivors requiring institutional care after 3 months and 15% to 30% being permanently disabled.[1] Stroke is a life-changing event that affects not only stroke patients themselves but their family members and caregivers as well. Utility analyses show that a major stroke is viewed by more than half of those at risk as being worse than death.[4] Despite the advent of treatment of selected patients with acute ischemic stroke with intravenous tissue-type plasminogen activator and the promise of other acute therapies, effective prevention remains the best approach for reducing the burden of stroke.[5–7] Primary prevention is particularly important because >77% of strokes are first events.[1] The age-specific incidence of major stroke in Oxfordshire, United Kingdom, fell by 40% over a 20-year period with increased use of preventive treatments and general reductions in risk factors.[9] Those who practice a healthy lifestyle have an 80% lower risk of a first stroke compared with those who do not.[8] As discussed in detail in the sections that follow, persons at high risk for or prone to stroke can now be identified and targeted for specific interventions.

This guideline provides an overview of the evidence on various established and emerging stroke risk factors and represents a complete revision of the 2006 statement on this topic.[9] One important change is the broader scope of this new guideline. Whereas the 2006 statement focused on ischemic stroke, because of the overlap of risk factors and prevention strategies, this guideline also addresses hemorrhagic stroke, primarily focusing on an individual patient–oriented approach to stroke prevention. This contrasts with a population-based approach in which "…the entire distribution of risk factors in the population is shifted to lower levels through population-wide interventions" and is reflected in the AHA statement on improving cardiovascular health at the community level.[10]

Writing group members were nominated by the committee chair on the basis of their previous work in relevant topic areas and were approved by the AHA Stroke Council Scientific Statement Oversight Committee and the AHA Manuscript Oversight Committee. The writing group used systematic literature reviews covering the time since the last statement was published in 2006 up to April 2009, reference to previously published guidelines, personal files, and expert opinion to summarize existing evidence, indicate gaps in current knowledge, and when appropriate, formulate recommendations using standard AHA criteria. All members of the writing group had the opportunity to comment on the recommendations and approved the final version of the document. The guideline underwent extensive peer review by the AHA Stroke Council leadership and the AHA Manuscript Oversight Committee before consideration and approval by the AHA Science Advisory and Coordinating Committee (Tables 1 and 2). Because of the diverse nature of the topics, it was not possible to provide a systematic, uniform summary of the magnitude of the effect associated with each recommendation. As with all therapeutic recommendations, patient preferences must be considered. As seen in Tables 3 through 5, risk factors (directly increase disease probability or, if absent or removed, reduce disease probability) or risk markers (attribute or exposure associated with increased probability of disease, but relationship is not necessarily causal)[11] of a first stroke were classified according to their potential for modification (nonmodifiable, modifiable, or potentially modifiable) and strength of evidence (well documented, less well documented).[7] Although this classification system is somewhat subjective, for well-documented *and* modifiable risk factors (Table 4) there was clear, supportive epidemiological evidence in addition to evidence of risk reduction with modification as documented by randomized trials. For less well-documented *or* potentially modifiable risk factors (Table 5), the epidemiological evidence was less clear or evidence was lacking from randomized trials that demonstrated reduction of stroke risk with modification. The tables give the estimated

Table 1. Applying Classification of Recommendations and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT →			
	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/administered	**CLASS IIa** *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	**CLASS IIb** *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	**CLASS III** *Risk ≥ Benefit* Procedure/Treatment should **NOT** be performed/administered **SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL**
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations†	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	is not recommended is not indicated should not is not useful/effective/beneficial may be harmful

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as gender, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use. A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

†For recommendations (Class I and IIa; Level of Evidence A and B only) regarding the comparative effectiveness of one treatment with respect to another, these words or phrases may be accompanied by the additional terms "in preference to" or "to choose" to indicate the favored intervention. For example, "Treatment A is recommended in preference to Treatment B for. . . " or "It is reasonable to choose Treatment A over Treatment B for. . . . " Studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

prevalence, population-attributable risk (ie, the proportion of ischemic stroke in the population that can be attributed to a particular risk factor, given by the formula $100\times([\text{Prevalence}\times(\text{Relative Risk}-1)]/[\text{Prevalence}\times(\text{Relative Risk}-1)+1])$,[12] relative risk, and risk reduction with treatment for each factor when known. Gaps in current knowledge are indicated by question marks. When referring to these data, it should be noted that comparisons of relative risks and population-attributable risks between different studies should be made with caution because of differences in study designs and patient populations. Precise estimates of attributable risk for factors such as hormone replacement therapy are not available because of variations in estimates of risk and changes in prevalence.

Other tables summarize endorsed guideline or consensus statements on management recommendations as available. Recommendations are indicated in the text and tables.

Generally Nonmodifiable Risk Factors

These factors are generally not modifiable but identify persons who are at increased risk of stroke and who may benefit from rigorous prevention or treatment of other modifiable risk factors (Table 3). In addition, although genetic predisposition itself is not modifiable, treatments for specific genetic conditions are available.

Age

Stroke is thought of as a disease of the elderly, but incidence rates for pediatric strokes have increased in recent years.[13,14] Although younger age groups (25 to 44 years) are at lower stroke risk,[15] the public health burden is high in these populations because of a relatively greater loss of productivity and wage-earning years. The cumulative effects of aging on the cardiovascular system and the progressive nature of stroke risk factors over a prolonged period substantially

Table 8. Dyslipidemia: Guideline Management Recommendations*[221,222]

Factor	Goal	Recommendations
LDL-C		
0–1 CHD risk factor*	LDL-C <160 mg/dL	Diet, weight management, and physical activity. Drug therapy recommended if LDL-C remains ≥190 mg/dL. Drug therapy optional for LDL-C 160–189 mg/dL.
2+ CHD risk factors and 10-year CHD risk <20%	LDL-C <130 mg/dL	Diet, weight management, and physical activity. Drug therapy recommended if LDL-C remains ≥160 mg/dL.
2+ CHD risk factors and 10-year CHD risk 10%–20%	LDL-C <130 mg/dL or optionally LDL-C <100 mg/dL	Diet, weight management, and physical activity. Drug therapy recommended if LDL-C remains ≥130 mg/dL (optionally ≥100 mg/dL).
CHD or CHD risk equivalent† (10-year risk >20%)	LDL-C <100 mg/dL or optionally LDL-C <70 mg/dL	Diet, weight management, and physical activity. Drug therapy recommended if LDL-C ≥130 mg/dL. Drug therapy optional for LDL-C 70–129 mg/dL.
Non–HDL-C in persons with triglyceride ≥200 mg/dL	Goals are 30 mg/dL higher than LDL-C goal	Same as LDL-C with goals 30 mg/dL higher.
Low HDL-C	No consensus goal	Weight management and physical activity. Consider niacin (nicotinic acid) or fibrate in high-risk persons with HDL-C <40 mg/dL.
Lp(a)	No consensus goal	Treat other atherosclerotic risk factors in patients with high Lp(a). Consider niacin (immediate- or extended-release formulation), up to 2000 mg/d for reduction of Lp(a) levels, optimally in conjunction with glycemic control and LDL control.

CHD indicates coronary heart disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and Lp(a), lipoprotein a.

*To screen for dyslipidemia, a fasting lipoprotein profile (cholesterol, triglyceride, HDL-C, and LDL-C) should be obtained every 5 y in adults. It should be obtained more often if ≥2 CHD risk factors are present (risk factors include cigarette smoking; hypertension; HDL-C <40 mg/dL; CHD in a male first-degree relative <55 y or in a female first-degree relative <65 y; or age >45 y for men or >65 y for women) or if LDL-C levels are borderline or high. Screening for Lp(a) is not recommended for primary prevention unless (1) unexplained early cardiovascular events have occurred in first-degree relatives or (2) high Lp(a) is known to be present in first-degree relatives.

†CHD risk equivalents include diabetes or other forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, or symptomatic carotid artery disease).

treatment with niacin reduced mortality, including a trend toward fewer deaths from cerebrovascular disease.[229] Fibric acid derivatives such as gemfibrozil, fenofibrate, and bezafibrate lower triglyceride levels and increase HDL cholesterol. The Bezafibrate Infarction Prevention study, which included patients with prior MI or stable angina and HDL-cholesterol levels ≤45 mg/dL, found bezafibrate did not significantly decrease risk of MI or sudden death (primary end point) nor stroke (secondary end point).[230] The VA-HIT, which included men with coronary artery disease and low HDL cholesterol, found gemfibrozil reduced the risk of all strokes, primarily ischemic strokes.[231] In the FIELD study, fenofibrate did not decrease the composite primary end point of coronary heart disease death or nonfatal MI, nor did it decrease risk of stroke, which was a secondary end point. Ezetimibe lowers cholesterol levels by reducing intestinal absorption of cholesterol. In a study of patients with familial hypercholesterolemia, the addition of ezetimibe to simvasatin did not affect progression of carotid IMT more than simvastatin alone.[232] In another trial of subjects receiving a statin, the addition of ezetimibe compared with niacin found niacin led to greater reductions in mean carotid IMT over 14 months ($P=0.003$), with those receiving ezetimibe who had greater reductions in LDL cholesterol having an increase in carotid IMT ($r=-0.31$; $P<0.001$).[233] The rate of major cardiovascular events was lower in those randomized to niacin (1% versus 5%; $P=0.04$). Stroke events were not reported. A clinical outcome trial comparing the effect of ezetimibe plus simvastatin with simvastatin monotherapy on cardiovascular outcomes is in progress.[234] There are no studies showing that ezetimibe treatment decreases cardiovascular events or stroke.

Recommendations

1. **Treatment with an HMG-CoA reductase inhibitor (statin) medication in addition to therapeutic lifestyle changes with LDL-cholesterol goals as reflected in the NCEP guidelines[221,222] is recommended for primary prevention of ischemic stroke in patients with coronary heart disease or certain high-risk conditions such as diabetes (*Class I; Level of Evidence A*).**
2. **Fibric acid derivatives may be considered for patients with hypertriglyceridemia, but their efficacy in the prevention of ischemic stroke is not established (*Class IIb; Level of Evidence C*).**
3. **Niacin may be considered for patients with low HDL cholesterol or elevated lipoprotein(a), but its efficacy in prevention of ischemic stroke in patients with these conditions is not established (*Class IIb; Level of Evidence C*).**
4. **Treatment with other lipid-lowering therapies, such as fibric acid derivatives, bile acid sequestrants, niacin, and ezetimibe, may be considered in patients who do not achieve target LDL cholesterol with statins or cannot tolerate statins, but the effectiveness of these therapies in decreasing risk of stroke is not established (*Class IIb; Level of Evidence C*).**

Atrial Fibrillation

Atrial fibrillation, even in the absence of cardiac valvular disease, is associated with a 4- to 5-fold increased risk of ischemic stroke due to embolism of stasis-induced thrombi forming in the left atrial appendage.[235] About 2.3 million Americans are estimated to have either sustained or paroxys-

mal atrial fibrillation.[235] Embolism of appendage thrombi associated with atrial fibrillation accounts for about 10% of all ischemic strokes and an even higher fraction in the very elderly in the United States.[236] The absolute stroke rate averages about 3.5% per year for persons aged 70 years with atrial fibrillation, but the risk varies 20-fold among patients depending on age and other clinical features (see below).[237,238] Atrial fibrillation is also an independent predictor of increased mortality.[239] Paroxysmal atrial fibrillation is associated with an increased stroke risk that is similar to that of chronic atrial fibrillation.[240]

There is an important opportunity for primary stroke prevention in patients with atrial fibrillation because atrial fibrillation is diagnosed before stroke in many patients. However, a substantial minority of atrial fibrillation–related stroke occurs in patients without a prior diagnosis of the condition. Studies of active screening for atrial fibrillation in patients >65 years of age in primary care settings show that pulse assessment by trained personnel increases detection of undiagnosed atrial fibrillation.[241,242] Systematic pulse assessment during routine clinic visits followed by 12-lead ECG in those with an irregular pulse resulted in a 60% increase in detection of atrial fibrillation.[241]

Stroke Risk Stratification in Atrial Fibrillation Patients

Estimating stroke risk for individual patients is a critical first step when balancing the benefits and risks of long-term antithrombotic therapy for primary stroke prevention. Four clinical features (prior stroke/transient ischemic attack [TIA], advancing age, hypertension/elevated systolic BP, and diabetes) have consistently been found to be independent risk factors for stroke in atrial fibrillation patients.[237] Although not relevant for primary prevention, prior stroke/TIA is the most powerful risk factor and reliably confers a high risk of stroke (>5% per year, averaging 10% per year). Female sex is inconsistently associated with stroke risk, and the evidence is inconclusive that either heart failure or coronary artery disease is independently predictive of stroke in patients with atrial fibrillation.[237]

More than a dozen stroke risk stratification schemes for patients with atrial fibrillation have been proposed based on various combinations of clinical and echocardiographic predictors.[238] None have been convincingly shown to be "the best." Two closely related schemes have received wide attention and are summarized in Table 9.

The $CHADS_2$ scheme uses a point system, with 1 point each for congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus, and 2 points for prior stroke/TIA.[243] This scheme has been tested in 6 independent cohorts of patients with atrial fibrillation, with a score of 0 points indicating low risk (0.5% to 1.7%); 1 point, moderate risk (1.2% to 2.2% per year); and ≥2 points, high risk (1.9% to 7.6% per year).[238] The American College of Cardiology/AHA/European Society of Cardiology (ACC/AHA/ESC) 2006 guideline recommendation for stroke risk stratification in atrial fibrillation patients is almost identical to the $CHADS_2$ scheme if patients with $CHADS_2$ scores of 2 are considered moderate risk, but the guideline also includes echocardiographically defined impaired left ventricular systolic function as a risk factor.[244] In either scheme, patients with recurrent paroxysmal atrial fibrillation are stratified according to the same criteria as those with persistent atrial fibrillation,[245,246] but those with a single brief episode or self-limited atrial fibrillation due to a reversible cause are not included.

Table 9. Stroke Risk Stratification Schemes for Patients With Atrial Fibrillation

$CHADS_2$[243]	ACC/AHA/ESC 2006 Guidelines*[244]
Congestive heart failure†–1 point	High risk
Hypertension‡–1 point	Prior thromboembolism
Age >75 y–1 point	>2 moderate risk features
Diabetes–1 point	Moderate risk
Stroke/TIA–2 points	Age >75 y
	Heart failure
Risk scores range from 0–6 points	Hypertension‡
Low risk=0 points	Diabetes
Moderate risk=1 point	LVEF <35% or fractional shortening <25%
High risk=>2 points	Low risk
	No moderate- or high-risk features

ACC/AHA/ESC indicates American College of Cardiology/American Heart Association/European Society of Cardiology; LVEF, left ventricular ejection fraction; and TIA, transient ischemic attack.

*This scheme is identical to the stratification recommended by the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition).[247]

†Recent heart failure exacerbation was used in original stratification, but subsequently any prior heart failure has supplanted.

‡History of hypertension; not specifically defined.

The threshold of absolute stroke risk warranting anticoagulation is importantly influenced by estimated bleeding risk during anticoagulation, patient preferences, and access to good monitoring of anticoagulation. Most experts agree that adjusted-dose warfarin should be given to high-risk patients with atrial fibrillation, with aspirin for those deemed to be at low risk. There is more controversy for those at moderate risk, with some favoring anticoagulation for all atrial fibrillation patients except those estimated to be at low risk.[247] The 2006 ACC/AHA/ESC guideline indicates that "antithrombotic therapy with either aspirin or vitamin K antagonists is reasonable based on an assessment of risk of bleeding complications, ability to safely sustain adjusted chronic anticoagulation, and patient preferences" for those deemed moderate risk (equivalent to a $CHADS_2$ score of 1).[244] A recent large cohort study did not find a net clinical benefit of warfarin for atrial fibrillation patients with a $CHADS_2$ score of 1 once intracranial hemorrhage was considered.[248] Patients >75 years of age with atrial fibrillation benefit substantially from anticoagulation,[242] and age is not a contraindication to use of anticoagulation.

Treatment to Reduce Stroke Risk in Atrial Fibrillation Patients

Therapeutic cardioversion and rhythm control do not reduce stroke risk,[249] and percutaneous left atrial occlusion is of unclear overall benefit.[250,251] On the basis of consistent results

Table 10. Efficacy of Warfarin and Aspirin for Stroke Prevention in Atrial Fibrillation: Meta-Analysis of Randomized Trials*

Comparison	No. of Trials	No.of Patients	Relative Risk Reduction, 95% CI	Estimated NNT for Primary Prevention†
Adjusted-dose warfarin vs control	6	2900	64% (49–74)	40
Aspirin vs control	7	3990	19% (−1–35)	140
Adjusted-dose warfarin vs aspirin	9	4620	39% (19–53)	90

CI indicates confidence interval, and NNT, No. needed to treat.

*Adapted from Hart et al.[252] Includes all strokes (ischemic and hemorrhagic).

†No. needed to treat for 1 y to prevent 1 stroke, based on a 3.5%/y stroke rate in untreated patients with atrial fibrillation and without prior stroke or TIA.

from >12 randomized trials, anticoagulation is established as highly efficacious for prevention of stroke and moderately efficacious for reducing mortality.[252]

Thirty-three randomized trials involving >60 000 participants have compared various antithrombotic agents with placebo/control or with one another.[252,253–256] Treatment with adjusted-dose warfarin (target INR, range 2.0 to 3.0) provides the greatest protection against stroke [relative risk reduction (RRR) 64%; 95% CI, 49% to 74%], virtually eliminating the excess number of ischemic strokes associated with atrial fibrillation if the intensity of anticoagulation is adequate and reducing all-cause mortality by 26% (95% CI, 3% to 23%) (Table 10).[252] In addition, anticoagulation reduces stroke severity and poststroke mortality.[257–259] Aspirin offers modest protection against stroke (RRR, 22%; 95% CI, 6% to 35%).[252] There are no convincing data that favor one dose of aspirin (50 mg to 325 mg daily) over another. Compared with aspirin, adjusted-dose warfarin reduces stroke by 39% (RRR; 95% CI, 22% to 52%) (Table 10).[252,259]

Two randomized trials assessed the potential role of the combination of clopidogrel (75 mg daily) plus aspirin (75 mg to 100 mg daily) for preventing stroke in patients with atrial fibrillation. The Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE) investigators compared this combination antiplatelet regimen with adjusted-dose warfarin (target INR, 2.0 to 3.0) in patients with atrial fibrillation with 1 additional risk factor for stroke in ACTIVE W and found a 40% relative risk reduction (95% CI, 18% to 56%, $P=0.001$) for stroke with warfarin compared with the dual antiplatelet regimen.[252,260] ACTIVE A compared clopidogrel combined with aspirin with aspirin alone in atrial fibrillation patients deemed unsuitable for warfarin anticoagulation and who had at least 1 additional risk factor for stroke (approximately 25% were deemed unsuitable because of concern for warfarin-associated bleeding).[253] Dual antiplatelet therapy resulted in a 28% relative risk reduction (95% CI, 17% to 38%; $P=0.0002$) in all strokes (including parenchymal ICH) over treatment with aspirin alone, but major bleeding was increased by 57% (increase in RR; 95% CI, 29% to 92%, $P<0.001$); overall and in absolute terms, major vascular events (the study primary end point) were decreased 0.8% per year, but major hemorrhages increased 0.7% per year (RR for major vascular events and major hemorrhages, 0.97; 95% CI, 0.89 to 1.06; $P=0.54$). Disabling/fatal stroke, however, was decreased by dual antiplatelet therapy (RRR, 26%; 95% CI, 11% to 38%; $P=0.001$).

On the basis of results from ACTIVE W and A, adjusted-dose warfarin is superior to clopidogrel plus aspirin, and clopidogrel plus aspirin is superior to aspirin alone for stroke prevention; however, it is important to recognize that the latter benefit is limited by a concomitant increase in major bleeding complications. Less clear is how bleeding risks and rates compare between adjusted-dose warfarin and clopidogrel plus aspirin in warfarin-naïve patients.[260,261]

The initial 3 months of adjusted-dose warfarin are a particularly high-risk period for bleeding,[262] and especially close monitoring of anticoagulation is advised during this interval. ICH is the most devastating complication of anticoagulation; the absolute increase in ICH remains relatively small if the INR is ≤3.5.[258] Treatment of hypertension in atrial fibrillation patients reduces the risk of both ICH and ischemic stroke; hence, it has double benefits for atrial fibrillation patients who have received anticoagulation.[263–265] Anticoagulation of elderly atrial fibrillation patients should come with a firm commitment both by the physician and patient to control BP (target systolic BP, <140 mm Hg). Warfarin therapy is inherently risky, and in 2008 The Joint Commission challenged hospitals to "reduce the likelihood of harm associated with the use of anticoagulation therapy" as a national patient safety goal.[266] A consensus statement about the delivery of optimal anticoagulant care has recently been published.[267]

The benefits versus risks of the combined use of antiplatelet agents in addition to warfarin in elderly atrial fibrillation patients are inadequately defined. Combined use of warfarin with antiplatelet therapy increases the risk of intracranial and extracranial hemorrhage.[268] Adjusted-dose anticoagulation (target INR, 2.0 to 3.0) appears to offer protection against MI that is comparable to aspirin in atrial fibrillation patients,[269] and the addition of aspirin to warfarin is not recommended for most atrial fibrillation patients with stable coronary artery disease.[244,247] Data are meager on the type and duration of optimal antiplatelet therapy when combined with warfarin in atrial fibrillation patients with recent coronary angioplasty and stenting.[270,271] Clopidogrel plus aspirin combined with warfarin has been suggested for 9 to 12 months after placement of bare-metal coronary stents. Because drug-eluting stents require even more prolonged antiplatelet therapy, bare-metal stents are generally preferred for atrial fibrillation patients taking warfarin.[272,273] A lower target INR of 2.0 to 2.5 has been recommended in patients requiring warfarin, aspirin, and clopidogrel after percutaneous coronary intervention during the period of combined antiplatelet and anticoagulant therapy.[274]

Direct thrombin inhibitors offer a potential alternative to warfarin in patients with atrial fibrillation. Ximelagatran showed promise, but the drug was associated with toxicity and was not approved for use in the United States.[275,276] In the Randomized Evaluation of Long-term anticoagulant therapy (RE-LY), 18 113 atrial fibrillation patients with at least 1 additional risk factor for stroke were randomly assigned to dabigatran 110 mg twice daily, dabigatran 150 mg twice daily

(double-blind), or adjusted-dose warfarin (target INR, 2.0 to 3.0, open label).[256] The primary outcome was stroke or systemic embolism during the mean follow-up of 2 years, which occurred at a rate of 1.7% per year in the warfarin group compared with 1.5% per year in the 110-mg dabigatran group (RR, 0.91; 95% CI, 0.74 to 1.1; $P<0.001$ for noninferiority) and 1.11% per year in the 150-mg dabigatran group (RR 0.66 versus warfarin; 95% CI, 0.53 to 0.82, $P<0.001$ for superiority). The rates of major bleeding were 3.4% per year in the warfarin group, 2.7% per year with 110 mg dabigatran ($P=0.003$), and 3.11% per year with 150 mg dabigatran ($P=0.31$). Therefore, dabigatran 110 mg/d was associated with rates of stroke and systemic embolism similar to warfarin but with lower rates of major hemorrhages. Dabigatran 150 mg/d was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage compared with warfarin. The comparison with warfarin was open label, a potential source of bias. The rate of major hemorrhage with warfarin was higher than in other recent international trials. Dabigatran may have important drug interactions with P-glycoprotein inhibitors, such as verapamil, amiodarone, and quinidine, and was not tested in patients with significant renal dysfunction.[257] The drug has been recently FDA approved for use in the United States.

Summary and Gaps

Atrial fibrillation is a major, prevalent, independent risk factor for ischemic stroke, and adjusted-dose warfarin is highly efficacious for reducing stroke and death in high-risk patients with this condition. Several validated stroke risk stratification schemes are available to identify atrial fibrillation patients who benefit most and least, in absolute terms, from long-term anticoagulation. However, there can be considerable variation in anticipated risk depending on the scheme used. Guidelines vary in recommendations about stroke risk stratification, resulting in confusion among clinicians and nonuniform antithrombotic prophylaxis. Additional research to identify an optimal valid scheme that could be widely endorsed would likely lead to more uniform antithrombotic prophylaxis and better outcomes for stroke prevention.

Adjusted-dose warfarin continues to be underused, particularly among very elderly atrial fibrillation patients. Development of safer, easier-to-use oral anticoagulants might improve the benefit-risk ratio. Novel oral anticoagulants (eg, direct thrombin inhibitors, factor Xa inhibitors) have and are being tested in several ongoing large randomized trials, and additional treatment options appear to be on the horizon. Whether aggressive treatment of systemic hypertension sufficiently lowers the risk of cardioembolic stroke in atrial fibrillation below the threshold warranting anticoagulation is a clinically important, but as yet unanswered, question. Additional large scale magnetic resonance imaging (MRI) studies of cerebral microhemorrhages as predictors of cerebral macrohemorrhages may prove to be useful in the future in relation to the safety of administration of antithrombotic agents, especially in the elderly.

Recommendations

1. **Active screening for atrial fibrillation in patients >65 years of age in primary care settings using pulse taking followed by an ECG as indicated can be useful (*Class IIa; Level of Evidence B*).**
2. **Adjusted-dose warfarin (target INR, 2.0 to 3.0) is recommended for all patients with nonvalvular atrial fibrillation deemed to be at high risk and many deemed to be at moderate risk for stroke who can receive it safely (*Class I; Level of Evidence A*).**
3. **Antiplatelet therapy with aspirin is recommended for low-risk and some moderate-risk patients with atrial fibrillation, based on patient preference, estimated bleeding risk if anticoagulated, and access to high-quality anticoagulation monitoring (*Class I; Level of Evidence A*).**
4. **For high-risk patients with atrial fibrillation deemed unsuitable for anticoagulation, dual antiplatelet therapy with clopidogrel and aspirin offers more protection against stroke than aspirin alone but with increased risk of major bleeding and might be reasonable (*Class IIb; Level of Evidence B*).**
5. **Aggressive management of BP coupled with antithrombotic prophylaxis in elderly patients with atrial fibrillation can be useful (*Class IIa; Level of Evidence B*).**

Other Cardiac Conditions

The elimination of possible cardiac sources of embolism is an important way to reduce stroke risk. Cardiogenic embolism is the cause of approximately 20% of ischemic strokes.[278] Cryptogenic strokes frequently have embolic features suggesting a cardiogenic origin.[279] Cardioembolic strokes are relatively severe, are associated with greater neurological deficits at admission, greater residual deficits at discharge, and greater neurological deficits after 6 months compared with noncardioembolic strokes.[280] Cardioembolic strokes may constitute >40% of strokes in patients with cryptogenic stroke.[279,281] The awareness that different forms of cardiac disease may place an individual patient at increased risk of stroke mandates a comprehensive diagnostic evaluation.[279,282]

Cardiac conditions associated with a high risk for stroke include atrial arrhythmias (eg, atrial fibrillation/flutter, sick sinus syndrome), left atrial thrombus, primary cardiac tumors, vegetations, and prosthetic cardiac valves.[279] Other cardiac conditions that increase the risk of stroke include dilated cardiomyopathy, coronary artery disease, valvular heart disease, and endocarditis. Stroke may occur in patients undergoing cardiac catheterization, pacemaker implantation, and coronary artery bypass surgery.[283,284] Although the increased risk of stroke associated with these procedures is related to the nature of the procedure, risk is also related to procedural duration.[285]

The incidence of stroke is inversely proportional to left ventricular ejection fraction.[286–288] Patients having an acute coronary syndrome are also at an increased risk for stroke,[289–291] with the risk also inversely proportional to left ventricular ejection fraction[286–288,289–291] and further increasing with associated atrial fibrillation.[289–291] The documentation of a left ventricular mural thrombus in these patients further adds to stroke risk.[286]

Patients with rheumatic mitral valve disease are at increased risk for stroke.[292] Mitral valvuloplasty does not eliminate this risk.[293] Thromboembolic events have been

European Heart Journal (2010) 31, 2369–2429
doi:10.1093/eurheartj/ehq278

Guidelines for the management of atrial fibrillation

The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC)

Developed with the special contribution of the European Heart Rhythm Association (EHRA)†

Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS)

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Keywords Atrial fibrillation • European Society of Cardiology • Guidelines • Anticoagulation • Rate control • Rhythm control • Upstream therapy • Pulmonary vein isolation • Left atrial ablation

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Abbreviations and acronyms

ACEI	angiotensin-converting enzyme inhibitor
ACS	acute coronary syndrome
ACTIVE	Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events
ADONIS	American–Australian–African trial with DronedarONe In atrial fibrillation or flutter for the maintenance of Sinus rhythm

AF-CHF	Atrial Fibrillation and Congestive Heart Failure
AFFIRM	Atrial Fibrillation Follow-up Investigation of Rhythm Management
ANDROMEDA	ANtiarrhythmic trial with DROnedarone in Moderate-to-severe congestive heart failure Evaluating morbidity DecreAse
AP	accessory pathway
APAF	Ablation for Paroxysmal Atrial Fibrillation study
ARB	angiotensin receptor blocker
ARMYDA	Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery
ATHENA	A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg b.i.d. for the prevention of cardiovascular Hospitalisation or death from any cause in patIENts with Atrial fibrillation/atrial flutter
ATRIA	AnTicoagulation and Risk factors In Atrial fibrillation
AVRO	A Phase III prospective, randomized, double-blind, Active-controlled, multicentre, superiority study of Vernakalant injection vs. amiodarone in subjects with Recent Onset atrial fibrillation
AVERROES	Apixaban VERsus acetylsalicylic acid to pRevent strOkES
BAFTA	Birmingham Atrial Fibrillation Treatment of the Aged
b.i.d.	bis in die (twice daily)
bpm	beats per minute
CABG	coronary artery bypass graft
CACAF	Catheter Ablation for the Cure of Atrial Fibrillation study
CFAE	complex fractionated atrial electrogram
CHA_2DS_2-VASc	cardiac failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled)-vascular disease, age 65–74 and sex category (female)
$CHADS_2$	cardiac failure, hypertension, age, diabetes, stroke (doubled)
CHARISMA	Clopidogrel for High Athero-thrombotic Risk and Ischemic Stabilisation, Management, and Avoidance
CHARM	Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPG	clinical practice guidelines
CRT	cardiac resynchronization therapy
CT	computed tomography
CV	cardioversion
DAFNE	Dronedarone Atrial FibrillatioN study after Electrical cardioversion
DCC	direct current cardioversion
DIONYSOS	Randomized Double blind trial to evaluate efficacy and safety of drOnedarone [400 mg b.i.d.] versus amiodaroNe [600 mg q.d. for 28 daYS, then 200 mg qd thereafter] for at least 6 mOnths for the maintenance of Sinus rhythm in patients with atrial fibrillation
EAPCI	European Association of Percutaneous Cardiovascular Interventions
EHRA	European Heart Rhythm Association
ECG	electrocardiogram
EMA	European Medicines Agency
EURIDIS	EURopean trial In atrial fibrillation or flutter patients receiving Dronedarone for the maIntenance of Sinus rhythm
GISSI-AF	Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca Atrial Fibrillation
GPI	glycoprotein inhibitor
GRACE	Global Registry of Acute Coronary Events
HAS-BLED	hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (>65), drugs/alcohol concomitantly (1 point each)
HOPE	Heart Outcomes Prevention Evaluation
HOT CAFE	How to Treat Chronic Atrial Fibrillation
HR	hazard ratio
HT	hypertension
INR	international normalized ratio
i.v.	intravenous
J-RHYTHM	Japanese Rhythm Management Trial for Atrial Fibrillation
LA	left atrial
LAA	left atrial appendage
LIFE	Losartan Intervention For Endpoint reduction in hypertension
LMWH	low molecular weight heparin
LoE	level of evidence
LV	left ventricular
LVEF	left ventricular ejection fraction
o.d.	omni die (every day)
OAC	oral anticoagulant
OR	odds ratio
MRI	magnetic resonance imaging
NYHA	New York Heart Association
PAD	peripheral artery disease
PCI	percutaneous intervention
PIAF	Pharmacological Intervention in Atrial Fibrillation
PPI	proton pump inhibitor
PROTECT-AF	System for Embolic PROTECTion in patients with Atrial Fibrillation
PUFA	polyunsaturated fatty acid
PV	pulmonary vein
PVI	pulmonary vein isolation
RACE	RAte Control versus Electrical cardioversion for persistent atrial fibrillation
RACE II	RAte Control Efficacy in permanent atrial fibrillation
RAAFT	Radiofrequency Ablation Atrial Fibrillation Trial
RE-LY	Randomized Evaluation of Long-term anticoagulant therapY with dabigatran etexilate
RIKS-HIA	Register of Information and Knowledge about Swedish Heart Intensive care Admissions
RR	relative risk

SAFE-T	Sotalol, Amiodarone, atrial Fibrillation Efficacy Trial
SAFE	Screening for AF in the Elderly
SCD	sudden cardiac death
SPAF	Stroke Prevention in Atrial Fibrillation
STAF	Strategies of Treatment of Atrial Fibrillation
STEMI	ST segment elevation myocardial infarction
STOP-AF	Sustained Treatment Of Paroxysmal Atrial Fibrillation
TIA	transient ischaemic attack
t.i.d.	ter in die (three times daily)
TIMI	Thrombolysis In Myocardial Infarction
TOE	transoesophageal echocardiogram
TRANSCEND	Telmisartan Randomized AssessmeNt Study in aCE iNtolerant subjects with cardiovascular Disease
UFH	unfractionated heparin
VALUE	Valsartan Antihypertensive Long-term Use Evaluation
VKA	vitamin K antagonist
WASPO	Warfarin versus Aspirin for Stroke Prevention in Octogenarians with AF

1. Preamble

Guidelines summarize and evaluate all currently available evidence on a particular issue with the aim of assisting physicians in selecting the best management strategy for an individual patient suffering from a given condition, taking into account the impact on outcome, as well as the risk–benefit ratio of particular diagnostic or therapeutic means. Guidelines are no substitutes for textbooks. The legal implications of medical guidelines have been discussed previously.

A large number of Guidelines have been issued in recent years by the European Society of Cardiology (ESC) as well as by other societies and organizations. Because of the impact on clinical practice, quality criteria for development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC Web Site (http://www.escardio.org/guidelines-surveys/esc-guidelines/about/Pages/rules-writing.aspx).

In brief, experts in the field are selected and undertake a comprehensive review of the published evidence for management and/or prevention of a given condition. A critical evaluation of diagnostic and therapeutic procedures is performed, including assessment of the risk–benefit ratio. Estimates of expected health outcomes for larger societies are included, where data exist. The level of evidence and the strength of recommendation of particular treatment options are weighed and graded according to pre-defined scales, as outlined in *Tables 1* and 2.

The experts of the writing panels have provided disclosure statements of all relationships they may have that might be perceived as real or potential sources of conflicts of interest. These disclosure forms are kept on file at the European Heart House, headquarters of the ESC. Any changes in conflict of interest that arise during the writing period must be notified to the ESC. The Task Force report received its entire financial support from the ESC and was developed without any involvement of the pharmaceutical, device, or surgical industry.

Table 1 Classes of recommendations

Classes of recommendations	Definition
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

Table 2 Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

The ESC Committee for Practice Guidelines (CPG) supervises and coordinates the preparation of new Guidelines produced by Task Forces, expert groups, or consensus panels. The Committee is also responsible for the endorsement process of these Guidelines or statements. Once the document has been finalized and approved by all the experts involved in the Task Force, it is submitted to outside specialists for review. The document is revised, finally approved by the CPG, and subsequently published.

After publication, dissemination of the message is of paramount importance. Pocket-sized versions and personal digital assistant-downloadable versions are useful at the point of care. Some surveys have shown that the intended users are sometimes unaware of the existence of guidelines, or simply do not translate them into practice. Thus, implementation programmes for new guidelines form an important component of knowledge dissemination. Meetings are organized by the ESC, and directed towards its member National Societies and key opinion leaders in Europe. Implementation meetings can also be undertaken at national

levels, once the guidelines have been endorsed by the ESC member societies, and translated into the national language. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Thus, the task of writing Guidelines covers not only the integration of the most recent research, but also the creation of educational tools and implementation programmes for the recommendations. The loop between clinical research, writing of guidelines, and implementing them into clinical practice can then only be completed if surveys and registries are performed to verify that real-life daily practice is in keeping with what is recommended in the guidelines. Such surveys and registries also make it possible to evaluate the impact of implementation of the guidelines on patient outcomes. Guidelines and recommendations should help the physicians to make decisions in their daily practice; however, the ultimate judgement regarding the care of an individual patient must be made by the physician in charge of their care.

2. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, occurring in 1–2% of the general population. Over 6 million Europeans suffer from this arrhythmia, and its prevalence is estimated to at least double in the next 50 years as the population ages. It is now 4 years since the last AF guideline was published, and a new version is now needed.

AF confers a 5-fold risk of stroke, and one in five of all strokes is attributed to this arrhythmia. Ischaemic strokes in association with AF are often fatal, and those patients who survive are left more disabled by their stroke and more likely to suffer a recurrence than patients with other causes of stroke. In consequence, the risk of death from AF-related stroke is doubled and the cost of care is increased 1.5-fold. There has been much research into stroke prevention, which has influenced this guideline.

In the majority of patients there appears to be an inexorable progression of AF to persistent or permanent forms, associated with further development of the disease that may underlie the arrhythmia. Some advance has been made in the understanding of the dynamic development of AF from its preclinical state as an 'arrhythmia-in-waiting' to its final expression as an irreversible and end-stage cardiac arrhythmia associated with serious adverse cardiovascular events. Much recent therapeutic effort with 'upstream therapies' has been expended to slow or halt the progression of AF due to underlying cardiovascular disease and to AF itself. Limited success has been achieved and is recognized in this guideline.

Clinical frustration has been fuelled by numerous clinical trials that have demonstrated that the strategic aim of maintaining sinus rhythm has no demonstrable value when compared with the *laissez-faire* approach of leaving AF unchecked apart from restriction of the ventricular rate. No advantage from strict rate control has been established. These sobering findings are clearly at odds with the severe complications associated with AF in surveys and epidemiological studies. However, new antiarrhythmic approaches may offer added value and have stimulated additions to these guidelines.

The problem of early recognition of AF is greatly aggravated by the often 'silent' nature of the rhythm disturbance. In about one-third of patients with this arrhythmia, the patient is not aware of so-called 'asymptomatic AF'. Much earlier detection of the arrhythmia might allow the timely introduction of therapies to protect the patient, not only from the consequences of the arrhythmia, but also from progression of AF from an easily treated condition to an utterly refractory problem. Monitoring and screening as advocated in this guideline may help to do this.

Non-pharmacological interventions to control the occurrence of AF or to limit its expression have been eagerly and substantially developed in the past decade. Ablation techniques, usually done percutaneously using a catheter, have proved successful in the treatment of AF, particularly by reducing the symptomatic burden associated with the arrhythmia, to such an extent that a 'cure' may be achieved in some patients. The new guidelines recognize these advances. When applied in concert with major new drug developments such as novel antithrombotic agents and emerging safer antiarrhythmic drugs, these therapeutic options should help to improve outcomes in AF patients.

The expanding and diversifying possibilities and restraints of medical care within Europe make it difficult to formulate guidelines that are valid throughout Europe. There are differences in the availability of therapies, delivery of care, and patient characteristics in Europe and in other parts of the world. Therefore, these European guidelines, though based largely on globally acquired data, are likely to require some modifications when applied to multiple healthcare settings.

2.1 Epidemiology

AF affects 1–2% of the population, and this figure is likely to increase in the next 50 years.[1–2] In acute stroke patients, systematic electrocardiographic (ECG) monitoring would identify AF in 1 in 20 subjects, a far greater number than would have been detected by standard 12-lead ECG recordings. AF may long remain undiagnosed (silent AF),[3] and many patients with AF will never present to hospital.[4] Hence, the 'true' prevalence of AF is probably closer to 2% of the population.[3]

The prevalence of AF increases with age, from <0.5% at 40–50 years, to 5–15% at 80 years.[1–2,5–7] Men are more often affected than women. The lifetime risk of developing AF is ~25% in those who have reached the age of 40.[8] The prevalence and incidence of AF in non-Caucasian populations is less well studied. The incidence of AF appears to be increasing (13% in the past two decades).

2.1.1 Atrial fibrillation-related cardiovascular events ('outcomes')

AF is associated with increased rates of death, stroke and other thrombo-embolic events, heart failure and hospitalizations, degraded quality of life, reduced exercise capacity, and left ventricular (LV) dysfunction (*Table 3*).

Death rates are doubled by AF, independently of other known predictors of mortality.[3,9] Only antithrombotic therapy has been shown to reduce AF-related deaths.[10]

inspected for signs of structural heart disease (e.g. acute or remote myocardial infarction, LV hypertrophy, bundle branch block or ventricular pre-excitation, signs of cardiomyopathy, or ischaemia).

Diagnostic evaluation

A recently suggested symptom score (EHRA score,[3] *Table 6*) provides a simple clinical tool for assessing symptoms during AF. A very similar scale has been validated by the Canadian Cardiovascular Society.[41] The EHRA score only considers symptoms that are attributable to AF and reverse or reduce upon restoration of sinus rhythm or with effective rate control.

The initial diagnostic work-up is driven by the initial presentation. The **time of onset of the arrhythmia episode** should be established to define the type of AF (*Figure 2*). Most patients with AF <48 h in duration can be cardioverted (see Section 4.1.7) on low molecular weight heparin (LMWH) without risk for stroke. If AF duration is >48 h or there is doubt about its duration, **TOE** may be used to rule out intracardiac thrombus prior to cardioversion,[42] although it can be difficult in patients in acute distress and may not be available in emergency settings. The transthoracic echocardiogram can provide useful information to guide clinical decision making, but cannot exclude thrombus in the LAA.

Patients with AF and **signs of acute heart failure** require urgent rate control and often cardioversion. An urgent echocardiogram should be performed in haemodynamically compromised patients to assess LV and valvular function and right ventricular pressure.

Patients with **stroke or TIA** require immediate stroke diagnosis, usually via emergency computed tomography (CT) and adequate cerebral revascularization.

Patients should be assessed for risk of stroke. Most patients with acute AF will require anticoagulation unless they are at low risk of thrombo-embolic complications (no stroke risk factors) *and* no cardioversion is necessary (e.g. AF terminates within 24–48 h).

After the initial management of symptoms and complications, **underlying causes of AF** should be sought. An *echocardiogram* is useful to detect ventricular, valvular, and atrial disease as well as rare congenital heart disease. *Thyroid function tests* (usually measurement of serum thyroid-stimulating hormone), a full *blood count*, a serum *creatinine* measurement and analysis for *proteinuria*, measurement of *blood pressure*, and a test for *diabetes mellitus* (usually a fasting glucose measurement) are useful. A serum test for hepatic function may be considered in selected patients. A *stress test* is reasonable in patients with signs or risk factors for coronary artery disease. Patients with persistent signs of LV dysfunction and/or signs of myocardial ischaemia are candidates for *coronary angiography*.

3.7 Clinical follow-up

The specialist caring for the AF patient should not only perform the baseline assessment and institute the appropriate treatment, but also suggest a structured plan for follow-up.

Important considerations during follow-up of the AF patient are listed below:

- Has the risk profile changed (e.g. new diabetes or hypertension), especially with regard to the indication for anticoagulation?
- Is anticoagulation now necessary—have new risk factors developed, or has the need for anticoagulation passed, e.g. post-cardioversion in a patient with low thrombo-embolic risk?
- Have the patient's symptoms improved on therapy; if not, should other therapy be considered?
- Are there signs of proarrhythmia or risk of proarrhythmia; if so, should the dose of an antiarrhythmic drug be reduced or a change made to another therapy?
- Has paroxysmal AF progressed to a persistent/permanent form, in spite of antiarrhythmic drugs; in such a case, should another therapy be considered?
- Is the rate control approach working properly; has the target for heart rate at rest and during exercise been reached?

At follow-up visits, a 12-ECG should be recorded to document the rhythm and rate, and to investigate disease progression. For those on antiarrhythmic drug therapy it is important to assess potential proarrhythmic ECG precursors such as lengthening of PR, QRS, or QT intervals, non-sustained ventricular tachycardia, or pauses. If any worsening of symptoms occurs, repeated blood tests, long-term ECG recordings and a repeat echocardiogram should be considered.

The patient should be fully informed about the pros and cons of the different treatment options, whether it is anticoagulation, rate control drugs, antiarrhythmic drugs, or interventional therapy. It is also appropriate to inform the patient with 'lone' or idiopathic AF about the good prognosis, once cardiovascular disease has been excluded.

4. Management

Management of AF patients is aimed at reducing symptoms and at preventing severe complications associated with AF. These therapeutic goals need to be pursued in parallel, especially upon the initial presentation of newly detected AF. Prevention of AF-related complications relies on antithrombotic therapy, control of ventricular rate, and adequate therapy of concomitant cardiac diseases. These therapies may already alleviate symptoms, but symptom relief may require additional rhythm control therapy by cardioversion, antiarrhythmic drug therapy, or ablation therapy (*Figure 3*).

4.1 Antithrombotic management

Cohort data as well as the non-warfarin arms of clinical trials have identified clinical and echocardiographic risk factors that can be related to an increased risk of stroke in AF.[47,48] These risk factors are limited to those documented in these studies, whilst many other potential risk factors were not systematically documented.

Two recent systematic reviews have addressed the evidence base for stroke risk factors in AF,[47,48] and concluded that prior stroke/TIA/thrombo-embolism, age, hypertension, diabetes, and structural heart disease are important risk factors. The presence of moderate to severe LV systolic dysfunction on two-dimensional transthoracic echocardiography is the only independent echocardiographic risk factor for stroke on multivariable analysis. On TOE, the presence of LA thrombus relative risk (RR) 2.5; $P = 0.04$], complex aortic plaques (RR 2.1; $P < 0.001$), spontaneous

Recommendations for diagnosis and initial management

Recommendations	Class[a]	Level[b]	Ref.[c]
The diagnosis of AF requires documentation by ECG.	I	B	3, 31
In patients with suspected AF, an attempt to record an ECG should be made when symptoms suggestive of AF occur.	I	B	3, 43
A simple symptom score (EHRA score) is recommended to quantify AF-related symptoms.	I	B	3, 41
All patients with AF should undergo a thorough physical examination, and a cardiac- and arrhythmia-related history should be taken.	I	C	
In patients with severe symptoms, documented or suspected heart disease, or risk factors, an echocardiogram is recommended.	I	B	3, 23, 44
In patients treated with antiarrhythmic drugs, a 12-lead ECG should be recorded at regular intervals during follow-up.	I	C	
In patients with suspected symptomatic AF, additional ECG monitoring should be considered in order to document the arrhythmia.	IIa	B	3, 33
Additional ECG monitoring should be considered for detection of 'silent' AF in patients who may have sustained an AF-related complication.	IIa	B	3, 34
In patients with AF treated with rate control, Holter ECG monitoring should be considered for assessment of rate control or bradycardia.	IIa	C	
In young active patients with AF treated with rate control, exercise testing should be considered in order to assess ventricular rate control.	IIa	C	
In patients with documented or suspected AF, an echocardiogram should be considered.	IIa	C	
Patients with symptomatic AF or AF-related complications should be considered for referral to a cardiologist.	IIa	C	
A structured follow-up plan prepared by a specialist is useful for follow-up by a general or primary care physician.	IIa	C	
In patients treated with rhythm control, repeated ECG monitoring may be considered to assess the efficacy of treatment.	IIb	B	3, 45, 46
Most patients with AF may benefit from specialist follow-up at regular intervals.	IIb	C	

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
AF = atrial fibrillation; ECG = electrocardiogram; EHRA = European Heart Rhythm Association.

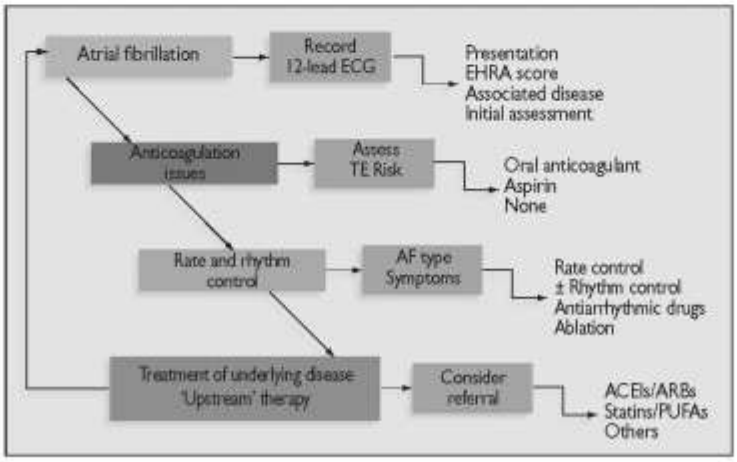

Figure 3 The management cascade for patients with AF. ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; PUFA = polyunsaturated fatty acid; TE = thrombo-embolism.

echo-contrast (RR 3.7; $P < 0.001$), and low LAA velocities (≤20 cm/s; RR 1.7; $P < 0.01$) are independent predictors of stroke and thrombo-embolism.

Patients with paroxysmal AF should be regarded as having a stroke risk similar to those with persistent or permanent AF, in the presence of risk factors.

Patients aged <60 years, with 'lone AF', i.e. no clinical history or echocardiographic evidence of cardiovascular disease, carry a very low cumulative stroke risk, estimated to be 1.3% over 15 years. The probability of stroke in young patients with lone AF appears to increase with advancing age or development of hypertension, emphasizing the importance of re-assessment of risk factors for stroke over time.

Caveats and inconsistencies

In some series, concomitant aspirin use may have influenced thrombo-embolic event rates. Of note, stroke rates are generally declining. In addition, anticoagulation monitoring is improving for those taking vitamin K antagonists (VKAs), and new oral anticoagulant (OAC) drugs that may not need monitoring are on the horizon.

Also, definitions and categorization of risk factors have been inconsistent over time. For example, age as a risk factor is not a 'yes/no' phenomenon, and stroke risk in AF starts to rise from age >65, although it is clear that AF patients aged ≥75 years (even with no other associated risk factors) have a significant stroke risk and derive benefit from VKA over aspirin.[47,48] As patients with AF get older, the relative efficacy of antiplatelet therapy to prevent ischaemic stroke decreases, whereas it does not change for VKAs. Thus, the absolute benefit of VKAs for stroke prevention increases as AF patients get older. This is supported by other 'real-world' data.

In the older trials, hypertension was often defined as untreated blood pressure >160/95 mmHg or the use of antihypertensive drugs. Well-controlled blood pressure may represent a low risk of stroke and thrombo-embolism. In addition, a clinical diagnosis of heart failure was not a consistent risk factor for stroke in the systematic reviews mentioned above; indeed, a label of 'heart failure' may not necessarily reflect systolic LV impairment. Whilst the risk of thrombo-embolism with moderate to severe systolic impairment is clear, the risk of thrombo-embolism with heart failure and preserved ejection fraction is less defined.[44,47,48]

The presence of atherosclerotic vascular disease may contribute to stroke risk. An increased risk of stroke and thrombo-embolism with previous myocardial infarction is present in most (but not all) studies,[49] but a diagnosis of 'angina' per se is unreliable, as many such patients do not have coronary heart disease. Also, AF confers a poor prognosis in patients with peripheral artery disease (PAD), and the presence of complex aortic plaque on the descending aorta on TOE is an independent risk factor for stroke and thrombo-embolism.

Female sex results in an adjusted RR of 1.6 [95% confidence interval (CI) 1.3–1.9] for thrombo-embolism. Gender analyses from population studies, cohort studies, trial cohorts, and surveys also suggest higher thrombo-embolism rates in female subjects.

Table 7 $CHADS_2$ score and stroke rate

$CHADS_2$ score	Patients (n = 1733)	Adjusted stroke rate (%/year)[a] (95% confidence interval)
0	120	1.9 (1.2–3.0)
1	463	2.8 (2.0–3.8)
2	523	4.0 (3.1–5.1)
3	337	5.9 (4.6–7.3)
4	220	8.5 (6.3–11.1)
5	65	12.5 (8.2–17.5)
6	5	18.2 (10.5–27.4)

[a]The adjusted stroke rate was derived from the multivariable analysis assuming no aspirin usage; these stroke rates are based on data from a cohort of hospitalized AF patients, published in 2001, with low numbers in those with a **$CHADS_2$ score** of 5 and 6 to allow an accurate judgement of the risk in these patients. Given that stroke rates are declining overall, actual stroke rates in contemporary non-hospitalized cohorts may also vary from these estimates. Adapted from Gage BF *et al.*[50]
AF = atrial fibrillation; $CHADS_2$ = cardiac failure, hypertension, age, diabetes, stroke (doubled).

A recent analysis suggested that proteinuria increased the risk of thrombo-embolism by 54% (RR 1.54; 95% CI 1.29–1.85), with higher stroke risk at an estimated glomerular filtration rate of <45 mL/min. Thus, chronic kidney disease may increase the risk of thrombo-embolism in AF, although such patients are also at increased mortality and bleeding risk and have not been studied in prospective clinical trials.

Patients with thyrotoxicosis are at risk of developing AF, but stroke risk may be more related to the presence of associated clinical stroke risk factors. Other conditions such as hypertrophic cardiomyopathy and amyloidosis may be risk factors for stroke, but have not been studied or included in clinical trials of thromboprophylaxis.

4.1.1 Risk stratification for stroke and thrombo-embolism

The identification of various stroke clinical risk factors has led to the publication of various stroke risk schemes. Most have (artificially) categorized stroke risk into 'high', 'moderate', and 'low' risk strata. The simplest risk assessment scheme is the **$CHADS_2$ score**, as shown in *Table 7*. The $CHADS_2$ [cardiac failure, hypertension, age, diabetes, stroke (doubled)] risk index evolved from the AF Investigators and Stroke Prevention in Atrial Fibrillation (SPAF) Investigators criteria, and is based on a point system in which 2 points are assigned for a history of stroke or TIA and 1 point each is assigned for age >75 years, a history of hypertension, diabetes, or recent cardiac failure.[50]

Thus, the $CHADS_2$ stroke risk stratification scheme should be used as an initial, rapid, and easy-to-remember means of assessing stroke risk. In patients with a $CHADS_2$ score ≥2, chronic OAC therapy with a VKA is recommended in a dose-adjusted approach to achieve an international normalized ratio (INR) target of 2.5

(range, 2.0–3.0), unless contraindicated. Such a practice appears to translate to better outcomes in AF patients in routine care.[10,51]

As shown in *Table 7*, there is a clear relationship between $CHADS_2$ score and stroke rate.[50] The original validation of this scheme classified a $CHADS_2$ score of 0 as low risk, 1–2 as moderate risk, and >2 as high risk.

The Stroke in AF Working Group performed a comparison of 12 published risk-stratification schemes to predict stroke in patients with non-valvular AF, and concluded that there were substantial, clinically relevant differences among published schemes designed to stratify stroke risk in patients with AF. Most had very modest predictive value for stroke (c-statistics—as a measure of the predictive value—of ~0.6); also, the proportion of patients assigned to individual risk categories varied widely across the schemes. The $CHADS_2$ score categorized most subjects as 'moderate risk' and had a c-statistic of 0.58 to predict stroke in the whole cohort.

In the present guidelines, we have tried to de-emphasize the use of the 'low', 'moderate', and 'high' risk categorizations, given the poor predictive value of such artificial categories, and recognize that risk is a continuum. Thus, we encourage a risk factor-based approach for more detailed stroke risk assessment, recommending the use of antithrombotic therapy on the basis of the presence (or absence) of stroke risk factors.

Support for this approach comes from various published analyses, where even patients at 'moderate risk' (currently defined as $CHADS_2$ score = 1, i.e. one risk factor) still derive significant benefit from OAC over aspirin use, often with low rates of major haemorrhage. Importantly, prescription of an antiplatelet agent was not associated with a lower risk of adverse events. Also, the $CHADS_2$ score does not include many stroke risk factors, and other 'stroke risk modifiers' need to be considered in a comprehensive stroke risk assessment (*Table 8*).

'Major' risk factors (previously referred to as 'high' risk factors) are prior stroke or TIA, or thrombo-embolism, and older age (≥75 years). The presence of some types of valvular heart disease (mitral stenosis or prosthetic heart valves) would also categorize such 'valvular' AF patients as 'high risk'.

'Clinically relevant non-major' risk factors (previously referred to as 'moderate' risk factors) are heart failure [especially moderate to severe systolic LV dysfunction, defined arbitrarily as left ventricular ejection fraction (LVEF) ≤40%], hypertension, or diabetes. Other 'clinically relevant non-major' risk factors (previously referred to as 'less validated risk factors') include female sex, age 65–74 years, and vascular disease (specifically, myocardial infarction, complex aortic plaque and PAD). Note that risk factors are cumulative, and the simultaneous presence of two or more 'clinically relevant non-major' risk factors would justify a stroke risk that is high enough to require anticoagulation.

This risk factor-based approach for patients with non-valvular AF can also be expressed as an acronym, **CHA_2DS_2-VASc** [congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, and sex category (female)].[52] This scheme is based on a point system in which 2 points are assigned for a history of stroke or TIA, or age ≥75; and 1 point each is assigned for age 65–74 years, a history of hypertension, diabetes, recent cardiac failure, vascular disease (myocardial infarction, complex aortic plaque, and PAD, including prior revascularization, amputation due to PAD, or angiographic evidence of PAD, etc.), and female sex (*Table 8*). Thus, this acronym extends the $CHADS_2$ scheme by considering additional stroke risk factors that may influence a decision whether or not to anticoagulate (see Section 4.1.1).

Table 8 CHA_2DS_2VASc score and stroke rate

(a) Risk factors for stroke and thrombo-embolism in non-valvular AF	
'Major' risk factors	**'Clinically relevant non-major' risk factors**
Previous stroke, TIA, or systemic embolism Age ≥75 years	Heart failure or moderate to severe LV systolic dysfunction (e.g. LV EF ≤40%) Hypertension - Diabetes mellitus Female sex - Age 65–74 years Vascular disease[a]

(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VASc (Note: maximum score is 9 since age may contribute 0, 1, or 2 points)	
Risk factor	**Score**
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease[a]	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

(c) Adjusted stroke rate according to CHA_2DS_2-VASc score		
CHA_2DS_2-VASc score	**Patients (n=7329)**	**Adjusted stroke rate (%/year)[b]**
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

See text for definitions.
[a]Prior myocardial infarction, peripheral artery disease, aortic plaque. Actual rates of stroke in contemporary cohorts may vary from these estimates.
[b]Based on Lip et al.[53]
AF = atrial fibrillation; EF = ejection fraction (as documented by echocardiography, radionuclide ventriculography, cardiac catheterization, cardiac magnetic resonance imaging, etc.); LV = left ventricular; TIA = transient ischaemic attack.

4.1.2 Antithrombotic therapy

Numerous clinical trials have provided an extensive evidence base for the use of antithrombotic therapy in AF.

4.1.2.1 Anticoagulation therapy with vitamin K antagonist vs. control

Five large randomized trials published between 1989 and 1992 evaluated VKA mainly for the primary prevention of thrombo-embolism in patients with non-valvular AF. A sixth trial focused on secondary prevention among patients who had survived non-disabling stroke or TIA.

In a meta-analysis, the RR reduction with VKA was highly significant and amounted to 64%, corresponding to an absolute annual risk reduction in all strokes of 2.7%.[54] When only ischaemic strokes were considered, adjusted-dose VKA use was associated with a 67% RR reduction. This reduction was similar for both primary and secondary prevention and for both disabling and non-disabling strokes. Of note, many strokes occurring in the VKA-treated patients occurred when patients were not taking therapy or were subtherapeutically anticoagulated. All-cause mortality was significantly reduced (26%) by adjusted-dose VKA vs. control. The risk of intracranial haemorrhage was small.

Four of these trials were placebo controlled; of the two that were double blind with regard to anticoagulation, one was stopped early because of external evidence that OAC with VKA was superior to placebo, and the other included no female subjects. In three of the trials, VKA dosing was regulated according to the prothrombin time ratio, while two trials used INR target ranges of 2.5–4.0 and 2.0–3.0.

Supported by the results of the trials cited above, VKA treatment should be considered for patients with AF with ≥1 stroke risk factor(s) provided there are no contraindications, especially with careful assessment of the risk–benefit ratio and an appreciation of the patient's values and preferences.

4.1.2.2 Antiplatelet therapy vs. control

Eight independent randomized controlled studies, together including 4876 patients, have explored the prophylactic effects of antiplatelet therapy, most commonly aspirin compared with placebo, on the risk of thrombo-embolism in patients with AF.[54]

When aspirin alone was compared with placebo or no treatment in seven trials, treatment with aspirin was associated with a non-significant 19% (95% CI −1% to −35%) reduction in the incidence of stroke. There was an absolute risk reduction of 0.8% per year for primary prevention trials and 2.5% per year for secondary prevention by using aspirin.[54] Aspirin was also associated with a 13% (95% CI −18% to −36%) reduction in disabling strokes and a 29% (95% CI −6% to −53%) reduction in non-disabling strokes. When only strokes classified as ischaemic were considered, aspirin resulted in a 21% (95% CI −1% to −38%) reduction in strokes. When data from all comparisons of antiplatelet agents and placebo or control groups were included in the meta-analysis, antiplatelet therapy reduced stroke by 22% (95% CI 6–35).

The dose of aspirin differed markedly between the studies, ranging from 50 to 1300 mg daily, and there was no significant heterogeneity between the results of the individual trials. Much of the beneficial effect of aspirin was driven by the results of one single positive trial, SPAF-I, which suggested a 42% stroke risk reduction with aspirin 325 mg vs. placebo. In this trial, there was internal heterogeneity, with inconsistencies for the aspirin effect between the results for the warfarin-eligible (RR reduction 94%) and warfarin-ineligible (RR reduction 8%) arms of the trial. Also, aspirin had less effect in people older than 75 years and did not prevent severe or recurrent strokes. The SPAF-I trial was also stopped early and its result may be exaggerated. Pharmacologically, near-complete platelet inhibition is achieved with aspirin 75 mg. Furthermore, low-dose aspirin (<100 mg) is safer than higher doses (such as 300 mg), given that bleeding rates with higher doses of aspirin are significant. Thus, if aspirin is used, it is reasonable to use doses in the lower end of the allowed range (75–100 mg daily).

The magnitude of stroke reduction from aspirin vs. placebo in the meta-analysis (19%) is broadly similar to that seen when aspirin is given to vascular disease subjects. Given that AF commonly co-exists with vascular disease, the modest benefit seen for aspirin in AF is likely to be related to its effects on vascular disease. More recent cardiovascular primary prevention trials in non-AF cohorts have not shown a significant benefit from aspirin in reducing risk of cardiovascular events.

In the Japan Atrial Fibrillation Stroke Trial,[55] patients with lone AF were randomized to an aspirin group (aspirin at 150–200 mg/day) or a control group without antiplatelet or anticoagulant therapy. The primary outcomes (3.1% per year) in the aspirin group were worse than those in the control group (2.4% per year), and treatment with aspirin caused a non-significant increased risk of major bleeding (1.6%) compared with control (0.4%).

4.1.2.3 Anticoagulation therapy with vitamin K antagonist vs. antiplatelet therapy

Direct comparison between the effects of VKA and aspirin has been undertaken in nine studies, demonstrating that VKA were significantly superior, with an RR reduction of 39%.

The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study showed that VKA (target INR 2–3) was superior to aspirin 75 mg daily in reducing the primary endpoint of fatal or disabling stroke (ischaemic or haemorrhagic), intracranial haemorrhage, or clinically significant arterial embolism by 52%, with no difference in the risk of major haemorrhage between warfarin and aspirin.[56] This is consistent with the small Warfarin versus Aspirin for Stroke Prevention in Octogenarians with AF (WASPO) trial, in which there were significantly more adverse events with aspirin (33%) than with warfarin (6%, $P = 0.002$), including serious bleeding. When the trials conducted prior to BAFTA were considered, the risk for intracranial haemorrhage was doubled with adjusted-dose warfarin compared with aspirin, although the absolute risk increase was small (0.2% per year).[54]

4.1.2.4 Other antithrombotic drug regimens

In the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events–Warfarin arm (ACTIVE W) trial, anticoagulation therapy was superior to the combination of clopidogrel plus aspirin (RR reduction 40%; 95% CI 18–56), with no difference in bleeding events between treatment arms.[57] The Aspirin arm (ACTIVE A) trial found that major vascular events were reduced in patients receiving aspirin–clopidogrel, compared with aspirin

monotherapy (RR 0.89; 95% CI 0.81–0.98; $P = 0.01$), primarily due to a 28% relative reduction in the rate of stroke with combination therapy.[58] Major bleeding was significantly increased (2.0% per year vs. 1.3% per year; RR 1.57; 95% CI 1.29–1.92; $P < 0.001$), broadly similar to that seen with VKA therapy. Of note, 50% of patients entered the trial due to 'physician's perception of being unsuitable for VKA therapy' and 23% had a risk factor for bleeding at trial entry. Thus, aspirin plus clopidogrel therapy could perhaps be considered as an interim measure where VKA therapy is unsuitable, but not as an alternative to VKA in patients at high bleeding risk.

Other antiplatelet agents such as indobufen and triflusal have been investigated in AF, with the suggestion of some benefit, but more data are required. Combinations of VKA (INR 2.0–3.0) with antiplatelet therapy have been studied, but no beneficial effect on ischaemic stroke or vascular events were seen, while more bleeding was evident. Thus, in patients with AF who sustain an ischaemic stroke despite adjusted dose VKA (INR 2.0–3.0), raising the intensity of anticoagulation to a higher INR range of 3.0–3.5 may be considered, rather than adding an antiplatelet agent, given that an appreciable risk in major bleeding only starts at INRs >3.5.

4.1.2.5 Investigational agents

Several new anticoagulant drugs—broadly in two classes, the oral direct thrombin inhibitors (e.g. dabigatran etexilate and AZD0837) and the oral factor Xa inhibitors (rivaroxaban, apixaban, edoxaban, betrixaban, YM150, etc.)—are being developed for stroke prevention in AF.

In the Randomized Evaluation of Long-term anticoagulant therapY with dabigatran etexilate (RE-LY) study,[59] dabigatran 110 mg b.i.d. was non-inferior to VKA for the prevention of stroke and systemic embolism with lower rates of major bleeding, whilst dabigatran 150 mg b.i.d. was associated with lower rates of stroke and systemic embolism with similar rates of major haemorrhage, compared with VKA.[59] The Apixaban VERsus acetylsalicylic acid to pRevent strOkES (AVERROES) study was stopped early due to clear evidence of a reduction in stroke and systemic embolism with apixaban 5 mg b.i.d. compared with aspirin 81–324 mg once daily in patients intolerant of or unsuitable for VKA, with an acceptable safety profile.

4.1.3 Current recommendations for antithrombotic therapy

Recommendations for antithrombotic therapy should be based on the presence (or absence) of risk factors for stroke and thrombo-embolism, rather than on an artificial division into high, moderate, or low risk categories.

The $CHADS_2$ stroke risk stratification scheme (see Section 4.1.1) should be used as a simple initial (and easily remembered) means of assessing stroke risk, particularly suited to primary care doctors and non-specialists. In patients with a $CHADS_2$ score of ≥2, chronic OAC therapy, e.g. with a VKA, is recommended in a dose adjusted to achieve an INR value in the range of 2.0–3.0, unless contraindicated.

In patients with a $CHADS_2$ score of 0–1, or where a more detailed stroke risk assessment is indicated, it is recommended to use a more comprehensive risk factor-based approach, incorporating other risk factors for thrombo-embolism (*Table 9* and *Figure 4*). This risk factor-based approach can also be expressed as a point-based scoring system, the CHA_2DS_2-VASc score[52] (see *Table 8* for definition). Many contemporary clinical trials of stroke prevention in AF have included some of these additional risk factors as part of their inclusion criteria.[57–59]

In all cases where OAC is considered, a discussion of the pros and cons with the patient, and an evaluation of the risk of bleeding complications, ability to safely sustain adjusted chronic anticoagulation, and patient preferences are necessary. In some patients, for example, women aged <65 years with no other risk factors

Table 9 Approach to thromboprophylaxis in patients with AF

Risk category	CHA_2DS_2-VASc score	Recommended antithrombotic therapy
One 'major' risk factor or ≥2 'clinically relevant non-major' risk factors	≥2	OAC[a]
One 'clinically relevant non-major' risk factor	1	Either OAC[a] or aspirin 75–325 mg daily. Preferred: OAC rather than aspirin.
No risk factors	0	Either aspirin 75–325 mg daily or no antithrombotic therapy. Preferred: no antithrombotic therapy rather than aspirin.

AF = atrial fibrillation; CHA_2DS_2-VASc = cardiac failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled)-vascular disease, age 65–74 and sex category (female); INR = international normalized ratio; OAC = oral anticoagulation, such as a vitamin K antagonist (VKA) adjusted to an intensity range of INR 2.0–3.0 (target 2.5).

[a]OAC, such as a VKA, adjusted to an intensity range of INR 2.0–3.0 (target 2.5). New OAC drugs, which may be viable alternatives to a VKA, may ultimately be considered. For example, should both doses of dabigatran etexilate receive regulatory approval for stroke prevention in AF, the recommendations for thromboprophylaxis could evolve as follows considering stroke and bleeding risk stratification:

(a) Where oral anticoagulation is appropriate therapy, dabigatran may be considered, as an alternative to adjusted dose VKA therapy. (i) If a patient is at low risk of bleeding (e.g. HAS-BLED score of 0–2; see Table 10 for HAS-BLED score definition), dabigatran 150 mg b.i.d. may be considered, in view of the improved efficacy in the prevention of stroke and systemic embolism (but lower rates of intracranial haemorrhage and similar rates of major bleeding events, when compared with warfarin); and (ii) If a patient has a measurable risk of bleeding (e.g. HAS-BLED score of ≥3), dabigatran etexilate 110 mg b.i.d. may be considered, in view of a similar efficacy in the prevention of stroke and systemic embolism (but lower rates of intracranial haemorrhage and of major bleeding compared with VKA). (b) In patients with one 'clinically relevant non-major' stroke risk factor, dabigatran 110 mg b.i.d. may be considered, in view of a similar efficacy with VKA in the prevention of stroke and systemic embolism but lower rates of intracranial haemorrhage and major bleeding compared with the VKA and (probably) aspirin. (c) Patients with no stroke risk factors (e.g. CHA_2DS_2-VASc = 0) are clearly at so low risk, either aspirin 75–325 mg daily or no antithrombotic therapy is recommended. Where possible, no antithrombotic therapy should be considered for such patients, rather than aspirin, given the limited data on the benefits of aspirin in this patient group (i.e., lone AF) and the potential for adverse effects, especially bleeding.

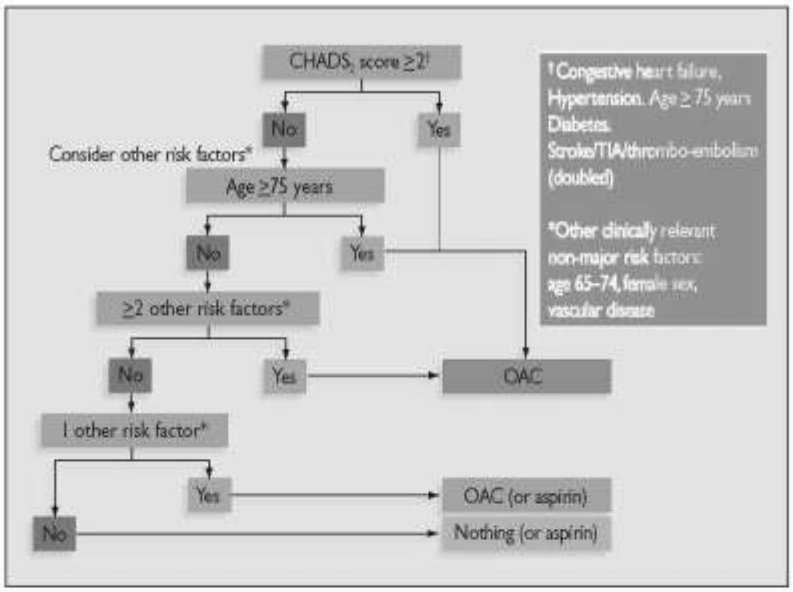

Figure 4 Clinical flowchart for the use of oral anticoagulation for stroke prevention in AF. AF = atrial fibrillation; OAC = oral anticoagulant; TIA = transient ischaemic attack. A full description of the $CHADS_2$ can be found on page 13.

(i.e. a CHA_2DS_2-VASc score of 1) may consider aspirin rather than OAC therapy.

4.1.4 Risk of bleeding

An assessment of bleeding risk should be part of the patient assessment before starting anticoagulation. Despite anticoagulation of more elderly patients with AF, rates of intracerebral haemorrhage are considerably lower than in the past, typically between 0.1 and 0.6% in contemporary reports. This may reflect lower anticoagulation intensity, more careful dose regulation, or better control of hypertension. Intracranial bleeding increases with INR values >3.5–4.0, and there is no increment in bleeding risk with INR values between 2.0 and 3.0 compared with lower INR levels.

Various bleeding risk scores have been validated for bleeding risk in anticoagulated patients, but all have different modalities in evaluating bleeding risks and categorization into low-, moderate-, and high-risk strata, usually for major bleeding risk. It is reasonable to assume that the major bleeding risk with aspirin is similar to that with VKA, especially in elderly individuals.[56] The fear of falls may be overstated, as a patient may need to fall ~300 times per year for the risk of intracranial haemorrhage to outweigh the benefit of OAC in stroke prevention.

Using a 'real-world' cohort of 3978 European subjects with AF from the EuroHeart Survey, a new simple bleeding risk score, **HAS-BLED** (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65), drugs/alcohol concomitantly), has been derived (*Table 10*).[60] It would seem reasonable to use the HAS-BLED score to assess bleeding risk in AF patients, whereby a score of ≥3 indicates 'high risk', and some caution and regular review of the patient is needed following the initiation of antithrombotic therapy, whether with VKA or aspirin.

Table 10 Clinical characteristics comprising the HAS-BLED bleeding risk score

Letter	Clinical characteristic[a]	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

[a]'Hypertension' is defined as systolic blood pressure >160 mmHg. 'Abnormal kidney function' is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥200 μmol/L. 'Abnormal liver function' is defined as chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin >2 x upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3 x upper limit normal, etc.). 'Bleeding' refers to previous bleeding history and/or predisposition to bleeding, e.g. bleeding diathesis, anaemia, etc. 'Labile INRs' refers to unstable/high INRs or poor time in therapeutic range (e.g. <60%). Drugs/alcohol use refers to concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs, or alcohol abuse, etc.
INR = international normalized ratio. Adapted from Pisters *et al.*[60]

4.1.5 Optimal international normalized ratio

Currently, the level of anticoagulation is expressed as the INR, which is derived from the ratio between the actual prothrombin time and that of a standardized control serum.

Based on achieving a balance between stroke risk with low INRs and an increasing bleeding risk with high INRs, an INR of 2.0–3.0 is the likely optimal range for prevention of stroke and systemic embolism in patients with non-valvular AF.

One of the many problems with anticoagulation with VKA is the high interindividual and intraindividual variation in INRs. VKAs also have significant drug, food, and alcohol interactions. On average, patients may stay within the intended INR range of 2.0–3.0 for 60–65% of the time in controlled clinical trials, but many 'real-life' studies suggest that this figure may be <50%. Indeed, having patients below the therapeutic range for <60% of the time may completely offset the benefit of VKA.

Whilst a lower target INR range (1.8–2.5) has been proposed for the elderly, this is not based on any large trial evidence base. Cohort studies suggest a 2-fold increase in stroke risk at INR 1.5–2.0 and, therefore, an INR <2.0 is not recommended.

The maintenance, safety, and effectiveness of INR within range can be influenced by the pharmacogenetics of VKA therapy, particularly the cytochrome P450 2C9 gene (*CYP2C9*) and the vitamin K epoxide reductase complex 1 gene (*VKORC1*). *CYP2C9* and *VKORC1* genotypes can influence warfarin dose requirements, whilst *CYP2C9* variant genotypes are associated with bleeding events. Systematic genotyping is not usually required, being unlikely to be cost-effective for typical patients with non-valvular AF, but it may be cost-effective in patients at high risk for haemorrhage who are starting VKA therapy.

Near-patient testing and self-monitoring of anticoagulation

Self-monitoring may be considered if preferred by a patient who is both physically and cognitively able to perform the self-monitoring test, and, if not, a designated carer could help. Appropriate training by a competent healthcare professional is important, and the patient should remain in contact with a named clinician. Self-monitoring devices also require adequate quality assurance and calibration.

4.1.6 Special situations

4.1.6.1 Paroxysmal atrial fibrillation

The stroke and thrombo-embolic risk in paroxysmal AF is less well defined, and such patients have represented the minority (usually <30%) in clinical trials of thromboprophylaxis. Stroke risk in paroxysmal AF is not different from that in persistent or permanent AF,[12] and is dependent upon the presence of stroke risk factors (see Section 4.1.1). Therefore, patients with paroxysmal AF should receive OAC according to their risk score.

4.1.6.2 Perioperative anticoagulation

Patients with AF who are anticoagulated will require temporary interruption of VKA treatment before surgery or an invasive procedure. Many surgeons require an INR <1.5 or even INR normalization before undertaking surgery. The risk of clinically significant bleeding, even among outpatients undergoing minor procedures, should be weighed against the risk of stroke and thrombo-embolism in an individual patient before the administration of bridging anticoagulant therapy.

If the VKA used is warfarin, which has a half-life of 36–42 h, treatment should be interrupted ~5 days before surgery (corresponding approximately to five half-lives of warfarin), to allow the INR to fall appropriately. If the VKA is phenprocoumon, treatment should be interrupted 10 days before surgery, based on the half-life of phenprocoumon of 96–140 h. It would be reasonable to undertake surgical or diagnostic procedures that carry a risk of bleeding in the presence of subtherapeutic anticoagulation for up to 48 h, without substituting heparin, given the low risk of thrombo-embolism in this period. VKA should be resumed at the 'usual' maintenance dose (without a loading dose) on the evening of (or the morning after) surgery, assuming there is adequate haemostasis. If there is a need for surgery or a procedure where the INR is still elevated (>1.5), the administration of low-dose oral vitamin K (1–2 mg) to normalize the INR may be considered.

In patients with a mechanical heart valve or AF at high risk for thrombo-embolism, management can be problematic. Such patients should be considered for 'bridging' anticoagulation with therapeutic doses of either LMWH or unfractionated heparin (UFH) during the temporary interruption of VKA therapy.

4.1.6.3 Stable vascular disease

Many anticoagulated AF patients have stable coronary or carotid artery disease and/or PAD, and common practice is to treat such patients with VKA plus one antiplatelet drug, usually aspirin. Adding aspirin to VKA does not reduce the risk of stroke or vascular events (including myocardial infarction), but substantially increases bleeding events.

4.1.6.4 Acute coronary syndrome and/or percutaneous coronary intervention

Current guidelines for ACS and/or percutaneous coronary intervention (PCI) recommend the use of aspirin–clopidogrel combination therapy after ACS, and a stent (4 weeks for a bare-metal stent, 6–12 months for a drug-eluting stent). VKA non-treatment is associated with an increase in mortality and major adverse cardiac events, with no significant difference in bleeding rates between VKA-treated and non-treated patients. The prevalence of major bleeding with triple therapy (VKA, aspirin, and clopidogrel) is 2.6–4.6% at 30 days, which increases to 7.4–10.3% at 12 months. Thus triple therapy seems to have an acceptable risk–benefit ratio provided it is kept short (e.g. 4 weeks) and the bleeding risk is low.

A systematic review and consensus document published by the ESC Working Group on Thrombosis, endorsed by the EHRA and the European Association of Percutaneous Cardiovascular Interventions (EAPCI), suggests that drug-eluting stents should be avoided and triple therapy (VKA, aspirin, and clopidogrel) used in the short term, followed by longer therapy with VKA plus a single antiplatelet drug (either clopidogrel or aspirin) (*Table 11*).[61] In patients with stable vascular disease (e.g. with no acute ischaemic events or PCI/stent procedure in the preceding year), VKA monotherapy should be used, and concomitant antiplatelet therapy should not be prescribed. Published data support the use of VKA for secondary prevention in patients with coronary artery disease, and VKA is at least as effective as aspirin.

Recommendations for prevention of thrombo-embolism

Recommendations	Class[a]	Level[b]	Ref.[c]
Antithrombotic therapy to prevent thrombo-embolism is recommended for all patients with AF, except in those at low risk (lone AF, aged <65 years, or with contraindications).	I	A	47, 48, 63
It is recommended that the selection of the antithrombotic therapy should be based upon the absolute risks of stroke/thrombo-embolism and bleeding, and the relative risk and benefit for a given patient.	I	A	47, 48, 50
The $CHADS_2$ [cardiac failure, hypertension, age, diabetes, stroke (doubled)] score is recommended as a simple initial (easily remembered) means of assessing stroke risk in non-valvular AF.	I	A	50
• For the patients with a $CHADS_2$ score of ≥2, chronic OAC therapy with a VKA is recommended in a dose-adjusted regimen to achieve an INR range of 2.0–3.0 (target 2.5), unless contraindicated.	I	A	47, 48, 54
For a more detailed or comprehensive stroke risk assessment in AF (e.g. with $CHADS_2$ scores 0–1), a risk factor-based approach is recommended, considering 'major' and 'clinically relevant non-major' stroke risk factors[d].	I	A	52
• Patients with 1 'major' or ≥ 2 'clinically relevant non-major' risk factors are high risk, and OAC therapy (e.g. with a VKA, dose adjusted to achieve the target intensity INR of 2.0–3.0) is recommended, unless contraindicated.	I	A	52
• Patients with one 'clinically relevant non-major' risk factor are at intermediate risk and antithrombotic therapy is recommended, either as:	I	A B	52
i. OAC therapy (e.g. VKA), or	I	A	52
ii. aspirin 75–325 mg daily	I	B	48
• Patients with no risk factors are at low risk (essentially patients aged <65 years with lone AF, with none of the risk factors) and the use of either aspirin 75–325 mg daily or no antithrombotic therapy is recommended.	I	B	52
For patients with AF who have mechanical heart valves, it is recommended that the target intensity of anticoagulation with a VKA should be based on the type and position of the prosthesis, maintaining an INR of at least 2.5 in the mitral position and at least 2.0 for an aortic valve.	I	B	63, 64
Antithrombotic therapy is recommended for patients with atrial flutter as for those with AF.	I	C	
The selection of antithrombotic therapy should be considered using the same criteria irrespective of the pattern of AF (i.e. paroxysmal, persistent, or permanent).	IIa	A	47, 48
Most patients with one 'clinically relevant non-major' risk factor should be considered for OAC therapy (e.g. with a VKA) rather than aspirin, based upon an assessment of the risk of bleeding complications, the ability to safely sustain adjusted chronic anticoagulation, and patient preferences.	IIa	A	47, 48
In patients with no risk factors who are at low risk (essentially patients aged <65 years with lone AF, with none of the risk factors), no antithrombotic therapy should be considered, rather than aspirin.	IIa	B	47, 48
Combination therapy with aspirin 75–100 mg plus clopidogrel 75 mg daily, should be considered for stroke prevention in patients for whom there is patient refusal to take OAC therapy or a clear contraindication to OAC therapy (e.g. inability to cope or continue with anticoagulation monitoring), where there is a low risk of bleeding.	IIa	B	58
Assessment of the risk of bleeding should be considered when prescribing antithrombotic therapy (whether with VKA or aspirin), and the bleeding risk with aspirin should be considered as being similar to VKA, especially in the elderly.	IIa	A	56, 60, 65
The HAS-BLED score [hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65), drugs/alcohol concomitantly] should be considered as a calculation to assess bleeding risk, whereby a score of ≥3 indicates 'high risk' and some caution and regular review is needed, following the initiation of antithrombotic therapy, whether with OAC or aspirin.	IIa	B	60
In patients with AF who do not have mechanical prosthetic heart valves or those who are not at high risk for thrombo-embolism who are undergoing surgical or diagnostic procedures that carry a risk of bleeding, the interruption of OAC (with subtherapeutic anticoagulation for up to 48 h) should be considered, without substituting heparin as 'bridging' anticoagulation therapy.	IIa	C	
In patients with a mechanical prosthetic heart valve or AF at high risk for thrombo-embolism who are undergoing surgical or diagnostic procedures, 'bridging' anticoagulation with therapeutic doses of either LMWH or unfractionated heparin during the temporary interruption of OAC therapy should be considered.	IIa	C	
Following surgical procedures, resumption of OAC therapy should be considered at the 'usual' maintenance dose (without a loading dose) on the evening of (or the next morning after) surgery, assuming there is adequate haemostasis.	IIa	B	
Re-evaluation at regular intervals of the benefits, risks, and need for antithrombotic therapy should be considered.	IIa	C	
In patients with AF presenting with acute stroke or TIA, management of uncontrolled hypertension should be considered before antithrombotic treatment is started, and cerebral imaging (computed tomography or magnetic resonance imaging) performed to exclude haemorrhage.	IIa	C	
In the absence of haemorrhage, OAC therapy should be considered ~2 weeks after stroke, but, in the presence of haemorrhage, anticoagulation should not be given.	IIa	C	
In the presence of a large cerebral infarction, delaying the initiation of anticoagulation should be considered, given the risk of haemorrhagic transformation.	IIa	C	

Continued

Continued

Recommendations	Class[a]	Level[b]	Ref.[c]
In patients with AF and an acute TIA, OAC therapy should be considered as soon as possible in the absence of cerebral infarction or haemorrhage.	IIa	C	
In some patients with one 'clinically relevant non-major' risk factor, e.g., female patients aged <65 years with no other risk factors, aspirin may be considered rather than OAC therapy.	IIb	C	
When surgical procedures require interruption of OAC therapy for longer than 48 h in high-risk patients, unfractionated heparin or subcutaneous LMWH may be considered.	IIb	C	
In patients with AF who sustain ischaemic stroke or systemic embolism during treatment with usual intensity anticoagulation with VKA (INR 2.0–3.0), raising the intensity of the anticoagulation to a maximum target INR of 3.0–3.5 may be considered, rather than adding an antiplatelet agent.	IIb	C	

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
[d]'Major' risk factors are those associated with the highest risk for stroke patients with AF are prior thrombo-embolism (stroke, TIA, or systemic embolism), age ≥75 years and rheumatic mitral stenosis. 'Clinically relevant non-major' risk factors include hypertension, heart failure, or moderate to severe LV dysfunction (ejection fraction 40% or less), and diabetes mellitus. (Level of evidence A). Other 'clinically relevant non-major' risk factors include female sex, age 65–74 years, and vascular disease (myocardial infarction, complex aortic plaque, carotid disease, peripheral artery disease). This risk factor-based approach for non-valvular AF can also be expressed by an acronym, CHA_2DS_2-VASc, [cardiac failure, hypertension, age ≥75 years (doubled), diabetes, stroke (doubled) vascular disease, age 65–74, and sex category (female)]. This scheme is based on a point system in which 2 points are assigned for a history of stroke or TIA, or age ≥75; and 1 point each is assigned for age 65–74 years, a history of hypertension, diabetes, recent cardiac failure, vascular disease (myocardial infarction, peripheral artery disease, complex aortic plaque), and female sex.
AF = atrial fibrillation; $CHADS_2$ = cardiac failure, hypertension, age, diabetes, stroke (doubled); INR = international normalized ratio; LMWH = low molecular weight heparin; OAC = oral anticoagulant; TIA = transient ischaemic attack; VKA = vitamin K antagonist.

Recommendations for antithrombotic therapy in AF and ACS/PCI

Recommendations	Class[a]	Level[b]	Ref.[c]
Following elective PCI in patients with AF with stable coronary artery disease, BMS should be considered, and drug-eluting stents avoided or strictly limited to those clinical and/or anatomical situations (e.g. long lesions, small vessels, diabetes, etc.), where a significant benefit is expected when compared with BMS.	IIa	C	
Following elective PCI, triple therapy (VKA, aspirin, clopidogrel) should be considered in the short term, followed by more long-term therapy (up to 1 year) with VKA plus clopidogrel 75 mg daily (or, alternatively, aspirin 75–100 mg daily, plus gastric protection with PPIs, H_2 antagonists, or antacids).	IIa	C	
Following elective PCI, clopidogrel should be considered in combination with VKA plus aspirin for a minimum of 1 month after implantation of a BMS, but longer with a drug-eluting stent (at least 3 months for a sirolimus-eluting stent and at least 6 months for a paclitaxel-eluting stent); following which VKA and clopidogrel 75 mg daily (or, alternatively, aspirin 75–100 mg daily, plus gastric protection with either PPIs, H_2 antagonists, or antacids) should be considered, if required.	IIa	C	
Following an ACS with or without PCI in patients with AF, triple therapy (VKA, aspirin, clopidogrel) should be considered in the short term (3–6 months), or longer in selected patients at low bleeding risk, followed by long-term therapy with VKA plus clopidogrel 75 mg daily (or, alternatively, aspirin 75–100 mg daily, plus gastric protection with PPIs, H_2 antagonists, or antacids).	IIa	C	
In anticoagulated patients at very high risk of thrombo-embolism, uninterrupted therapy with VKA as the preferred strategy and radial access used as the first choice even during therapeutic anticoagulation (INR 2–3).	IIa	C	
When VKA is given in combination with clopidogrel or low-dose aspirin, careful regulation of the anticoagulation dose intensity may be considered, with an INR range of 2.0–2.5.	IIb	C	
Following revascularization surgery in patients with AF, VKA plus a single antiplatelet drug may be considered in the initial 12 months, but this strategy has not been evaluated thoroughly and is associated with an increased risk of bleeding.	IIb	C	
In patients with stable vascular disease (e.g. >1 year, with no acute events), VKA monotherapy may be considered, and concomitant antiplatelet therapy should not be prescribed in the absence of a subsequent cardiovascular event.	IIb	C	

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
ACS = acute coronary syndrome; AF = atrial fibrillation; BMS = bare-metal stent; INR = international normalized ratio; PCI = percutaneous intervention; PPIs = proton pump inhibitors; VKA = vitamin K antagonist.

before cardioversion. Thromboprophylaxis is recommended for electrical and pharmacological cardioversion of AF >48 h. VKA should be continued for a minimum of 4 weeks after cardioversion because of risk of thrombo-embolism due to post-cardioversion left atrial/LAA dysfunction (so-called 'atrial stunning'). In patients with risk factors for stroke or AF recurrence, VKA treatment should be continued lifelong irrespective of apparent maintenance of sinus rhythm following cardioversion.

In patients with a definite AF onset <48 h, cardioversion can be performed expediently under the cover of UFH administered i.v. followed by infusion or subcutaneous LMWH. In patients with risk factors for stroke (see Section 4.1.1), OAC should be started after cardioversion and continued lifelong. UFH or LMWH should be continued until the INR is at the therapeutic level (2.0–3.0). No OAC is required in patients without thrombo-embolic risk factors.

In patients with AF >48 h with haemodynamic instability (angina, myocardial infarction, shock, or pulmonary oedema), immediate cardioversion should be performed, and UFH or LMWH should be administered before cardioversion. After cardioversion, OAC should be started and heparin should be continued until the INR is at the therapeutic level (2.0–3.0). Duration of OAC therapy (4 weeks or lifelong) will depend on the presence of risk factors for stroke.

4.1.7.1 Transoesophageal echocardiogram-guided cardioversion

The mandatory 3-week period of OAC prior to cardioversion can be shortened if TOE reveals no LA or LAA thrombus. TOE may not only show thrombus within the LAA or elsewhere in the left atrium, but may also identify spontaneous echo-contrast or complex aortic plaque. A TOE-guided cardioversion strategy is recommended as an alternative to 3-week pre-cardioversion anticoagulation if experienced staff and appropriate facilities are available, and, when early cardioversion is needed, pre-cardioversion OAC is not indicated due to patient choice or potential bleeding risks, or when there is a high risk of LA/LAA thrombus.[42]

If no LA thrombus is detected on TOE, UFH or LMWH should be started prior to cardioversion and continued thereafter until the target INR is achieved with OAC.

If TOE detects a thrombus in the left atrium or LAA, VKA (INR 2.0–3.0) treatment is required for at least 3 weeks and TOE should be repeated. If thrombus resolution is evident, cardioversion can be performed, and post-cardioversion OAC is continued lifelong. If thrombus is still evident, the rhythm control strategy may be changed to a rate control strategy, especially when AF-related symptoms are controlled, since there is a high risk of thrombo-embolism if cardioversion is performed (*Figure 5*).

4.1.8 Non-pharmacological methods to prevent stroke

The LAA is considered the main site of atrial thrombogenesis. Thus, occlusion of the LAA orifice may reduce the development of atrial thrombi and stroke in patients with AF. Of note, incomplete occlusion may occur in up to 40% of cases during follow-up, and such incomplete LAA occlusion is considered as a risk factor for the occurrence of stroke. In particular, patients with contraindications to chronic anticoagulation therapy might be considered as candidates for LAA occlusion. The PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic PROTECTion in Patients with Atrial Fibrillation) trial[62] randomized 707 eligible patients to percutaneous closure of the LAA (using a WATCHMAN device) and subsequent discontinuation of warfarin (intervention, $n = 463$), or to VKA treatment (INR range 2–3; control, $n = 244$). The primary efficacy event rate (a composite endpoint of stroke, cardiovascular death, and systemic embolism) of the WATCHMAN device was considered non-inferior to that of VKA (rate ratio 0.62; 95% credible interval 0.35–1.25). There was a higher rate of adverse safety events in the intervention group than in the control group, due mainly to periprocedural complications.

4.2 Rate and rhythm management

4.2.1 Acute rate and rhythm management

The acute management of patients with AF is driven by acute protection against thrombo-embolic events and acute improvement of cardiac function. The severity of AF-related symptoms should drive the decision for acute restoration of sinus rhythm (in severely compromised patients) or acute management of the ventricular rate (in most other patients).

4.2.1.1 Acute rate control

An inappropriate ventricular rate and irregularity of the rhythm can cause symptoms and severe haemodynamic distress in AF patients. Patients with a rapid ventricular response usually need acute control of their ventricular rate. In stable patients, this can be achieved by oral administration of β-blockers or non-dihydropyridine calcium channel antagonists. In severely compromised patients, i.v. verapamil or metoprolol can be very useful to slow atrioventricular node conduction rapidly. In the acute setting, the target ventricular rate should usually be 80–100 bpm. In selected patients, amiodarone may be used, especially in those with severely depressed LV function. AF with slow ventricular rates may respond to atropine (0.5–2 mg i.v.), but many patients with symptomatic bradyarrhythmia may require either urgent cardioversion or placement of a temporary pacemaker lead in the right ventricle.

Acute initiation of rate control therapy should usually be followed by a long-term rate control strategy; details of drugs and doses are given in Section 4.3.2.

4.2.1.2 Pharmacological cardioversion

Many episodes of AF terminate spontaneously within the first hours or days. If medically indicated (e.g. in severely compromised patients), in patients who remain symptomatic despite adequate rate control, or in patients in whom rhythm control therapy is pursued, pharmacological cardioversion of AF may be initiated by a bolus administration of an antiarrhythmic drug.

The conversion rate with antiarrhythmic drugs is lower than with DCC, but does not require conscious sedation or anaesthesia, and may facilitate the choice of antiarrhythmic drug therapy to prevent recurrent AF. Most patients who undergo pharmacological cardioversion require continuous medical supervision and ECG monitoring during the drug infusion and for a period afterwards (usually about half the drug elimination half-life) to detect proarrhythmic events such as ventricular proarrhythmia, sinus node

Recommendations for AF in acute coronary syndrome

Recommendations	Class[a]	Level[b]	Ref.[c]
DCC is recommended for patients with severe haemodynamic compromise or intractable ischaemia, or when adequate rate control cannot be achieved with pharmacological agents in patients with ACS and AF.	I	C	
Intravenous administration of amiodarone is recommended to slow a rapid ventricular response to AF in patients with ACS.	I	C	
Intravenous β-blockers are recommended to slow a rapid ventricular response to AF in patients with ACS.	I	C	
Intravenous administration of non-dihydropyridine calcium antagonists (verapamil, diltiazem) should be considered to slow a rapid ventricular response to AF in patients with ACS and no clinical signs of heart failure.	IIa	C	
Intravenous administration of digoxin may be considered to slow a rapid ventricular response in patients with ACS and AF associated with heart failure.	IIb	C	
Administration of flecainide or propafenone is not recommended in patients with AF in the setting of ACS.	III	B	124

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
AF = atrial fibrillation; ACS = acute coronary syndrome; DCC = direct current cardioversion.

myocardial oxygen demand. Digoxin and/or i.v. amiodarone is an appropriate alternative for patients with ACS associated with severe LV dysfunction and heart failure. For details on anticoagulation management of AF patients with ACS, as well as recommendations, see Section 4.1.

5.5 Diabetes mellitus

Diabetes and AF frequently co-exist because of associations such as coronary artery disease, hypertension, and LV dysfunction, and possibly as a result of autonomic dysfunction and ion channelopathy. Community studies demonstrate the presence of diabetes in 13% of patients with AF. Diabetes is an independent risk factor (RR 1.4–1.8) for incident AF. The presence of diabetes confers an adverse prognosis in AF with an increase in death and cardiovascular events. A comprehensive approach to risk management, including blood pressure control, statin therapy, etc., is desirable. The significance of diabetes is recognized in each of the major stroke risk stratification schemes, and antithrombotic therapy is recommended in diabetic subjects (see Section 4.1).

Recommendations for diabetes mellitus

Recommendation	Class[a]	Level[b]	Ref.[c]
AF patients with diabetes are recommended to undergo full assessment and management of all cardiovascular risk factors, including blood pressure, lipids, etc.	I	C	

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
AF = atrial fibrillation.

5.6 The elderly

The prevalence of AF is ~10% at the age of 80 years, and 18% in those aged ≥85 years. In the primary care setting, the Screening for AF in the Elderly (SAFE) study[43] found that opportunistic screening by the general practitioner, followed by an ECG when the pulse was irregular, is as effective as systematic screening with an ECG.

All patients aged >75 years with AF have an individual yearly risk of thrombo-embolism >4%, a level above which prescription of a VKA is preferred unless there is too high a bleeding risk. Of the individual components of the $CHADS_2$ score, age ≥75 carries a worse prognosis for stroke and mortality, over hypertension, diabetes, or heart failure (see the CHA_2DS_2VASc score in Section 4.1.1).

In general, VKA treatment is reasonably tolerated in the elderly.[5,6] Randomized controlled trials with VKA in AF have shown sustained reductions in ischaemic stroke and cardiovascular events, with only a slight increase in serious bleeds, resulting in a clear positive net effect of VKA in the elderly, compared with aspirin. In contrast, the beneficial effect of antiplatelet therapy on ischaemic stroke appears to decrease with age and was no longer apparent at the age of 77 years (see Section 4.1 for recommendations).

DCC is little used in the elderly because sinus rhythm is often difficult to maintain.[183] For rate control, β-blockers and non-

Recommendations for AF in the elderly

Recommendation	Class[a]	Level[b]	Ref.[c]
Every patient aged 65 years and older who attends their general practitioner should be screened by checking the pulse, followed by an ECG in case of irregularity.	I	B	43

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
ECG = electrocardiogram.

dihydropyridine calcium channel antagonists are effective. β-Blockers can be used cautiously for elderly patients with COPD.

An elderly patient with AF differs considerably from younger patients:

- Fragile, multiple co-morbidities, including cardiovascular and non-cardiac disease.
- High incidence and prevalence rates of AF.
- Higher thrombo-embolic and bleeding risks.
- Most often permanent and not recurrent (paroxysmal and/or persistent) AF.
- Atypical symptoms and complaints are common.
- Less sensitive to sympathetic effects on ventricular response rates in AF ('aged' conduction system).
- More sensitive to proarrhythmic effects of drugs (decreased renal and hepatic function).
- More often underdiagnosed than in younger patients.

5.7 Pregnancy

AF is rare during pregnancy in women without previously detected AF and without pre-existing heart disease. In patients with previously diagnosed AF, 52% experienced new episodes during pregnancy; in addition more foetal complications occur in those women who develop arrhythmias during pregnancy. AF during pregnancy is well tolerated in most patients without congenital or valvular disease.

Rate control drugs

β-Blockers cross the placenta and are associated with various adverse effects including intra-uterine growth retardation, neonatal respiratory depression, bradycardia, and hypoglycaemia, especially if treatment is initiated early in pregnancy (i.e. 12–24 weeks). In pregnancies complicated by hypertension and treated with propranolol, no congenital anomalies were seen,[184] but growth retardation has been reported. Atenolol given in the first trimester, but not later, has been associated with foetal growth retardation. A meta-analysis in patients with hypertension assessing risks of β-receptor blockers in pregnancy found a borderline increase in 'small for gestational age' infants. Digoxin crosses the placenta freely, and digitalis intoxication in the mother has been associated with foetal death. Limited data exist for verapamil and diltiazem, but oral use for rate control is generally safe.

Drugs for atrial fibrillation conversion

Flecainide has been used for converting foetal arrhythmias without negative effects. Amiodarone has demonstrated negative foetal effects when used in pregnant women, and should only be used in urgent situations. All drugs should, if possible, be avoided during the period of organogenesis in the first trimester of pregnancy.

Direct current cardioversion

Several case reports have demonstrated successful cardioversion of maternal AF, without harm to the foetus. Energy requirements in pregnant and non-pregnant women are similar.

Anticoagulation

VKA can be teratogenic and in many cases should be substituted with UFH or LMWH for the first trimester.[185] In one systematic review, foetal malformations associated with warfarin occurred in 6.4% of cases when given throughout the pregnancy, compared with no events when the treatment was changed to heparins between weeks 6 and 12. Warfarin crosses the placenta freely, and the foetus may be overdosed even when the mother is in the therapeutic INR range.

Recommendations for AF in pregnancy

Recommendations	Class[a]	Level[b]	Ref.[c]
DCC can be performed safely at all stages of pregnancy, and is recommended in patients who are haemodynamically unstable due to AF, and whenever the risk of ongoing AF is considered high, for the mother or for the foetus.	I	C	
Protection against thrombo-embolism is recommended throughout pregnancy in AF patients with a high thrombo-embolic risk; the choice of agent (heparin or warfarin) should be made according to the stage of pregnancy.	I	C	
Administration of an oral VKA is recommended from the second trimester, until 1 month before expected delivery.	I	B	185
Subcutaneous administration of LMWH in weight-adjusted therapeutic doses is recommended during the first trimester and during the last month of pregnancy. Alternatively, UFH may be given, to prolong the activated partial thromboplastin time to 1.5 times the control.	I	B	185
If rate control is necessary, a β-blocker or a non-dihydropyridine calcium channel antagonist should be considered. During the first trimester of pregnancy, the use of β-blockers must be weighed against the potential risk of negative foetal effects.	IIa	C	
In haemodynamically stable patients with structurally normal hearts, flecainide or ibutilide given intravenously to terminate recent-onset AF may be considered, if arrhythmia conversion is mandatory and DCC considered inappropriate.	IIb	C	
If rate control is indicated, and β-blockers or non-dihydropyridine calcium channel antagonists are contraindicated, digoxin may be considered.	IIb	C	

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
AF = atrial fibrillation; DCC = direct current cardioversion; LMWH = low molecular weight heparin; UFH = unfractionated heparin; VKA = vitamin K antagonist.

Hemorrhagic Complications of Anticoagulant and Thrombolytic Treatment*

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

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This article about hemorrhagic complications of anticoagulant and thrombolytic treatment is part of the Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Bleeding is the major complication of anticoagulant and fibrinolytic therapy. The criteria for defining the severity of bleeding vary considerably between studies, accounting in part for the variation in the rates of bleeding reported. The major determinants of vitamin K antagonist (VKA)-induced bleeding are the intensity of the anticoagulant effect, underlying patient characteristics, and the length of therapy. There is good evidence that VKA therapy, targeted international normalized ratio (INR) of 2.5 (range, 2.0-3.0), is associated with a lower risk of bleeding than therapy targeted at an INR > 3.0.

The risk of bleeding associated with IV unfractionated heparin (UFH) in patients with acute venous thromboembolism is < 3% in recent trials. This bleeding risk may increase with increasing heparin dosages and age (> 70 years). Low-molecular-weight heparin (LMWH) is associated with less major bleeding compared with UFH in acute venous thromboembolism. Higher doses of UFH and LMWH are associated with important increases in major bleeding in ischemic stroke. In ST-segment elevation myocardial infarction, addition of LMWH, hirudin, or its derivatives to thrombolytic therapy is associated with a small increase in the risk of major bleeding, whereas treatment with fondaparinux or UFH is associated with a lower risk of bleeding.

Thrombolytic therapy increases the risk of major bleeding 1.5-fold to threefold in patients with acute venous thromboembolism, ischemic stroke, or ST-elevation myocardial infarction.

(CHEST 2008; 133:257S–298S)

Key words: anticoagulant; bleeding; complications; thrombolysis

Abbreviations: APTT = activated partial thromboplastin time; ASSENT = Assessment of the Safety and Efficacy of a New Thrombolytic Agent; CI = confidence interval; COX = cyclooxygenase; DTI = direct thrombin inhibitor; DVT = deep vein thrombosis; FRIC = Fragmin in Unstable Coronary Artery Disease; FRISC = Fragmin during Instability in Coronary Artery Disease; GISSI = Gruppo Italiano per lo Studio della Sopravivenza nell Infarto Miocardico; GUSTO = Global Utilization of Streptokinase and tPA for Occluded Coronary Arteries; HIT = Hirudin for Improvement of Thrombolysis; ICH = intracranial hemorrhage; INR = international normalized ratio; ISIS = International Study on Infarct Survival; LMWH = low-molecular-weight heparin; NSAIDs = nonsteroidal antiinflammatory drugs; OASIS = Organization to Assess Strategies for Ischemic Syndromes; OR = odds ratio; PCI = percutaneous coronary intervention; PE = pulmonary embolism; RCT = randomized controlled trial; RR = relative risk; rt-PA = recombinant tissue plasminogen activator; SPAF = Stroke Prevention in Atrial Fibrillation; TEE = transesophageal echocardiography; TIMI = Thrombolysis in Myocardial Infarction; tPA = tissue plasminogen activator; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

The major complication of anticoagulant and thrombolytic therapy is bleeding. This review addresses the incidence of hemorrhage in patients receiving oral anticoagulants, heparin, or thrombolytic agents and the clinical and laboratory risk factors that predispose to bleeding. The focus is on

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Manuscript accepted December 20, 2007.

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DOI: 10.1378/chest.08-0674

major bleeding, intracranial bleeding, and fatal bleeding. Readers can find details of the method used to select relevant articles in the seven previous symposia of the American College of Chest Physicians.[1–7]

Studies varied in their definition of bleeding complications. Bleeding was generally classified as major if it was intracranial or retroperitoneal, if it led directly to death, or if it resulted in hospitalization or transfusion.[3,4] In some studies major bleeding only included "fatal or life-threatening bleeding." The component "bleeding requiring blood transfusions" was in some studies based on a minimum requirement of a certain number of units, in other studies defined as a certain reduction of the hemoglobin level. Studies of postoperative prophylaxis against thrombosis sometimes also used "bleeding index" of ≥ 2 as a criterion for major bleeding. The index is calculated as the number of units of packed blood cells or whole blood transfused + (prebleeding − postbleeding hemoglobin values in grams per deciliter). Section 1.3 discusses the classifications used for bleeding after thrombolytic therapy. The International Society on Thrombosis and Hemostasis issued in 2005 a recommendation for definition of major bleeding in studies on antihemostatic products (anticoagulant, antiplatelet or thrombolytic drugs) in nonsurgical studies.[8]

This chapter focuses on bleeding related to vitamin K antagonists (VKAs), heparins, thrombin inhibitors, and thrombolytic agents. The first section considers risk factors for bleeding in patients receiving any of these agents and the second reviews bleeding rates for specific clinical conditions. Weitz et al briefly discusses bleeding related to emerging antithrombotic agents in another article in this supplement. Table 1 describes the search and eligibility criteria used for our review.

1.0 Treatment and Risk of Bleeding

1.1 VKAs

The increase in risk of major bleeding in patients treated with VKA compared to controls is low in well-controlled patients. In the pooled analysis of the first five trials with warfarin in atrial fibrillation the annual rate of major bleeding was 1.0% in control patients vs 1.3% in patients treated with warfarin.[9] The annual rate of intracranial hemorrhage (ICH) was 0.1% in controls and 0.3% in patients treated with warfarin.[9] In a metaanalysis of trials with different durations of VKA therapy after venous thromboembolism (VTE), analyzing the period from the discontinuation of treatment in the short-duration arm until discontinuation of treatment in the long-duration arm, Ost et al[10] reported an annual rate of major bleeding of 0.6% among those who had stopped anticoagulation vs 1.1% among those continuing with anticoagulation. Go et al[11] followed a cohort of 11,526 patients with atrial fibrillation from the integrated health system in Northern California and found that the risk of major bleeding was similarly low in routine clinical care without a statistically significant difference in nonintracranial major hemorrhage between those treated and not treated with VKA. The annual rate of ICH was 0.23% without VKA and 0.46% with VKA ($p = 0.003$). In a prospective inception cohort of 2,745 patients with mixed indications for warfarin, Palareti et al[12] described a rate of fatal or major bleeding (including fatal events) of 1.35 per 100 patient years, and the rate of ICH was 0.4 per 100 patient-years. Higher annual rates of major hemorrhage in patients treated with warfarin in clinical routine practice have been reported, for example, 1.7% in a prospective cohort of 402 patients[13] and 3.4% in a retrospective study of 505 patients.[14]

In conclusion, in clinical studies characterized by careful monitoring of anticoagulant intensity, treatment with VKA increases the risk of major bleeding by 0.3–0.5%/yr and the risk of ICH by approximately 0.2%/yr compared to controls. In clinical routine practice the rates are less consistent.

Determinants of Bleeding: The major determinants of oral VKA-induced bleeding are the intensity of the anticoagulant effect, patient characteristics, the concomitant use of drugs that interfere with hemostasis, and the length of therapy.

1.1.1 Intensity of Anticoagulant Effect

Randomized controlled trials (RCTs) enrolling patients with deep vein thrombosis (DVT),[15] artificial heart valves,[16–21] ischemic stroke,[22] atrial fibrillation,[23–25] or antiphospholipid antibody syndrome with previous thromboembolism[26,27] have all reported a strong relationship between the targeted intensity of anticoagulant therapy and the risk of bleeding. The frequency of major bleeding in patients assigned to warfarin therapy at a targeted international normalized ratio (INR) of approximately 2.0–3.0 was less than half the frequency in patients assigned to warfarin therapy at a targeted INR > 3.0.[15,17,19,21] In a case-control study, the risk of ICH doubled for each increase of approximately 1 in the INR.[28]

The actual intensity of the treatment with VKA is strongly associated with the risk of bleeding. In multivariable analysis of risk factors for bleeding in an inception cohort, actual INR of at least 4.5 vs

1.1.4 Risk of Bleeding and the Length of Time Relative to When Anticoagulant Therapy Started

In an RCT comparing warfarin with aspirin plus clopidogrel in patients with atrial fibrillation, 2,627 patients who had been on VKA already before the study and were randomized to continue with warfarin had a risk of major bleeding of 2.02%/yr, whereas the 744 warfarin-naïve patients had a risk of 2.92%/yr ($p = 0.028$ for interaction with the study treatment).[100] Six studies reported higher frequencies of bleeding early in the course of therapy.[12,41,60,83,101–103] In one of these studies,[60] the frequency of major bleeding decreased from 3%/mo the first month of outpatient warfarin therapy to 0.8%/mo during the rest of the first year of therapy, and to 0.3%/mo thereafter. It is plausible that many patients prone to bleeding for various reasons will discontinue the VKA therapy during the early phase of treatment, and those remaining on therapy therefore are perceived to tolerate the treatment better.

1.1.5 Bleeding Prediction Models

Investigators have developed models for estimating the risk for major bleeding during VKA therapy. These models are based on the identification of independent risk factors for VKA-related bleeding, such as a history of stroke, history of GI bleeding, age ≥ 65 years, and higher levels of anticoagulation.[12,41,51,55,69,104,105] Such prediction rules can be useful in clinical practice because although physicians' estimates of risk for anticoagulant-related bleeding are reasonably accurate during hospitalization, they are inaccurate during long-term outpatient therapy.[55,104]

Three prediction models have been validated in outpatients treated with warfarin. Beyth et al[55] identified four independent risk factors for bleeding: age > 65 years, history of GI bleeding, history of stroke, and one or more of four specific comorbid conditions. This Outpatient Bleeding Risk Index was validated in another cohort of patients treated in another city; the cumulative incidence of major bleeding at 48 months was 53% in high-risk patients (three or four risk factors), 12% in middle-risk patients (one or two risk factors), and 3% in low-risk patients (no risk factors).

Kuijer et al[69] developed another prediction model based on age, sex, and the presence of malignancy. In patients classified at high, middle, and low risk, the frequency of major bleeding was 7%, 4%, and 1%, respectively, after 3 months of therapy in patients with VTE.

Shireman et al[106] included eight variables—age of at least 70 years, gender, remote bleeding, bleeding during the index hospitalization, alcohol or drug abuse, diabetes, anemia, and antiplatelet therapy—in a risk score model for patients with atrial fibrillation. Major bleeding events occurred in 5.4%, 2.0%, and 0.9%, respectively, for the groups classified as high, moderate, and low risk. Furthermore, Gage et al[107] developed a bleeding risk score (HEMORR2HAGES- in analogy with the stroke risk score CHADS2) for patients with atrial fibrillation, by adding 2 points for a prior bleed and 1 point each for hepatic or renal disease, ethanol abuse, malignancy, older (age > 75 years), reduced platelet count or function, hypertension (uncontrolled), anemia, genetic factors, excessive fall risk, and stroke. The rate of bleeding requiring hospitalization per 100 patient-years of warfarin was 1.9 for 0 points, 2.5 for 1, 5.3 for 2, 8.4 for 3, 10.4 for 4, and 12.3 for 5 points or more.

The Outpatient Bleeding Risk Index[55] has been prospectively validated by others.[108–110] These prediction models should not be the sole criterion of deciding whether to initiate therapy, but may be helpful in the conjunction with other assessments, such as the patients functional and cognitive state, likelihood of adherence to therapy, risk of thromboembolism, and personal preference.[111] Clinicians can use these prediction models to help weigh the risks and benefits of therapy with VKA, potentially adjusting the intensity, type, or length of therapy or the frequency of INR monitoring. Clinicians can review these assessments at the initiation of therapy and periodically reassess throughout the course of therapy. It remains unclear whether assessment for the polymorphisms of cytochrome P450 to help identify patients at risk for bleeding during initiation of VKA therapy will enhance bleeding prediction models.[73–75,112]

1.2 Heparins

Heparin is usually given in low doses by subcutaneous injection to prevent venous thrombosis (prophylactic heparin), in higher doses to treat patients with acute VTE or with acute coronary syndromes (therapeutic heparin), and in very high doses in patients during open-heart surgery. In this chapter, we will only discuss bleeding associated with therapeutic heparin. (See the article by Geerts et al for a discussion of bleeding associated with prophylactic heparin). Heparin has the potential to induce bleeding by inhibiting blood coagulation, by impairing platelet function,[113] and by increasing capillary permeability.[114] Heparin can also produce thrombocytopenia, but this is rarely an important cause of bleeding.

Antithrombotic Therapy in Atrial Fibrillation*

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

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This chapter about antithrombotic therapy in atrial fibrillation (AF) is part of the American College of Chest Physicians Evidence-Based Guidelines Clinical Practice Guidelines (8th Edition). Grade 1 recommendations indicate that most patients would make the same choice and Grade 2 suggests that individual patient's values may lead to different choices (for a full understanding of the grading see Guyatt et al, *CHEST* 2008; 133[suppl]:123S–131S). Among the key recommendations in this chapter are the following (all vitamin K antagonist [VKA] recommendations have a target international normalized ratio [INR] of 2.5; range 2.0–3.0, unless otherwise noted). In patients with AF, including those with paroxysmal AF, who have had a prior ischemic stroke, transient ischemic attack (TIA), or systemic embolism, we recommend long-term anticoagulation with an oral VKA, such as warfarin, because of the high risk of future ischemic stroke faced by this set of patients (Grade 1A). In patients with AF, including those with paroxysmal AF, who have two or more of the risk factors for future ischemic stroke listed immediately below, we recommend long-term anticoagulation with an oral VKA (Grade 1A). Two or more of the following risk factors apply: age > 75 years, history of hypertension, diabetes mellitus, moderately or severely impaired left ventricular systolic function and/or heart failure. In patients with AF, including those with paroxysmal AF, with only one of the risk factors listed immediately above, we recommend long-term antithrombotic therapy (Grade 1A), either as anticoagulation with an oral VKA, such as warfarin (Grade 1A), or as aspirin, at a dose of 75–325 mg/d (Grade 1B). In these patients at intermediate risk of ischemic stroke we suggest a VKA rather than aspirin (Grade 2A). In patients with AF, including those with paroxysmal AF, age ≤ 75 years and with none of the other risk factors listed above, we recommend long-term aspirin therapy at a dose of 75–325 mg/d (Grade 1B), because of their low risk of ischemic stroke. For patients with atrial flutter, we recommend that antithrombotic therapy decisions follow the same risk-based recommendations as for AF (Grade 1C). For patients with AF and mitral stenosis, we recommend long-term anticoagulation with an oral VKA (Grade 1B). For patients with AF and prosthetic heart valves we recommend long-term anticoagulation with an oral VKA at an intensity appropriate for the specific type of prosthesis (Grade 1B). See *CHEST* 2008; 133(suppl):593S–629S. For patients with AF of ≥ 48 h or of unknown duration for whom pharmacologic or electrical cardioversion is planned, we recommend anticoagulation with an oral VKA, such as warfarin, for 3 weeks before elective cardioversion and for at least 4 weeks after sinus rhythm has been maintained (Grade 1C). For patients with AF of ≥ 48 h or of unknown duration undergoing pharmacological or electrical cardioversion, we also recommend either immediate anticoagulation with unfractionated IV heparin, or low-molecular-weight heparin (LMWH), or at least 5 days of warfarin by the time of cardioversion (achieving an INR of 2.0–3.0) as well as a screening multiplane transesophageal echocardiography (TEE). If no thrombus is seen, cardioversion is successful, and sinus rhythm is maintained, we recommend anticoagulation for at least 4 weeks. If a thrombus is seen on TEE, then cardioversion should be postponed and anticoagulation should be continued indefinitely. We recommend obtaining a repeat TEE before attempting later cardioversion (Grade 1B addressing the equivalence of TEE-guided vs non–TEE-guided cardioversion). For patients with AF of known duration < 48 h, we suggest cardioversion without prolonged anticoagulation (Grade 2C). However, in patients without contraindications to anticoagulation, we suggest beginning IV heparin or LMWH at presentation (Grade 2C). *(CHEST 2008; 133:546S–592S)*

Key words: antithrombotic; atrial fibrillation; mitral stenosis; prophylaxis; stroke

Abbreviations: ACTIVE-W = Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events-Warfarin; ACUTE = Assessment of Cardioversion Using Transesophageal Echocardiography; AF = atrial fibrillation; AFASAK = Atrial Fibrillation Aspirin and Anticoagulation; AFFIRM = Atrial Fibrillation Follow-up Investigation of Rhythm Management; AFI = Atrial Fibrillation Investigators; AMADEUS = Atrial Fibrillation Trial of Monitored Adjusted Dose Vitamin-K Antagonist, Comparing Efficacy and Safety With Unadjusted SanOrg34006/idraparinux; ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation; BAATAF = Boston Area Anticoagulation Trial for Atrial Fibrillation; BAFTA = Birmingham Atrial Fibrillation Treatment of the Aged; CABG = coronary artery bypass grafting surgery; CAD = coronary artery disease; CAFA = Canadian Atrial Fibrillation Anticoagulation; $CHADS_2$ = Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke (doubled) risk scoring system; CI = confidence interval; DC = direct current; DVT = deep venous thrombosis; EAFT = European Atrial Fibrillation Trial; ESPS = European Stroke Prevention Study; FFAACS = Fluindione, Fibrillation Auriculaire, Aspirin et Contraste Spontane trial; ICD-9 = International Statistical Classification of Diseases and Related Health Problems; ICH = intracranial hemorrhage; INR = international normalized ratio; ISCOAT = Italian Study on Complications of Oral Anticoagulant Therapy; ITT = intention-to-treat; JAST = Japan Atrial Fibrillation Stroke Trial; LAA = left atrial appendage; LMWH = low-molecular-weight heparin; LV = left ventricular; NASPEAF = National Study for Prevention of Embolism in Atrial Fibrillation; NICE = National Institute for Health and Clinical Excellence; NNT = number needed to treat for 1 year; NSR = normal sinus rhythm; NVAF = nonvalvular atrial fibrillation; OAC = oral anticoagulation; OT = on-treatment; PAF = paroxysmal atrial fibrillation; PATAF = Primary Prevention of Arterial Thromboembolism in Nonrheumatic AF in Primary Care Trial; PCI = percutaneous coronary intervention; PE = pulmonary embolism; PIAF = Pharmacologic Intervention in Atrial Fibrillation Trial; PTR = prothrombin time ratio; PTT = partial thromboplastin time; PY = person-years; RACE = Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation Study; RCT = randomized clinical trial; RR = risk reduction; RRR = relative risk reduction; SAFT = Swedish Atrial Fibrillation Trial; SIFA = Studio Italiano Fibrillazione Atriale; SPAF = Stroke Prevention in Atrial Fibrillation; SPINAF = Stroke Prevention in Nonrheumatic Atrial Fibrillation; SPIRIT = Stroke Prevention In Reversible Ischemia Trial; SPORTIF = Stroke Prevention Using an Oral Thrombin Inhibitor in Patients With AF; TEE = transesophageal echocardiography; TIA = transient ischemic attack; VKA = vitamin K antagonist; WASPO = Warfarin vs Aspirin for Stroke Prevention in Octogenarians With AF

Summary of Recommendations

1.1 AF

1.1.1. In patients with AF, including those with paroxysmal AF, who have had a prior ischemic stroke, TIA, or systemic embolism, we recommend long-term anticoagulation with an oral vitamin K antagonist, such as warfarin, targeted at an INR of 2.5 (range, 2.0 to 3.0) because of the high risk of future ischemic stroke faced by this set of patients (Grade 1A). **Timing of the initiation of VKA therapy after an acute ischemic stroke involves balancing the risk of hemorrhagic conversion with short-term risk of recurrent ischemic stroke and is addressed in the chapter by Albers et al in this supplement.**

1.1.2. In patients with AF, including those with paroxysmal AF, who have two or more of the following risk factors for future ischemic stroke, we recommend long-term anticoagulation with an oral VKA, such as warfarin, targeted at an INR of 2.5 (range, 2.0 to 3.0) because of the increased risk of future ischemic stroke faced by this set of patients (Grade 1A). **Two or more of the following risk factors apply: (1) age > 75 years; (2) history of hypertension; (3) diabetes mellitus; and (4) moderately or severely impaired left ventricular systolic function and/or heart failure.**

Remark: Recommendations 1.1.1 and 1.1.2 correspond to a recommendation of oral VKA therapy for individuals with a score ≥ 2 using the $CHADS_2$ classification. For these and all other recommendations of long-term therapy in this chapter, *long-term* means lifelong unless a contraindication emerges.

1.1.3. In patients with AF, including those with paroxysmal AF, with only one of the risk factors

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Drs. Go and Singer acknowledge partial support for their efforts from US Public Health Service research grant AG15478 from the National Institute on Aging, National Institutes of Health. Dr. Singer also received support from the Eliot B. and Edith C. Shoolman Fund of the Massachusetts General Hospital. Dr. Fang acknowledges partial support for her efforts from a Hartford Geriatrics Health Outcomes Research Scholar Award from the American Geriatrics Society Foundation for Health in Aging, as well as a Paul B. Beeson career development award (The National Institute on Aging, John A. Hartford Foundation, The Atlantic Philanthropies, and the Starr Foundation).

Manuscript accepted December 20, 2007.

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DOI: 10.1378/chest.08-0678

listed below, we recommend long-term antithrombotic therapy (Grade 1A), **either as anticoagulation with an oral VKA, such as warfarin, targeted at an INR of 2.5 (range, 2.0 to 3.0)** (Grade 1A), **or as aspirin, at a dose of 75 to 325 mg/d** (Grade 1B). **For these patients at intermediate risk of ischemic stroke, we suggest a VKA rather than aspirin** (Grade 2A). **This set of patients with AF is defined by having one of the following risk factors: (1) age > 75 years; (2) history of hypertension; (3) diabetes mellitus; or (4) moderately or severely impaired left ventricular systolic function and/or heart failure.**

1.1.4. In patients with AF, including those with paroxysmal AF, aged ≤ 75 years and with none of the other risk factors listed above, we recommend long-term aspirin therapy at a dose of 75 to 325 mg/d (Grade 1B) **because of their low risk of ischemic stroke.**

Underlying values and preferences: Anticoagulation with oral VKAs, such as warfarin, has far greater efficacy than aspirin in preventing stroke, and particularly in preventing severe ischemic stroke, in AF. We recommend the option of aspirin therapy for lower risk groups in 1.1.3 and 1.1.4, above, estimating the absolute expected benefit of anticoagulant therapy may not be worth the increased hemorrhagic risk and burden of anticoagulation. Individual lower-risk patients may rationally choose anticoagulation over aspirin therapy to gain greater protection against ischemic stroke if they value protection against stroke much more highly than reducing risk of hemorrhage and the burden of managing anticoagulation. Our recommendations assume that the patient is not at high risk for bleeding and that good control of anticoagulation will occur.

Remarks: These recommendations apply to patients with persistent or paroxysmal AF and not to patients with a single brief episode of AF due to a reversible cause, such as an acute pulmonary infection. The optimal dose of aspirin for patients with AF is unclear. The largest effect of aspirin was seen in the first Stroke Prevention in Atrial Fibrillation (SPAF I) trial, which used aspirin at 325 mg/d.[1] However, generalizing from trials of aspirin for all antithrombotic indications and from physiologic studies, we feel the best balance of efficacy and safety is achieved at low doses of aspirin, *ie*, 75 to 100 mg/d (see chapter on "Antiplatelet Drugs" in this supplement).[2]

1.2 Atrial Flutter

1.2. For patients with atrial flutter, we recommend that antithrombotic therapy decisions follow the same risk-based recommendations as for AF (Grade 1C).

1.3 Valvular Heart Disease and AF

1.3.1. For patients with AF and mitral stenosis, we recommend long-term anticoagulation with an oral VKA, such as warfarin (target INR, 2.5; range, 2.0 to 3.0) [Grade 1B].

1.3.2. For patients with AF and prosthetic heart valves we recommend long-term anticoagulation with an oral VKA, such as warfarin, at an intensity appropriate for the specific type of prosthesis (Grade 1B). **See chapter on "Valvular and Structural Heart Disease" in this supplement.**

1.4 AF Following Cardiac Surgery

1.4. For patients with AF occurring shortly after open-heart surgery and lasting ≥ 48 h, we suggest anticoagulation with an oral VKA, such as warfarin, if bleeding risks are acceptable (Grade 2C). **The target INR is 2.5 (range, 2.0 to 3.0). We suggest continuing anticoagulation for 4 weeks following reversion to and maintenance of normal sinus rhythm (NSR), particularly if patients have risk factors for thromboembolism** (Grade 2C).

2.1 Anticoagulation for Elective Cardioversion of AF

2.1.1. For patients with AF of ≥ 48 h or of unknown duration for whom pharmacologic or electrical cardioversion is planned, we recommend anticoagulation with an oral VKA, such as warfarin, at a target INR of 2.5 (range, 2.0 to 3.0) for 3 weeks before elective cardioversion and for at least 4 weeks after sinus rhythm has been maintained (Grade 1C).

Remark: This recommendation applies to all patients with AF, including those whose risk factor status would otherwise indicate a low risk for stroke. Patients with risk factors for thromboembolism should continue anticoagulation beyond 4 weeks unless there is convincing evidence that sinus rhythm is maintained. For patients with recurrent episodes of AF, Recommendations 1.1.1, 1.1.2, 1.1.3, and 1.1.4 apply.

2.1.2. For patients with AF of ≥ 48 h or of unknown duration who are undergoing pharmacologic or electrical cardioversion, we recommend either immediate anticoagulation with IV unfractionated heparin (target partial thromboplastin time [PTT], 60 s; range, 50 to 70 s), or LMWH (at full deep venous thrombosis [DVT] treatment doses), or at least 5 days of warfarin (target INR of 2.5; range, 2.0 to 3.0) at the time of cardioversion and performance of a screening multiplane TEE. If no thrombus is seen, cardioversion is successful, and sinus rhythm is

maintained, we recommend anticoagulation (target INR, 2.5; range, 2.0 to 3.0) for at least 4 weeks. If a thrombus is seen on TEE, then cardioversion should be postponed and anticoagulation should be continued indefinitely. We recommend obtaining a repeat TEE before attempting later cardioversion (all Grade 1B addressing the equivalence of TEE-guided vs non-TEE–guided cardioversion; see recommendation 2.1.1, above).

Remark: The utility of the conventional and TEE-guided approaches is likely comparable. This recommendation applies to all patients with AF, including those whose risk factor status would otherwise indicate a low risk for stroke. Patients with risk factors for thromboembolism should continue anticoagulation beyond 4 weeks unless there is convincing evidence that sinus rhythm is maintained. For patients with recurrent episodes of AF, Recommendations 1.1.1, 1.1.2, 1.1.3, and 1.1.4 apply.

2.1.3. For patients with AF of known duration < 48 h, we suggest that cardioversion be performed without prolonged anticoagulation (Grade 2C). **However, in patients without contraindications to anticoagulation, we suggest beginning IV heparin (target PTT, 60 s; range, 50 to 70 s) or LMWH (at full DVT treatment doses) at presentation** (Grade 2C).

Remark: For patients with risk factors for stroke, it is particularly important to be confident that the duration of AF is < 48 h. In such patients with risk factors, a TEE-guided approach (see 2.12, above) is a reasonable alternative strategy. Postcardioversion anticoagulation is based on whether the patient has experienced more than one episode of AF and on his or her risk factor status. For patients with recurrent episodes of AF, Recommendations 1.1.1, 1.1.2, 1.1.3, and 1.1.4 apply.

2.1.4. For emergency cardioversion in the hemodynamically unstable patient, we suggest that IV unfractionated heparin (target PTT of 60 s with a target range of 50 to 70 s) or low-molecular-weight heparin (at full DVT treatment doses) be started as soon as possible, followed by at least 4 weeks of anticoagulation with an oral VKA, such as warfarin (target INR of 2.5; range, 2.0 to 3.0) if cardioversion is successful and sinus rhythm is maintained (Grade 2C).

Remark: Long-term continuation of anticoagulation is based on whether the patient has experienced more than one episode of AF and on his or her risk factor status. For patients experiencing more than one episode of AF, Recommendations 1.1.1, 1.1.2, 1.1.3, and 1.1.4 apply.

2.1.5. For cardioversion of patients with atrial flutter, we suggest use of anticoagulants in the same way as for cardioversion of patients with AF (Grade 2C).

Atrial fibrillation (AF) is the most common significant cardiac rhythm disorder and is an important independent risk factor for ischemic stroke. AF affects nearly two and a half million people in the United States.[3,4] Its prevalence is strongly dependent on age. AF is uncommon among individuals < 50 years old. Its frequency rises rapidly from the sixth decade onward, reaching a prevalence of nearly 10% in those > 80 years old.[3–5] Analyses from the Framingham Study indicate that the lifetime risk of AF for an individual age 40 years is about 25%.[9] The occurrence of AF may be even higher given the potential for AF to remain undiagnosed. The median age of patients with AF is approximately 72 years. AF is more prevalent in men than in women at all ages.[3,5–7] Because of the projected aging of the United States population, the number of individuals with AF is likely to increase substantially in coming decades.[3,10]

The rate of ischemic stroke among patients with AF included in primary prevention clinical trials and not treated with antithrombotic therapy averaged 4.5% per year, similar to estimates of stroke risk from the Framingham Heart Study.[11,12] AF increases the risk of stroke 4–5-fold, across all age groups.[12] As a consequence of its increasing prevalence, AF becomes an increasingly important cause of stroke with advancing age. In the Framingham Study, the percentage risk of stroke attributable to AF rose from 1.5% in the age group 50 to 59 years to 23.5% in the age group 80 to 89 years.[13] Overall, AF accounts for about 15% of all strokes in the United States.

Stroke in AF appears to be predominantly the result of cardiogenic embolism. This is based on clinical assessment, by extension of operative findings of intracardiac thrombus in patients with rheumatic mitral valve disease, and more recently, by transesophageal echocardiography (TEE) imaging of thrombus in the left atrium of patients with AF, mainly in the left atrial appendage.[14–16] Trials of anticoagulant and antiplatelet medications to prevent stroke in AF were conducted to interrupt the presumed cardioembolic mechanism of stroke in AF.

This chapter deals primarily with stroke prevention in nonvalvular AF when the dysrhythmia is not associated with rheumatic mitral valve disease or prosthetic heart valves. At least one recent trial studied patients with rheumatic mitral valve disease and its findings were quite similar to results in patients with nonrheumatic heart disease.[17] Further discussion of management of antithrombotic therapy in AF patients with valvular heart disease and prosthetic heart valves is provided in the chapter by

Table 5—*Patient-Level Metaanalyses of the Efficacy of Antithrombotic Therapies in AF From Pooled Data of Randomized Trials (Section 1.1.1)*

Treatment Comparisons	RRR* (95% CI)
Adjusted-dose OAC vs no antithrombotic therapy[11]	68% (50–79)
Aspirin vs no antithrombotic therapy[106]	21% (0–38)
Adjusted-dose OAC vs ASA[40]	52% (37–63)

*Outcome is ischemic stroke. Note that trials involved in each analysis are not identical.

of strokes in the warfarin arms of the trials occurred among patients who had either stopped warfarin or had an international normalized ratio (INR) or prothrombin time ratio (PTR) below the target range. In the European Atrial Fibrillation Trial (EAFT) that enrolled only patients with a transient ischemic attack (TIA) or minor stroke within the previous 3 months, the relative risk reduction was virtually identical, although the absolute risk of stroke was higher, reflecting the high risk status of EAFT patients; the annual rate of stroke in control patients was 12% vs 4% in anticoagulated patients (risk reduction 66%; 95% CI, 43 to 80%; $p < 0.001$; NNT = 13).[20,21] In five of the studies (EAFT, the secondary prevention trial, was not included in this analysis), anticoagulation lowered the all-cause mortality rate by 33% (95% CI, 9 to 51%) and lowered the combined outcome of stroke, systemic embolism, and death by 48% (95% CI, 34 to 60%).[11] Overall, the evidence for the efficacy of anticoagulation in AF is strong, consistent, and based on high quality studies.

In these trials, particularly those with INR targets of 3.0 or less, anticoagulation proved adequately safe. There was no statistically significant increase in major bleeding events in patients treated with adjusted-dose anticoagulation in any of the randomized trials compared with control subjects (Table 4). The pooled analysis of the first five primary prevention trials reported an annual rate of major bleeding of 1.0% in control patients compared to 1.3% in warfarin-treated patients. These included an annual rate of intracranial hemorrhage (ICH) of 0.1% in controls compared to 0.3% in warfarin-users.[11]

Description of Individual Studies: There have been six randomized trials comparing oral anticoagulation (OAC) with no antithrombotic treatment in patients with AF.[1,19,20,22–24] Five were primary prevention studies in which most subjects had not had a prior stroke, TIA, or systemic embolic event and the sixth was the secondary prevention EAFT study (Tables 2–4).

These trials had notable differences in study design. First, warfarin was the oral anticoagulant used in all these trials except for EAFT which used phenprocoumon or acenocoumarol.[20] Second, the target intensity of anticoagulation differed. The Canadian AF (CAFA) trial, the AF, Aspirin, and Anticoagulation (AFASAK) trial, and EAFT used INR levels, with INR targets of 2.0 to 3.0, 2.8 to 4.2, and 2.5 to 4.0, respectively.[19,20,22] The United States-based trials used the less standardized prothrombin time ratios (PTRs): the Boston Area Anticoagulation Trial for AF (BAATAF)[23] and the Stroke Prevention in AF (SPINAF)[24] trial had a target of PTR 1.2 to 1.5, while the first Stroke Prevention in AF (SPAF I)[1] used PTR of 1.3 to 1.8. The INR equivalent of these PTR targets in the American trials has been roughly estimated as an INR of 1.4 to 2.8 for BAATAF and SPINAF and an INR of 2.0 to 4.5 for SPAF I (Table 2).[23–25] Third, SPINAF and CAFA were blinded trials while the others were open-label trials. Fourth, in BAATAF the control group was not given anticoagulation but could choose to take aspirin (46% of the patient-years in the control group were contributed by patients who were taking aspirin regularly). Finally, the definition of primary outcome and hemorrhagic outcomes varied among the trials (Tables 2, 4). All studies considered ischemic stroke a primary event, and some also included other vascular events as primary events. The definition of major bleeding varied slightly among studies. In general, bleeding was classified as major if it involved transfusion, hospitalization, or death, permanent disability, or a critical anatomic location (*eg*, intracranial). The criteria used by the BAATAF investigators were different: intracranial bleeding, fatal bleeding, or bleeding leading to transfusion of ≥ 4 U of blood within 48 h.

1.1.2 Risk of ICH During Anticoagulation

A general discussion of the hemorrhagic complications of anticoagulants is covered in the chapter by Schulman et al in this supplement. We focus on ICH in this chapter because it is the only hemorrhagic complication that regularly produces deficits as great or greater than those produced by the ischemic strokes antithrombotic therapy is designed to prevent. ICHs include both intraparenchymal hemorrhages, *ie*, hemorrhagic strokes, and nonintraparenchymal ICHs, primarily subdural bleeds. While the benefits of VKA are often balanced against the risks of aggregate major hemorrhage induced by such therapy, the preponderance of fatal or disabling hemorrhagic events on VKA are due to ICH. Ninety percent of the fatalities due to hemorrhage on VKA and nearly all persisting disability are due to intracranial, as opposed to extracranial, hemorrhage.[26]

Major extracranial hemorrhages, primarily GI hemorrhages, are certainly not trivial events, but their lasting impact is generally minor compared to ICHs. Overall, the rates of ICH were reassuringly low in the initial AF randomized trials comparing anticoagulation with control or placebo (Table 4). However, a substantially higher rate of ICH was observed in the SPAF II study, with seven ICHs observed among 385 patients > 75 years for an annualized rate of 1.8%, compared with 0.8% in patients on aspirin.[25] In contrast, in the pooled primary prevention trials the rate of ICH was only 0.3% per year among those > 75 years.[27] In the secondary prevention EAFT study, the average age at entry was 71 years and no ICHs were diagnosed, although a CT scan was not done in all patients with symptoms of stroke.[20] In the high-risk trial of SPAF III, (mean age, 71 years; mean INR, 2.4), the rate of ICH was 0.5% per year compared to a rate of 0.9% per year in the aspirin plus low-dose warfarin arm.[28] The AFASAK 2 study reported two ICHs in the INR 2.0 to 3.0 arm for an annual rate of 0.6%, compared to 0 to 0.3% per year rates in the three other treatment arms during a shorter period of follow-up.[29] In the more recent SPORTIF III and V trials, a low annual incidence of ICHs (0.2%) was observed among the 3665 patients randomized to warfarin, of whom 39% were > 75 years old.[30,31] Another recent trial, the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events-Warfarin (ACTIVE-W) study, observed somewhat more ICHs among patients randomized to oral anticoagulants compared to those taking aspirin plus clopidogrel (21 vs 11, $p = 0.08$), but again, overall incidence was low (0.36 vs 0.12% per year for anticoagulants and clopidogrel/aspirin, respectively).[32]

The reasons for the high ICH rate in the SPAF II trial in patients > 75 years old as compared with the other studies are not entirely clear, although the patients were older than in any other AF trial, and the target anticoagulation intensity was high (INR, 2.0 to 4.5).[33] The importance of high INR levels in increasing the risk of VKA was further reinforced by the SPIRIT trial, a non-AF secondary stroke prevention trial which used an INR target intensity of 3.0 to 4.5.[34] In SPIRIT, the annual rate of ICH was > 3% among patients treated with anticoagulants. This rate was strongly related to INR values, particularly INR > 4.0.[35] In cohort studies of older patients anticoagulated for AF, observed rates of ICH have not been as high as in the SPAF II or SPIRIT trials.[36–38]

While ICHs are crucial events, they occurred at such a low rate that the individual and the aggregated AF trials observed only a small number of such events.[11] As a consequence, these randomized trials have not been a rich source of information on the determinants of ICH. By contrast, large observational studies can accumulate informative numbers of ICHs on anticoagulation. These studies reveal a dramatic increase in the risk of ICH at INR values > 4.0, though most ICHs among patients treated with anticoagulants occur at INR values < 4.0. In addition, the risk of ICH appears to rise with patient age and in those with prior ischemic stroke.[39]

1.1.3 Efficacy of Aspirin vs Placebo

Results of Systematic Reviews of Aspirin vs No Aspirin: In contrast to the consistent evidence demonstrating the marked efficacy of VKA therapy in preventing stroke in AF, the trials of aspirin suggest little, if any, such efficacy. Five older and two more recent studies, described below, compared aspirin with control. An individual patient-level metaanalysis pooling data from the AFASAK 1, SPAF I, and EAFT trials resulted in an estimated relative risk reduction of 21% compared to placebo.[40] The associated confidence interval ranged from 0 to 38% RRR, indicating results at the cusp of statistical significance (Table 5). This metaanalysis did not account for the marked heterogeneity of effect of aspirin seen in the two component trials of SPAF I (discussed below). Accounting for such heterogeneity would have resulted in the lower bound of the confidence interval extending well into the negative range of efficacy.

In addition to the pooled patient-level analysis described above, there have been other study-level metaanalyses of aspirin vs control in patients with AF. The first found a 22% (95% CI, 2 to 38%) reduction in the risk of stroke.[41] This has been updated recently.[42] A second metaanalysis concluded that aspirin results were heterogeneous because of disparate results in the two cohorts of the SPAF I trial. The random effects analysis employed produced a similar point estimate but much wider confidence intervals: RRR = 24% (− 33% to + 66%).[43]

Description of Individual Studies: Four trials were placebo-controlled, and three studies had a nontreatment control. The dose of aspirin varied between 50 and 325 mg/d. Three of the original trials of OAC with VKAs included aspirin arms, AFASAK 1 (75 mg/d),[22] SPAF I (325 mg/d),[1] and EAFT (300 mg/d).[20] Aspirin was not statistically significantly more effective than placebo in AFASAK 1 and EAFT. Evidence of aspirin efficacy comes mainly from the SPAF I trial, in which a statistically significant 42% relative risk reduction was reported. SPAF I was composed of two separately randomized cohorts, one consisting of individuals

orrhagic outcome events leading to imprecise estimates of event rates.[92–98] Among survivors of ischemic stroke with AF, warfarin was more effective than aspirin for reducing recurrent stroke, and recurrent stroke rates were lower during periods on vs off warfarin.[99,100] In two studies of hospitalized patients with nonvalvular AF, the risk of stroke or transient ischemic attack was lower in patients discharged on warfarin than in those given no antithrombotic therapy (adjusted relative risks 0.76 and 0.31) and thromboembolic rates were lower with warfarin than aspirin.[93,95] In selected cohorts of patients with AF treated with anticoagulation, the risk of stroke varied from 1.3% annually to 2.0 per 100 person-years.[97,98] In a large study from Denmark involving 5124 persons with AF based on hospital discharge or outpatient diagnoses between 1991 and 1998, investigators observed stroke rates of 3% per year overall, with a protective effect of warfarin in men (adjusted relative risk, 0.6; 95 CI, 0.4 to 1.0) but not in women.[101] In these observational studies, annual rates of ICH on anticoagulation were relatively low (range, 0 to 0.8%) and comparable to rates in prior randomized trials, although confidence limits were wide.[92,94,96,100] More recent studies from Italy, England, and United States Medicare populations all find reduced rates of stroke among AF patients treated with VKAs.[8,102–104] As with most studies of the effect of antithrombotic therapy for AF in usual clinical care, these studies used database coding of outcome events without clinical validation and inferred use of warfarin through indirect methods (*eg*, via coding for INR tests). Similarly, assembly of AF patients was typically based on International Statistical Classification of Diseases and Related Health Problems (ICD-9) codes without validation and several studies assembled their cohorts from hospitalized patients. These methodologic limitations probably bias the estimates of VKA effectiveness to the null and may also identify patients with somewhat higher risk of stroke than the typical AF patient.

The AnTicoagulation and Risk Factors In Atrial Fibrillation (ATRIA) Study assembled a community-based cohort of 13,559 ambulatory adults with nonvalvular AF diagnosed in the outpatient setting.[81] Use of warfarin was established by prescription records and INR testing and test results. All ICD-9 identified events were validated by clinical record review. During the first follow-up of the entire cohort 598 validated thromboembolic events were observed and the rate of thromboembolism was significantly less on adjusted-dose warfarin compared to no warfarin therapy (including aspirin and no antithrombotic therapy): (1.36% vs 2.53% per year, respectively, $p < 0.001$), with a 49% (95% CI, 39 to 57%) adjusted risk reduction. Intracranial hemorrhage rates were low on or off warfarin (0.51% vs 0.33% per year, respectively), although warfarin was associated with an increased risk of ICH (adjusted RR, 1.57; 95% CI, 1.10 to 2.26). In the subgroup of 11,526 cohort members without potential contraindications to anticoagulation at study entry, use of adjusted-dose warfarin was associated with a 51% (95% CI, 39 to 60%) lower adjusted risk of thromboembolism and a moderately increased risk of ICH (0.46% vs 0.23% per year, respectively, $p = 0.003$) compared with no warfarin therapy. ATRIA patients on warfarin were predominantly managed by dedicated anticoagulation units and INR time-in-range was > 60%. Such INR control is not far below figures reported for recent randomized trials (*eg*, SPORTIF[31] and ACTIVE[32]) although extended gaps in testing were probably greater. Similar quality of INR control has been reported for other AF cohorts.[105]

Overall, existing data indicate significant effectiveness and relative safety of oral VKAs in patients with AF treated in clinical practice as long as high quality management of anticoagulation is maintained. Additional studies of the oldest patients with AF are needed, however, since these individuals face the highest risk of both stroke and hemorrhagic complications and were not well represented in prior randomized trials. Cohorts enriched with patients initiating VKA therapy are needed to give more precise assessments of bleeding risks during this particularly vulnerable period.

1.1.13 Risk Stratification in Patients With AF

Oral VKA therapy is very effective in decreasing the risk of ischemic stroke in patients with AF.[11,41,43,106] In trials enrolling average risk patients without a history of recent stroke or with no history of stroke ("primary prevention" patients),[11] in trials with very high risk patients with a relatively recent history of stroke ("secondary prevention" patients),[20] and in trials with increased risk patients having a mix of qualifying risk factors,[28] adjusted-dose VKA therapy consistently proved extremely effective at preventing ischemic stroke and was adequately safe. Indeed, there is no specific subset of AF patients where VKAs have been shown to be inferior to any comparator. A reasonable interpretation of this large set of trials would be to recommend VKA therapy for all patients with AF. This conclusion should be kept in mind as we discuss the alternative "risk-based" approach to selecting AF patients for VKA therapy currently favored by published guidelines.

Guidelines have recommended that use of VKA therapy in AF be based on the patient's risk of ischemic stroke off VKA therapy; the higher this risk the stronger the indication for VKAs.[107,108] These

recommendations target use of VKAs in AF because such anticoagulants raise the risk of major hemorrhage and because necessary INR monitoring and dose-adjustment make VKA therapy burdensome. The goal of risk-based approaches is to avoid the use of VKAs in patients at such low risk of stroke, untreated, that toxicity may outweigh benefit, and to urge the use of VKAs in patients at high enough risk of stroke that use of VKAs has a clear expected net health benefit. Such recommendations assume that VKA therapy's relative risk reduction for stroke remains constant across patient subgroups, an assumption that has not been explicitly tested but is supported by trial results.[11,20,28] Guidelines generally pose the risk-based therapeutic decisions as VKAs vs aspirin. However, it should be clear that the core decision is VKAs, yes or no. Aspirin is typically used when the decision is "no VKA" because of a hopeful rather than critical assessment of the evidence bearing on aspirin and because aspirin may safely afford some protection against other vascular disease, in particular, coronary disease. While guidelines are explicit about risk factors for ischemic stroke in AF they tend to be vague about risk of hemorrhage with VKAs, leaving the assessment of this latter risk up to the managing physician. Variation in guideline recommendations for antithrombotic therapy for AF results from differences in risk stratification for ischemic stroke.[109,110] These differences, in turn, result from modest differences in assessing stroke risk and larger differences in setting stroke risk thresholds for use of VKAs.[110–112] The current section of this chapter focuses on evidence informing risk stratification for stroke based primarily on randomized trials and large observational studies, while the chapter by Schulman et al in this supplement discusses hemorrhage associated with antithrombotic therapy.

Clinical Risk Factors for Stroke in AF: The risk of stroke among patients with AF not receiving anticoagulants has been studied in subjects participating in several randomized trials of antithrombotic therapy.[11,20,41,113–115] The most commonly cited risk schema are derived from the pooled analyses from the Atrial Fibrillation Investigators[11] and two analyses from the Stroke Prevention in Atrial Fibrillation (SPAF) investigators (Table 6).[116,117]

The Atrial Fibrillation Investigators group analyzed data from the pooled control groups of the first five primary prevention trials and found the following independent risk factors for stroke in AF: age (RR, 1.4 per decade); prior stroke or TIA (RR, 2.5); history of hypertension (RR, 1.6); and diabetes mellitus (RR, 1.7).[11]

The SPAF Investigators conducted a pooled analysis of 854 patients assigned to aspirin from the first two SPAF trials.[117] They identified three independent risk factors for stroke: the combination of female sex and age older than 75 years (RR, 3.7); systolic BP > 160 mm Hg (RR, 2.2); and impaired left ventricular function defined as a recent diagnosis of congestive heart failure or a fractional shortening < 25% by transthoracic echocardiography (RR 1.8). The SPAF Investigators extended their analysis of risk factors for stroke among the 2012 patients allocated to the aspirin or combination therapy arms of the SPAF I-III randomized trials as well as the SPAF III low-risk cohort treated with aspirin.[116] Five features were significantly associated with an increased risk of stroke: age (RR, 1.8 per decade); female sex (RR, 1.6); prior stroke or TIA (RR, 2.9); history of hypertension (RR, 2.0); and systolic BP > 160 mm Hg (RR, 2.3). Although diabetes was a univariate risk factor for stroke (RR 1.6), it was not a significant predictor in the multivariable model nor was impaired left ventricular systolic function or a history of coronary heart disease. Of note, when patients with a prior stroke or TIA were excluded from the analysis, female sex was no longer a significant predictor, but the other characteristics remained significant independent risk factors. This SPAF analysis provided an additional provocative finding that requires validation. Among women in the SPAF III studies without prior stroke or TIA, use of estrogen-containing hormone replacement therapy was found to be an independent correlate of stroke risk (RR, 3.2).

Studies from the large ATRIA AF cohort study largely confirmed the relative impact of the risk factors of prior stroke, hypertension, age, and diabetes.[81] These investigators also found that women with AF faced an increased risk of stroke (adjusted odds ratio, 1.6; 95% CI, 1.6 to 1.9) consistent with the Framingham Study analysis (described below).[118,119] The ATRIA results did not find this effect isolated to older women and also found no impact of estrogen replacement therapy on stroke risk.

Patients in the AFI analysis with coronary disease had an elevated crude annual risk of stroke (*eg*, 8.2% for those with a history of myocardial infarction).[11] However, in both the AFI and SPAF risk schemes, a history of coronary heart disease (*eg*, myocardial infarction or angina) was not an independent risk factor for stroke after adjusting for other stroke risk factors including prior stroke or TIA, age, diabetes, hypertension, and congestive heart failure/impaired left ventricular systolic function. Presumably, much of the elevated risk of stroke in patients with coronary heart disease is explained by coexisting vascular risk factors.

The independent contribution of severe hyperthy-

roidism, specifically thyrotoxicosis or thyroid storm, to the risk of stroke in AF is not well understood. AF develops in 10 to 15% of patients with thyrotoxicosis and is most common in patients ≥ 60 years of age, presumably reflecting an age-related reduction in the threshold for developing AF.[120] The prevalence of thyrotoxicosis in patients with AF is 2 to 5%.[120] Some studies[121–125] have reported a high frequency of stroke and systemic embolism in patients with thyrotoxic AF, although one study[120] did not find a statistically significant difference when patients with AF were compared to age- and sex-matched patients with NSR. Some of these studies have significant methodologic problems, which complicate interpretation of the results.[120] Accordingly, currently available studies have not confirmed that thyrotoxic AF is a more potent risk factor for stroke than other causes of AF. Since the incidence of thromboembolic events in patients with thyrotoxic AF appears similar to other etiologies of AF,[120] antithrombotic therapies should be chosen based on the presence of validated stroke risk factors (see Recommendations section).

Comparison and Validation of Stroke Risk Stratification Schemes: There are many published stroke risk stratification schemes for AF which have been proposed to identify "high risk" (who should be targeted for anticoagulation) and "low risk" patients with AF.[126] Most have been validated in trial populations. Earlier schemes tended to use two or three risk categories. Later, the $CHADS_2$ and Framingham risk scores provided a graded scale of risk with increasing numbers of risk factors.[119,127]

The AFI and SPAF-based risk stratification schemes are largely consistent with each other.[11,116,117] Prior stroke or TIA, older age, hypertension, and diabetes mellitus emerge from both analyses as risk factors for stroke in patients with AF. Unlike the AFI analysis, the later SPAF scheme found an adverse association with female sex and separated the effect of "hypertension" into an effect associated with the diagnosis itself and an effect due to elevated systolic BP at examination (> 160 mm Hg). Another difference involves the observed absolute risks of stroke. For patients without a history of stroke or transient ischemic attack, the annual risk of stroke in the AFI data was 4.0% vs 2.7% in the SPAF data, although these estimates were based on relatively small numbers of thromboembolic events and 95% confidence bounds around the point estimates overlap. The apparent difference may be the result of variation in patient populations, chance, or a therapeutic benefit of aspirin among the SPAF participants. Such small differences can affect the decision to use anticoagulants in apparently lower risk patients. The differential impact of age in the AFI and SPAF risk schema probably affects the greatest percentage of patients with AF. Specifically, the AFI scheme would consider all patients with AF aged 65 years or older at high risk for stroke, including those without any other risk factor for stroke. By contrast, the SPAF scheme would view women with AF ≤ 75 years of age and men of any age, without other risk factors, as at low risk of stroke. The resulting uncertainty about the risk faced by patients with AF age 65–75 years and men of any age without other risk factors applies to roughly 20% of the entire population with nonvalvular AF.[111]

On the basis of these analyses, the AFI and SPAF Investigators proposed stratifying patients with AF into different stroke risk categories. The AFI Investigators categorized patients with AF as at either high or low risk for stroke; high risk was defined as having any of the following characteristics: prior stroke or TIA, age ≥ 65 years, history of hypertension, or diabetes. Low risk was defined as the absence of these characteristics. Within the placebo arms of the analyzed trials, high risk patients suffered an increased annual risk of stroke (range 4.3%–8.1%) while low risk patents had a much lower annual risk of stroke of approximately 1.0%. The SPAF Investigators categorized subjects into three groups: high, moderate, and low risk of stroke (among patients taking aspirin). The features qualifying for these three risk strata are: (1) high risk (any of the following): prior stroke or TIA; women > 75 years; age > 75 years with a history of hypertension; or systolic BP > 160 mm Hg (at any age); (2) moderate risk (any of the following): history of hypertension and age ≤ 75 years; or diabetes; and (3) low risk: no high or moderate risk features. Among patients without a prior stroke or TIA (*ie*, primary prevention), high-risk patients overall faced a 7.1% (5.4 to 9.5%) annual risk of stroke; moderate risk subjects had a 2.6% (1.9 to 3.6%) annual stroke risk; and low risk subjects had a 0.9% (0.6 to 1.6%) annual risk of stroke. Patients with multiple risk factors were at substantially higher stroke risk than those with one risk factor.[115,116]

A modified stroke risk classification scheme, $CHADS_2$, integrates elements from the AFI and SPAF I–II schemes and was tested among 1733 hospitalized Medicare beneficiaries aged 65 to 95 years with nonvalvular AF that were not discharged on warfarin.[127] The $CHADS_2$ risk index uses a point system in which two points are given for a history of stroke or TIA, and one point each for age ≥ 75 years, a history of hypertension, diabetes, or recent congestive heart failure. The rate of stroke increased with an increasing $CHADS_2$ score in this elderly cohort, although few patients had a very high score of ≥ 5, and < 7% had a score of zero (Table 7). Modified

Table 6–*Comparison of Clinical Risk Factors for Stroke in AF in Randomized Trials of Antithrombotic Therapy (Section 1.1.13)**

Characteristics	Atrial Fibrillation Investigators[11]		SPAF I–II†[117]		SPAF I–III‡[116]	
	RR	Annual Risk	RR (95% CI)	Annual Risk	RR	Annual Risk
Age, per decade	1.4	NA	3.7 (2.2–6.2)§	10.4%	1.8	NA
Female	NS	NA			1.6	NA
Prior stroke or TIA	2.5	11.7%	NS	6.4%	2.9	13.0%
Hypertension	1.6	5.6%	2.2 (1.3–3.6)‖	7.6%	95% CI 2.0–2.3¶	NA
Diabetes mellitus	1.7	8.6%	NS	NA	NS	NA
Congestive heart failure	NS	6.8%	1.8 (1.1–3.0)#	5.5%	NS	NA
Coronary heart disease	NS	95% CI 6.7–8.2	NS	NA	NS	NA

*NS = not statistically significant. See Table 2 for expansion of abbreviation.
†Among pooled aspirin arms of two trials.
‡Among pooled aspirin arms of SPAF I and II trials, SPAF III aspirin cohort, and SPAF III aspirin plus low-dose warfarin (target INR > 1.5).
§RR refers to the combination of being female and ≥ 75 yr old.
‖Defined as systolic BP > 160 mm Hg.
¶History of hypertension (RR 2.0), systolic BP > 160 mm Hg (RR 2.3).
#Defined as diagnosed congestive heart failure within 100 days or a fractional shortening ≤ 25% by echocardiography.

AFI and SPAF I–II risk schemes were also tested in this cohort. The modified AFI scheme had high (prior stroke or TIA, hypertension, or diabetes) and moderate (age > 65 years and no high-risk features) risk categories, corresponding to stroke rates (per 100 person-years) of 5.4 (4.2 to 6.5) for high risk and 2.2 (1.1 to 3.5) for moderate risk persons. The modified SPAF I-II scheme had high (prior stroke or TIA, women > 75 years, or recent congestive heart failure diagnosis), moderate (hypertension diagnosis and no high risk features), and low risk (no moderate or high risk features) categories. In this cohort, SPAF I–II high-risk persons had a stroke rate of 5.7 (4.4 to 7.0), moderate risk persons had a rate of 3.3 (1.7 to 5.2), while low-risk subjects had a rate of 1.5 (0.5 to 2.8).

A study from the Framingham Heart Study examined risk factors for stroke among 705 patients with new-onset AF, after excluding patients who suffered an ischemic stroke, TIA, or death within 30 days of the AF diagnosis.[119] The only significant multivariable predictors of ischemic stroke off oral VKAs were age per decade (RR, 1.3), female sex (RR, 1.9), prior stroke or TIA (RR, 1.9), and diabetes (RR, 1.8), which are consistent with prior studies as described above, with the exception that systolic BP was not found to be an independent predictor of stroke in this population. Using a scoring system that assigned points according to age, sex, systolic BP, and the presence of diabetes, prior stroke or TIA, the proportion of newly diagnosed AF patients considered at "low-risk" varied from 14.3 to 30.6% if the threshold annual predicted rate of stroke ranged from ≤ 1.5 per 100 person-years to ≤ 2 per 100 person-years (actual observed annual stroke rates of 1.1 to 1.5, based on total of 88 validated strokes). As expected, there was variation in the proportion of patients considered "low-risk" by the AFI (6.4%), SPAF (17.3%), and $CHADS_2$ (10.2%) risk schemes. The observed annual stroke rates in these differently defined low-risk categories of patients were: AFI: 0.9%; SPAF: 2.3%; and $CHADS_2$: 1.7%.

The AFI, SPAF, and Sixth ACCP Consensus Conference (ACCP-6)[128] risk schemes were assessed in the Cardiovascular Health Study. Among 259 elderly (≥ 65 years) participants with nonvalvular AF in this research cohort, annual rates of stroke using modified AFI/ACCP-6 criteria were 2.7% (1.7 to 4.1%) for high risk (prior stroke or TIA, hypertension, diabetes, congestive heart failure, or coronary heart disease) and 2.4% (0.9 to 5.1%) for moderate risk (age ≥ 65 years and no high risk features) subjects off anticoagulation.[129] Using the SPAF III criteria, annual stroke rates were relatively similar, ranging from 3.7% (2.1 to 5.8%) for high risk (prior stroke or TIA, women > 75 years old, systolic BP > 160 mm Hg, or impaired left ventricular systolic function), 2.0% (0.7 to 4.7%) for moderate risk (history of hypertension and no high risk features), and 1.7% (0.6 to 3.8%) for low risk (no moderate or high risk features). Among 1073 patients without prior stroke or TIA who participated in the SPAF III trial's aspirin plus low-dose warfarin arm or SPAF III aspirin cohort study, the AFI, ACCP, and SPAF I–II criteria were evaluated.[130] The stroke rates for each risk stratum differed across the different risk schemes, with consistently low stroke rates in the low risk categories for all schemes but significant variation in the moderate to high risk categories as well as the proportion of subjects in each category.

The AFI, SPAF, ACCP 6, $CHADS_2$, and Framingham risk schema were compared using the pooled individual data from aspirin treated arms from five randomized trials.[131] These included primary and secondary prevention trials with an overall annualized rate of stroke in the aspirin arms of 4.2%. All schema could be adapted to identify a low-risk group (annualized rate of 0.9 to 1.4%) and a "high-risk" group (annualized rate of 3.0 to 5.3%) and an intermediate-risk group (annualized rate of 1.0 to 3.2%), though this last category tended to overlap substantially with adjacent categories. The various risk schema assigned very different proportions of patients into the three categories of risk. For example, 49% of patients were considered low-risk using the Framingham scheme as compared to 8.7% of patients using the ACCP-6 scheme. However, these proportions reflected different risk thresholds (*eg*, 1.4%/yr vs 0.5%/yr for Framingham and ACCP-6, respectively). Using the c-statistic criterion for discrimination, $CHADS_2$ was marginally better than the other schema, with a c-statistic of 0.70, likely reflecting its higher weighting of the impact of prior stroke. When these schema were assessed among patients who had not had a prior stroke, $CHADS_2$ was still marginally better than the other schema, but with a diminished c-statistic of 0.63. Since prior stroke is universally recognized as a strong indication for VKA therapy, performance of risk schema among primary prevention patients is the pressing clinical need. C-statistics in the 0.58 to 0.63 range are mediocre.[132]

Risk Stratification Schemes in Other Guidelines: The 2006 American College of Cardiology/American Heart Association/European Society of Cardiology management guidelines for AF classify those at 'high risk' as those with prior thromboembolism (stroke, TIA, systemic embolism), rheumatic mitral stenosis, or more than one of: age $\geq$ 75 years, hypertension, heart failure, impaired LV systolic function, or diabetes mellitus.[108] "Moderate risk" is where there is only one of: age $\geq$ 75 years, hypertension, heart failure, impaired LV systolic function, or diabetes mellitus. "Low risk" are essentially those with AF with no risk factors. Less validated or weaker risk factors in this schema were female gender, age 65 to 74 years, coronary artery disease or thyrotoxicosis. Broadly, the high risk category refers to $CHADS_2$ scores of $\geq$ 2, where warfarin is recommended; the intermediate risk corresponds to a $CHADS_2$ score of 1, where warfarin or aspirin 81 to 325 mg/d is recommended; and the low risk category refers to a $CHADS_2$ score of 0, where aspirin 81 to 325 mg is recommended. The 2006 American College of Cardiology/American Heart Association/European Society of Cardiology schema has not been prospectively validated.

In 2006, the UK National Institute for Health and Clinical Excellence (NICE) published the UK national guidelines for AF management, which proposed an algorithm-based stroke risk stratification which is largely based on the AFI-scheme.[133] The NICE risk stratification schema has been compared against the $CHADS_2$ in a prospective cohort, and the accuracy of both clinical risk stratification schemes were found to be similar for predicting stroke and vascular event rates.[134]

Echocardiographic Predictors of Stroke in AF: An AFI analysis of transthoracic echocardiograms done in three of the original trials found that moderate-to-severe left ventricular systolic dysfunction was an incremental, strong risk factor above clinical risk factors (RR, 2.5), but left atrial diameter was not independently related to risk of stroke in AF after adjusting for other clinical risk factors.[113] While left atrial size and left ventricular systolic function can be adequately assessed by transthoracic echocardiography, transesophageal echocardiography (TEE) is needed to consistently visualize important abnormalities of the left atrium and aortic arch. This modestly invasive approach is commonly used as an adjunct to elective cardioversion (see below), but it has also been applied to studies of outpatients with chronic AF.[135,136] Visible thrombus and dense spontaneous echo contrast (a marker of blood stasis) in the left atrium conferred a twofold to fourfold increase in risk of subsequent stroke. More than 90% of these thrombi involve or are confined to the left atrial appendage.[16,137] In addition, patients with TEE-detected aortic plaques with complex features (mobile, pedunculated, ulcerated, or $>$ 4 mm in thickness) had extremely high stroke rates in the SPAF III study. Of note, many of these abnormalities were

Table 7—*Risk of Stroke (Section 1.1.13)**

$CHADS_2$ Score	Patients (n = 1,733), No.	Adjusted Stroke Rate per 100 Person-yr† (95% CI)
0	120	1.9 (1.2–3.0)
1	463	2.8 (2.0–3.8)
2	523	4.0 (3.1–5.1)
3	337	5.9 (4.6–7.3)
4	220	8.5 (6.3–11.1)
5	65	12.5 (8.2–17.5)
6	5	18.2 (10.5–27.4)

*According to $CHADS_2$ score.[127]

†The adjusted stroke rate was the expected stroke rate per 100 person-years derived from the multivariable model assuming that aspirin was not taken.

observed in the descending aorta.[136] Additional TEE measures have been suspected as risk factors for stroke (*eg*, depressed left atrial appendage flow velocity; *ie*, <20 cm/s). At present, however, there is no clear evidence that TEE findings add sufficient independent information to stroke risk stratification for most patients with chronic AF, when clinical and transthoracic echocardiographic risk factors are considered, to merit the additional risks, discomfort, and costs.

Other Potential Risk Factors for Stroke in AF: Other potential risk factors that may refine current clinical and echocardiographic stroke risk schemes include genetic polymorphisms, abnormalities in hemostatic and thrombotic factors, platelet activation and aggregation pathways, and endothelial or vascular dysfunction.[129,136,139] The pathophysiology of thromboembolism in AF is multifactorial, but it appears that AF confers a prothrombotic or hypercoagulable state.[140] Indeed, patients with AF demonstrate abnormalities of hemostasis, platelets and endothelial function, which have been shown to be independent of associated structural heart disease or underlying etiology of AF. This prothrombotic state can be altered by cardioversion and antithrombotic therapy. Recent studies have suggested that elevated levels of plasma biomarkers, such as von Willebrand factor (an index of endothelial damage/dysfunction), fibrin d-dimer (an index of fibrin turnover and thrombogenesis) and interleukin-6 (an index of inflammation) may be predictive of subsequent cardiovascular events in patients with AF, independent of known clinical risk factors.[141] In particular, plasma von Willebrand factor (a marker of endothelial damage/dysfunction) levels may add information to clinical risk stratification schemes.[134] However, at this point, there is not sufficient supportive evidence to include such biomarkers as standard risk factors for stroke in AF.

Pattern of AF and Risk of Stroke: A recurrent clinical concern is whether patients with paroxysmal, or intermittent, AF (PAF) face the same risk of stroke as those with persistent, ie, sustained AF. Periods of NSR should theoretically lessen the risk of stroke, yet transitions from AF to NSR may acutely heighten risk in a manner similar to the increase in risk caused by cardioversion (see below). Retrospective studies suggested that PAF is associated with a lower risk of stroke than chronic AF.[120,142] However, when associated stroke risk factors are controlled for, clinical trial data suggest that PAF confers a relative risk of stroke similar to persistent or permanent AF.[11,143] Patients with PAF are generally younger and have a lower prevalence of associated clinical risk factors than those with persistent AF; therefore, their absolute stroke rate is lower. The relative risk reduction provided by warfarin also appears similar for patients with paroxysmal AF and persistent AF. This conclusion, however, is limited by the relatively small number of patients with PAF participating in the trials (about 12% of subjects in the first 5 randomized trials).[11] Analyses of PAF are further complicated by the fact that patients with PAF differ greatly in the frequency and duration of AF episodes[144] and differences across studies in the definition of PAF. Studies of PAF are also limited by significant differences in patient awareness of episodes of AF. Indeed, studies document a high prevalence of asymptomatic PAF, even among patients who are symptomatic with some episodes.[145-147] There is some evidence suggesting that stroke risk in patients with PAF increases with more time spent in AF.[148,149] This relationship is being explored using implanted devices that can report episodes of AF in patients with PAF.[150] Despite the uncertainty in the underlying evidence, it seems reasonable to treat patients with PAF in a manner similar to those with persistent AF, basing use of anticoagulants on the presence of risk factors for stroke.

Are Absolute Rates of Stroke With AF Lower Today Than During the Period of the Original Trials of VKA Therapy?: Most stroke risk stratification schemes for patients with AF are based on the placebo or aspirin arms of the early trials of VKA treatment conducted in the 1980s and early 1990s. There is accumulating evidence that the absolute risk of stroke faced by patients with AF is lower currently than when the initial trials were conducted. This appears to translate into lower risks across risk strata. In the metaanalysis of the first five primary prevention trials of VKA therapy the overall annual rate of stroke in the placebo arms was 4.5%.[11] This contrasts with an annual rate of 2.4% in the more recently assembled ATRIA cohort.[81] In the SPAF III trial that enrolled patients with at least one risk factor the overall annual rate of thromboembolism was 7.9% in the aspirin plus mini-warfarin arm.[25] This contrasts with a rate of 2.2%/year in the clopidogrel plus aspirin arm of the ACTIVE-W trial conducted a decade later which selected patients in a manner similar to the SPAF III trial.[32] In both SPAF III and ACTIVE-W, VKA therapy was far superior to the comparator and the difference in the rates in the trials' respective antiplatelet therapy arms is not explainable by putative effect of clopidogrel. Focusing specifically on patients in the intermediate risk stratum of $CHADS_2 = 1$, a prior metaanalysis estimated a stroke risk of 2.2%/year.[131] In the ATRIA

Top Eight Differences Among the AF Guidelines: Canadian, European, and US

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July 05, 2011

Ed. note: This article is based on Gillis AM, Skanes AC. Comparing the 2010 North American and European Atrial Fibrillation Guidelines. Can J Cardiol. 2011; 27: 7-13.

Over the last five years major advances in the management of atrial fibrillation (AF) have occurred. These include the publication of clinical trials on pharmacologic approaches for management of AF,[1-3] clinical trials of new antithrombotic therapies for prevention of stroke,[4-6] as well as the continuing evolution of catheter ablation for treatment of AF.[7-9] The European Society of Cardiology (ESC) published guidelines for the management of AF in September 2010.[10] A focused update on the management of AF was been published by the American College of Cardiology Foundation (ACCF)/the American Heart Association (AHA)/Heart Rhythm Society (HRS) in their respective journals in January 201111 and a second update addressing dabigatran in Mar 201112. The Canadian Cardiovascular Society (CCS) 2010 AF Guidelines were presented at the Canadian Cardiovascular Congress in October 2010[13] and published in the Canadian Journal of Cardiology February 2011.[14-21] We have been invited to comment on some of the important differences in the recommendations that exist among the three sets of guidelines.[22]

1. Both the ESC and the ACCF/AHA/HRS guideline panels used the ACC/AHA process for rating the quality of evidence and grading the strength of the recommendations.[10-12] In contrast, the CCS used the GRADE (Grading of Recommendations Assessment Development and Evaluation) approach.[14, 23, 24] GRADE has recently been adopted by the World Health Organization for guideline development and allows separation of the quality of evidence from the strength of the recommendation. In addition to evaluating the quality of the evidence, GRADE considers the balance of desirable and undesirable effects, patients' values and preferences and resource utilization to determine the strength of a recommendation (Strong or Conditional, i.e., weak).

2. The CCS guidelines were the first set of guidelines to recommend the use of dabigatran for prevention of stroke in patients with a CHADS2 score ≥1 and suggest that dabigatran is preferred over warfarin in most patients.[18] The CCS guidelines suggest that warfarin is preferred over dabigatran in patients with coronary artery disease at high risk of ischemic events. The European guidelines make no specific recommendation regarding the use of dabigatran as it has not yet been approved in Europe for prevention of stroke.[10] The ACCF/AHA/HRS recently published focused update state that dabigatran may be used as an alternative to warfarin for stroke prevention.[12]

3. The Canadian guidelines recommend that treatment for rate control of persistent/permanent AF should aim for a resting heart rate of <100 bpm[19] whereas the European and American guidelines suggest that it is reasonable to aim for a resting heart rate of <110 bpm and aim for stricter rate control if patients remain symptomatic.[10, 11]The Canadian recommendation is more conservative because only 22% of patients in RACE II randomized to the lenient rate control strategy had a target heart rate of >100-110 bpm.[3]

4. All guidelines recommend that the selection of antiarrhythmic drug therapy for maintenance of sinus rhythm be based on the underlying cardiovascular disease. The American and European guidelines do not recommend the use of Class IC antiarrhythmic drugs or sotalol in patients with left ventricular

hypertrophy.[10,11] The Canadian guidelines do not make the presence of left ventricular hypertrophy an exclusion factor for the use of class IC agents or sotalol feeling that the scientific data supporting this recommendation was weak.[16] The CCS guidelines suggest that the decision not to use these drugs in the presence of left ventricular hypertrophy should be based on the presence of significant repolarization abnormalities which is a risk marker for proarrhythmia.

5. Dronedarone has been incorporated into the antiarrhythmic drug algorithms.[10,11,16] Unlike the American and European guidelines, the Canadian guidelines did not make a specific recommendation that dronedarone could be considered to decrease the risk of hospitalization for cardiovascular causes. The efficacy of dronedarone for maintenance of sinus rhythm is modest and equivalent to other first line agents based on the clinical condition. Both the Canadian and European guidelines suggest that dronedarone may be used as a second line therapy for rate control in the absence of unstable heart failure.[10,16]

6. All guidelines recommend catheter ablation for symptomatic patients with paroxysmal AF who have failed at least one anti-arrhythmic drug, although interpretation of the data led to differences in how these recommendations were graded.[10,11,17]The American guidelines assign a Class I recommendation based on high level of evidence, whereas, the European and Canadian guidelines assign a IIa or conditional recommendation based on high and moderate quality of evidence, respectively. The ACCF/AHA/HRS recommendation comes with an important footnote that these procedures be performed in experienced center with a volume >50 cases per year. All three guidelines give a Class IIa or conditional recommendation for catheter ablation in symptomatic patients with persistent AF. Recommendations for catheter ablation as first line therapy are highly nuanced and graded as either conditional or Class IIb.

7. The European guidelines have incorporated what have traditionally been "less validated risk factors" such as female gender, age >75 years and the presence of vascular disease into a new validated scheme – CHA2DS2-VASc score.[10] In addition to the traditional CHADS2 score, two points are now allotted for age >75 years and a single point each for female gender, age over 65, and vascular disease (coronary, carotid or peripheral). The Canadian and American guidelines have maintained use of the traditional risk factors incorporated into the CHADS2 score.[11,16]

8. Both the Canadian and European guidelines have become more aggressive in the recommendation that oral anticoagulation is preferred over aspirin (ASA) in low risk patients (CHADS2 =1, CHA2DS2-VASc =1) based on new data that these patients receive substantial benefit over ASA alone.[10,16]) ASA is reserved for those with substantial bleeding risk where the benefit of oral anticoagulation is outweighed by the risk of a significant complication. In the American guidelines either ASA or warfarin are recommended in this "lower risk" group.[11] All guidelines recommend oral anticoagulation for patients at higher risk with CHADS2 ≥2 or CHA2DS2-VASc ≥2 in the case of European guidelines. Because the latter includes added risk factors, oral anticoagulation will be recommended in a greater proportion of patients with AF, including populations of patients that would not otherwise receive oral anticoagulation using the traditional CHADS2 risk score recommended by the Canadian or American guidelines.

NEED FOR OPTIMAL TOOLS & GUIDELINES

Not only do health care professionals need consistent and clear guidelines on which risk assessment tools to use, but these tools need to appropriately weigh risk and produce patient-tailored assessments. There is some disagreement within the medical community as to which available tools are the best and if additional tools are needed. Many feel that the limited precision of current tools remains a barrier to patient-tailored decision-making.

Tools that are more "discriminating and accurate risk models...would encourage more uniform use of antithrombotic agents and would likely lead to better patient outcomes."[1] While there is considerable overlap of the current available tools, "differences alter the predicted risk status of hundreds of thousands of atrial fibrillation patients."[2]

The gray area produced by many tools leave room for flexibility but also allow for subjectivity that can lead to improper treatment decisions, particularly with older patients, women, and other subpopulations. "Sensitive to problems that result from commission more than omission, physicians often overestimate the likelihood of hemorrhagic complications and underestimate the consequences of failing to prevent embolic events…This is especially true in older patients whom prescribers excessively perceive to be poor risks for anticoagulation because they are frail or more likely to fall—even though these are the very patients at highest risk for preventable a-fib-induced stroke."[3] This is also true with women who are more likely "to experience symptomatic attacks, a higher frequency of recurrences, and significantly higher heart rates during atrial fibrillation, which increases the risk of stroke."[4]

Optimal tools should properly translate results, acknowledge differences between subpopulations, be based on sound data, consider both stroke and bleeding risk, eliminate physician and patient subjectivity in order to produce definitive decisions, and be scientifically AND practically valuable—making adoption in a clinical setting realistic. Additionally, considering the rapidly changing landscape of anticoagulation, these tools should also work for emerging anticoagulants.

[1] Stroke Risk in Atrial Fibrillation Working Group. 2008. Comparison of 12 Risk Stratification Schemes to Predict Stroke in Patients With Nonvalvular Atrial Fibrillation. *Stroke* 39(6):1901-10.
[2] Ibid.
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Age and Ageing 2011; **40:** 675–683
doi: 10.1093/ageing/afr097
Published electronically 5 August 2011

Attitudes of physicians regarding anticoagulation for atrial fibrillation: a systematic review

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Abstract

Background: the efficacy of warfarin for prevention of stroke in patients with atrial fibrillation (AF) is well established, but many people with AF who would benefit from warfarin are not receiving it. This systematic review aims to determine physicians' attitudes to the prescription of warfarin for AF, and identify reasons for its underuse.
Methods: an electronic search of MEDLINE (1950–present), EMBASE (1980–present), CINAHL (1994–present), PsycINFO (1987–present) and Web of Knowledge (1970–present) was performed in November 2010 to identify all studies which addressed, via survey, physicians' attitudes regarding anticoagulation for patients with AF.
Results: a total of 1,375 citations were identified. Of these citations, 44 full text studies were obtained for scrutinisation; 14 of these studies were rejected leaving 30 studies which were included in the review. All included studies were cross-sectional surveys and addressed physicians' opinions of anticoagulation in AF as a primary or secondary aim. Increasing age, increased bleeding risk, previous bleeds, falls risk, co-morbidities and ability to comply with treatment influenced whether physicians would prescribe anticoagulation for AF.
Conclusion: physicians are reticent to recommend warfarin for elderly patients in AF, despite evidence of increased benefit in these patients compared with younger patients. Risk of falls and previous bleeding were also shown to be disproportionate barriers to warfarin prescription. Further studies are required to determine how best to overcome these perceived barriers to appropriate anticoagulation.

Keywords: *atrial fibrillation, anticoagulation, physician attitude, systematic review, ageing, elderly*

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia [1]. The prevalence of AF in those >65 years of age is 4.7%, rising to around 9% in those aged 80–89 years [2, 3]. Owing to the growing population of elderly individuals, the prevalence of AF is expected to increase 2.5-fold during the first half of this century [4].

A diagnosis of AF is associated with serious health implications, including a 5-fold increase in stroke risk [1]. When stroke occurs in association with AF, the outcome is less favourable, with longer hospital stays compared with stroke patients without AF [14].

Several randomised controlled trials show that warfarin reduces stroke risk significantly when compared with aspirin or placebo [7–11]. A recent systematic review of this evidence suggests that this amount to 25 ischaemic strokes saved yearly per 1,000 participants given warfarin [12].

However, anticoagulation is associated with a small but significant increase in the risk of major bleeding [12]. Thus, when prescribing warfarin for AF, physicians must weigh up the potential benefits (stroke prevention) against potential risks (increased risk of bleeding) in consultation with the patient. To aid clinical decision-making, several tools have been developed including the $CHADS_2$ (Congestive heart failure, history of Hypertension, Age

≥75, Diabetes mellitus, past history of Stroke) scoring system [13].

Despite this, many patients who, according to guidelines, should be anticoagulated, are not receiving this treatment [6, 15, 16]. A recent publication by the National Institute for Health and Clinical Excellence (NICE) suggests that, in the UK, 40% of patients with AF who are eligible for anticoagulation are not receiving it [17].

A better understanding of the factors perceived by physicians to be barriers to anticoagulation is critical before we can address the widespread underprescription of anticoagulation for AF. Thus, the aim of this systematic review was to identify and collate all studies where clinicians' views about anticoagulation have been sought, and their practice assessed via hypothetical case scenarios. In doing so, we wished to identify the factors which physicians have reported as important when making decisions about anticoagulation for AF.

Methods

Search strategy

Our search strategies are available as supplementary data in *Age and Ageing* online (Appendix 1). The aim of these searches was to identify all studies which provided data on physicians' attitudes and hypothetical practice regarding the use of anticoagulation therapy in patients with AF. The databases included were MEDLINE (1950-present), EMBASE (1980-present), CINAHL (1994-present), PsycINFO (1987-present) and Web of Knowledge (1970-present). Each database was searched using the corresponding search strategy between 18/11/10 and 22/11/10.

Study selection

One author (D.P.) assessed all titles and abstracts and obtained full text articles of potentially relevant studies. One author (D.P.) applied the following inclusion criteria to retrieved full texts; any uncertainties about fulfilment of inclusion criteria were discussed with a second reviewer (G. M.) and a consensus reached:

- Study type: observational studies using surveys to examine physicians' attitudes and hypothetical practice regarding anticoagulation for patients in AF.
- Study group: practicing physicians of any medical specialty or grade.
- Date of publication: Only studies published after 1989 were included as this was the year of publication of the first large randomised controlled trial of anticoagulation for stroke prevention in people with chronic AF [7].
- Sampling method: no restrictions based on sampling method.
- Sample size: no restrictions based on sample size.
- Method of data collection: any form of physician survey, including (but not restricted to) questionnaire, clinical vignette and interview, which explores physicians' attitudes regarding anticoagulation therapy for patients in AF.

The following types of study were excluded:

- Qualitative studies
- Unpublished studies
- Studies not available in the English language

Data extraction and analysis

Data from eligible studies were independently extracted by two reviewers (D.P. and J.P.) into a paper data extraction form. Methodological quality of included studies was assessed based on criteria listed in the 'Strengthening the Reporting of Observational Studies (STROBE)' statement and the Cochrane Reviewer's Handbook [48, 49]. All extracted data were tabulated, and a narrative synthesis was performed. The data were not suitable for meta-analysis, as different clinical scenarios had been provided in different papers.

Results

Study characteristics

The authors identified 30 studies [**18–47**] which fulfilled the inclusion criteria (Figure 1).

Fourteen studies [50–63] were excluded after assessment of the full text versions for the reasons shown in Figure 1.

The included studies comprised 8,768 responding physicians in total (Table 1). The number of physicians included in each study ranged from 14 [**41**] to 711 [**32**], with a mean number of 292 physicians. Response rate (number of physicians included/number of physicians approached) ranged from 18 [**45**] to 90% [**36**].

The primary aim of 25 studies [**18–23, 25–30, 32–38, 40–45**] was to assess attitudes, practice and/or knowledge regarding anticoagulation therapy for patients in AF among different physician groups. The five other studies did include this aim; however, it was not the primary aim.

In 19 of the studies, physicians were given a range of clinical vignettes and asked what their course of action would be in the care of each hypothetical patient [**18–23, 25, 27, 31–33, 35, 37–38, 40–42, 44–45**]. In the remaining 11 studies, and as additional information in some of the aforementioned 19 studies, attitudes were assessed via different methods.

The results from all 30 studies are presented in Table S1 (see Supplementary data available in *Age and Ageing* online).

Patient age

Twenty-two studies discussed the importance of patient age [**18–26, 28–29, 32, 34–38, 42–45, 47**]. Several studies used a matched pair of clinical vignettes in which the only

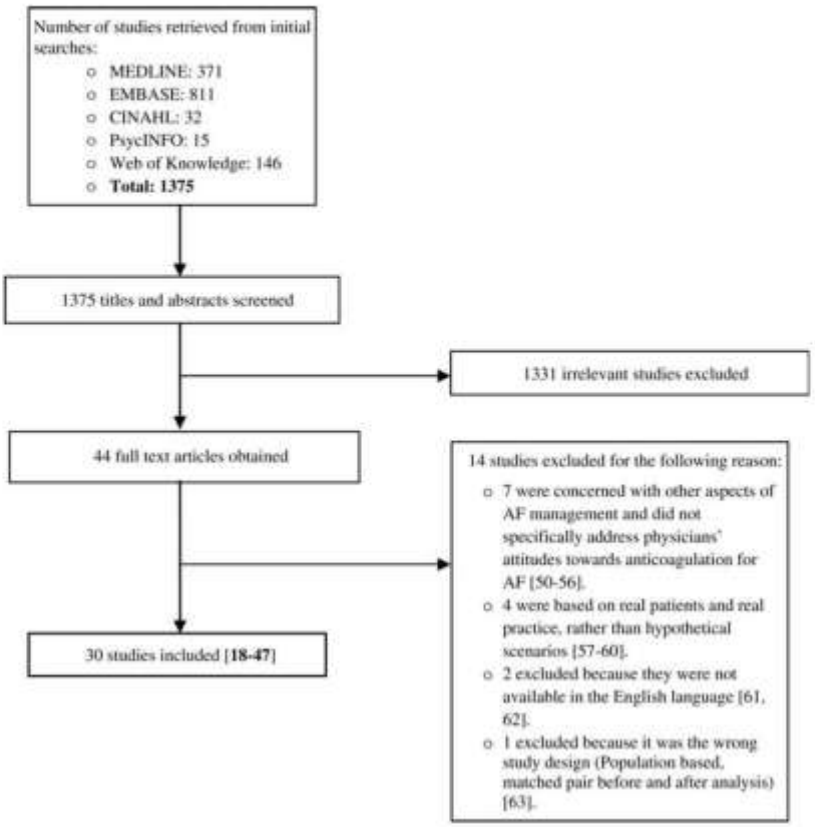

Figure 1. Flow diagram of study search and selection.

difference between vignettes was the age of the patient (Table 2) [18, 20–23, 32, 35, 47]. The results of these comparisons show that physicians were less likely to anticoagulate patients over 70 compared with patients under 70 in all but one of the matched pairs, when both groups are asymptomatic and have no contraindications to warfarin therapy [18, 20–22, 35]. When patients in both age groups have an additional risk factors for stroke, the results are similar [23, 32, 47].

In some studies, physicians were asked direct questions regarding their opinion of anticoagulating elderly patients, rather than linking this to a hypothetical situation. When this was the case, advanced age was still considered an important barrier in relation to prescribing warfarin therapy, and was consistently associated with lower rates of anticoagulation (see Table S1, Supplementary data available in *Age and Ageing* online) [19, 20, 24–26, 28, 29, 34, 36, 37].

In two studies [29, 43] physicians were asked if they thought that the benefits of anticoagulation therapy outweighed the risks in elderly patients. One study [29] found that only 56% of physicians agreed with this statement (when elderly considered >75 years). The second study [43] reported agreement from 63% of physicians (when elderly considered >65 years).

Bleeding risk

Thirteen studies discussed the importance of bleeding risk as a factor in the prescription of anticoagulation for AF [20, 23–25, 32–37, 39, 41, 42]. Having a history of bleeding or significant risk of bleeding was seen as an important barrier to anticoagulation by 12 of these 13 studies [20, 23, 25, 32–37, 39, 41, 42]. In the remaining study, bleeding risk was considered important in determining whether to start warfarin by only 8% of physicians [24].

Three studies [23, 35, 42] sent out a matched pair of clinical vignettes between which the only variable was the bleeding risk, or the bleeding history, of the patient involved. Direct comparison of these vignettes showed rates of warfarin use of 41 [26], 58 [35] and 31% [42] when the patient had a history of bleeding, compared with rates of warfarin use of 81 [26], 91 [35] and 63% [42], respectively, when the same patient had no history of bleeding.

Table 1. Characteristics of studies included in the review

First author and date	Country where based	Study design	No. of physicians sent questionnaire	Response rate, *n* (%)	Specialty of responding physicians	Grade of responding physicians
Chang *et al.* (1990) [18]	USA	Cross-sectional survey: mailed questionnaire based on five clinical vignettes	274	134 (49)	40% GPs, 40% internists, 20% cardiologists	No data
Kumar *et al.* (1991) [19]	USA	Cross-sectional survey: mailed questionnaire based on four clinical vignettes	480	261 (52)	43% internists, 25% cardiologists, 8% neurologists, 24% other specialists	100% attending physicians
McCreary *et al.* (1995) [20]	USA	Cross-sectional survey: mailed questionnaire based on four clinical vignettes	1,189	450 (38)	42% primary care physicians, 31% neurologists, 27% cardiologists	No data
King *et al.* (1998) [21]	UK	Cross-sectional survey: mailed questionnaire based on four clinical vignettes	600	294 (49)	48% cardiologists, 52% geriatricians	100% consultants
Lip *et al.* (1996) [22]	UK	Cross-sectional survey: mailed questionnaire based on six clinical cases	500	214 (44)	41% cardiologists, 59% other specialists	100% consultants
Beyth *et al.* 1996 [23]	USA	Cross-sectional survey: mailed questionnaire based on eight clinical vignettes	80	58 (73)	52% internists, 21% cardiologists, 19% other specialists, 9% family physicians	72% ≥ 10 years in practice
Maud *et al.* (1996) [24]	UK	Cross-sectional survey: mailed questionnaire assessing practice regarding patients with minor strokes, AF and hypertension	640	294 (46)	100% GPs	No data
Monette *et al.* (1997) [25]	Canada + USA	Cross-sectional survey: mailed questionnaire based on two clinical vignettes	269	182 (68)	36% family physicians, 32% internists, 31% geriatricians, 1% other specialists	42% graduated after 1980
Bush *et al.* (1998) [26]	USA	Cross-sectional survey: mailed questionnaire (no further data)	358	150 (42)	Family physicians, GPs, Internists, Cardiologists (no figures given)	No data
Kelles *et al.* (1998) [27]	Canada	Cross-sectional survey: mailed questionnaire based on two clinical vignettes	223	159 (71)	62% GPs, 20% internists, 11% cardiologists, 7% other specialists	Mean years in practice = 19
Stallow *et al.* (1998) [28]	UK	Cross-sectional survey: mailed questionnaire based on a list of patient	1,051	622 (60)	74% GPs, 26% other specialists	Specialists: 100% consultants GPs: no data
Vanithra *et al.* (2001) [29]	UK	Cross-sectional study: mailed questionnaire explaining physicians' attitudes to patient age and co-morbidity when considering anticoagulation	100	68 (63)	37% geriatricians, 63% other specialists	100% consultants
Fryksmus *et al.* (2001) [30]	Sweden	Cross-sectional survey: mailed questionnaire which assessed theoretical compliance with AF guidelines	728	495 (68)	52% cardiologists, 37% internists, 12% other specialists	No data
Williams *et al.* (2001) [31]	UK	Cross-sectional survey: questionnaire based on five case scenarios to assess A&E physicians' treatment of AF. Distribution method not stated	287	124 (45)	100% A&E physicians	100% consultants
Peterson *et al.* (2002) [32]	Australia	Cross-sectional survey: mailed questionnaire based on six clinical cases	2,500	711 (33)	74% GPs, 7% cardiologists, 19% other specialists	Median years in practice = 21
Pradhan *et al.* (2002) [33]	Canada	Cross-sectional survey: mailed questionnaire based on four clinical scenarios	1,000	324 (32)	100% primary care physicians	Mean years in practice = 19 (SD ± 11)

Bungard *et al.* (2000) [34]	Canada	Cross-sectional survey: mailed questionnaire based on rating the relative importance of potential barriers to anticoagulation	520	349 (67)	42% family physicians, 31% internists, 16% cardiologists, 11% neurologists	Median years in practice = 17.9 (range 0–55)
Gross *et al.* (2005) [35]	USA	Cross-sectional survey: mailed questionnaire based on 14 clinical vignettes	426	142 (33)	100% internists	No data
Deplanque *et al.* (2004) [36]	Austria, France, Belgium, Italy, Portugal	Prospective observational study including a cross-sectional survey: telephone questionnaire	478	402 (90)	61% GPs, 39% cardiologists	Median years in practice = 21 (range 2–46)
Maeda *et al.* (2004) [37]	Japan	Cross-sectional survey: hand-delivered questionnaire based on eight clinical vignettes	209	126 (67)	58% internists, 12% cardiologists, 30% other specialists	60% ≥ 11 years in practice
Anderson DR *et al.* (2005) [38]	Canada	Cross-sectional survey: mailed questionnaire based on one case scenario	986	591 (57)	83% primary care, 17% specialists (cardiologists and internists)	Mean years in practice = 15.3
Ingelgård *et al.* (2006) [39]	USA	Literature review and cross-sectional survey: literature review designed to identify potential barriers to anticoagulation, which were then assessed via questionnaire. Distribution method not stated	35	30 (86)	50% family physicians, 35% cardiologists, 15% internists, 3% other specialist	No data
Dharmarajan *et al.* (2006) [40]	USA	Cross-sectional survey: questionnaire based on one clinical vignette. Distribution method not stated	No data	107 (no data)	81% internists, 19% other specialists	46% residents, 19% fellows, 35% attending physicians
Anderson *et al.* (2007) [41]	UK	Cross-sectional survey: hand-delivered questionnaire based on five clinical vignettes	20	14 (70)	36% cardiologists, 64% specialists (geriatrics and general medicine)	43% consultants, 57% specialist registrars
Gurellas *et al.* (2008) (1) [42]	Australia	Representative, national survey: questionnaire based on eight clinical vignettes. Distribution method not stated	926	596 (64)	100% family physicians	49% ≥ 20 years in practice
Gurellas *et al.* (2008) (2) [43]	Australia	Representative, national survey: mailed questionnaire which explored issues relevant to the diagnosis and management of AF	926	596 (64)	100% GPs	49% ≥ 20 years in practice
Shen *et al.* (2008) [44]	Australia	Cross-sectional survey: mailed questionnaire based on five case scenarios	532	182 (34)	100% GPs	No data
Arendts *et al.* (2010) [45]	Australia and New Zealand	Cross-sectional survey: emailed questionnaire based on seven clinical vignettes	1,800	315 (18)	76% emergency physicians, 24% cardiologists	'specialists'
Ampalp *et al.* (2010) [46]	USA	Cross-sectional survey: emailed individual surveys depending on specialty	959	647 (67)	41% cardiologists, 59% other specialists	No data
Vassilikos *et al.* (2010) [47]	Greece	Cross-sectional survey: mailed/hand-delivered questionnaire concerning practice patterns regarding the management of AF	500	309 (62)	65% cardiologists, 37% internists or GPs	No data

GP, general practitioner; AF, atrial fibrillation; A&E, accident and emergency.

Table 2. Comparison of matched pair vignettes in which patient age was the only variable

Study author and date	Percentage of physicians recommending warfarin for patient in AF with no contraindications to warfarin (age)	
	Patient <70 years	Patient >70 years
Chang *et al.* (1990) [18]	47% (59)	31% (73)
McCrory *et al.* (1995) [20]	90% (65)	88% (75)
King *et al.* (1995) [21]	45% (<40)	26% (74)
Lip *et al.* (1996) [22]	86% (40)	43% (72)
Beyth *et al.* (1996) [23]	81% (65)	45% (85)
Peterson *et al.* (2002) [32]	98% (65)	91% (75)
Gross *et al.* (2003) [35]	78% (62)	91% (76)
Vassilikos *et al.* (2010) [47]	64% (25–50)	90% (>75)

Risk of falls

Ten studies reported physicians' views in relation to the risk of falls [25, 29, 34–36, 39–42, 44]. Falls risk was perceived to be an important barrier in nine of these studies [25, 29, 34, 35, 39–42, 44]. In the remaining study [36], falls risk was considered a significant barrier to warfarin prescription by only 10% of general practitioners and 8% of cardiologists. The meaning of 'risk of falls' was variable between papers, with the majority not providing a specific definition.

Co-morbidities

Seventeen studies [18, 19, 21, 22, 25, 29, 32, 35, 36, 39–46] reported physicians' views in relation to co-morbidities. Chronic alcoholism was included in the scenarios in two studies [18, 39] and was an important barrier in both studies. Data regarding cognitive impairment were provided by six studies [25, 29, 35, 36, 40, 44]. Five studies asked physicians if cognitive impairment was an important barrier to anticoagulation. The results of this, in terms of percentage of physicians who agreed, ranged from 3 [36] to 98% [29], showing wide variation in opinion between physicians.

Patient's ability to comply with treatment

Seven studies [20, 26, 34–36, 44, 47] reported physicians' views relating to patients' ability to comply with treatment, and this was considered an important barrier by all seven of these studies.

Most cited reasons not to anticoagulate

In addition to providing the outcomes discussed above, 19 studies [18–20, 25, 26, 28, 29, 32–37, 39–42, 44, 46] also produced a ranking order of outcomes most commonly cited by physicians as barriers to the administration of anticoagulation. Bleeding risk was the most cited reason not to anticoagulate in 11 studies, falls risk in 4 studies, age of patient in 2 studies and patient compliance in 2 studies (a table of this information is available as supplementary data in *Age and Ageing* online).

Methodological quality

The use of the methodological quality checklist showed that the quality of reporting was generally good. Ten studies [23, 25, 27, 30, 34, 36, 37, 39, 41, 46] had a response rate over 65%. Eight studies [36, 37, 39, 42–45, 47] actively described efforts to reduce potential sources of bias. However, six studies [19, 21, 25, 28, 29, 32] did not discuss limitations of the studies and eleven authors [18, 20, 21, 24, 25, 28, 32, 38, 39, 45, 47] did not adequately discuss the possibility that the physicians who participated in the study were not representative of the population. This information is presented in tabular format as Supplementary data in *Age and Ageing* online.

Discussion

Key findings

Age, risk of bleeding, risk of falls, co-morbidities (cognitive impairment and alcoholism) and patients' ability to comply with treatment were all important barriers to effective anticoagulation.

The most striking result of the review is the extent to which physicians are reticent to administer warfarin to elderly patients, even if these patients are otherwise healthy. Physicians become even more reluctant when a patient is aged greater than 80 years. This pattern is observed throughout all specialties and grades of medical practice included in the review (Table 1 and see Table S1, Supplementary data available in *Age and Ageing* online.).

How does reported practice relate to evidence?

NICE guidelines suggest that warfarin therapy has a greater benefit in patients over 75 as they are at a higher risk of stroke than those under 75 [6]. They also suggest that patients aged 65–75 may benefit from warfarin, especially if there are co-existing risk factors for stroke. Finally, patients under 65 are at a relatively low risk of stroke, even in the presence of additional risk factors and thus are better treated with an anti-platelet agent [6].

A recent analysis by van Walraven *et al.* suggests that the absolute therapeutic benefit of anticoagulation for patients at risk of stroke rises significantly with age. In accordance with this, they strongly recommend that advanced age should not be considered a contraindication to anticoagulation [74].

Recent guidelines issued by the European Society of Cardiology (ECS) have echoed this, giving even more weight to advanced age as a risk factor for stroke, and thus as an incentive for prescription of anticoagulation [73].

This review suggests that these guidelines are not being adhered to in clinical practice. Of the eight studies [18, 20–

23, 32, 35, 47] which directly compared matched pairs of patients with age as the only variable, six studies [18, 20–23, 32] showed that physicians were less inclined to administer warfarin therapy in a patient over 70 years of age, when compared with a matched patient under 70 years of age.

Why does this discrepancy between evidence and reported practice exist?

Physicians may argue that it is unusual to see a patient over 70 years old with no health problems other than AF, and who is directly comparable with a younger patient with AF. Advanced age often goes hand-in-hand with other risk factors for bleeding such as polypharmacy, cognitive impairment and risk of falls.

However, this review highlights that even when an elderly patient is in good health, and when that patient does qualify for anticoagulation, it is often still assumed by physicians that contraindications to warfarin therapy are present. These assumption may be a crucial reason as to why 40% of patients with AF who are eligible for anticoagulation therapy are not receiving this potentially lifesaving treatment [6].

Additional findings

Bleeding risk was also considered an important barrier to anticoagulation and was the most commonly cited reason not to anticoagulate. Several of the included studies reported that a history of gastrointestinal (GI) bleeding would significantly deter physicians from anticoagulating a patient [25, 32, 35]. Recent evidence suggests, however, that due to advances in detection and eradication of *Helicobacter pylori*, patients who have had an ulcer-related GI bleed in the past and have subsequently received treatment for this are at no greater risk of a re-bleed than a person without this history [64]. Care must be taken however in patients taking non-steroidal anti-inflammatory drugs as these medications confer an ongoing GI bleeding risk [65].

With regards to intracranial bleeding risk, physicians often consider a patient's risk of falling before anticoagulating. Falls risk was an important barrier to anticoagulation in the studies we included, with one study reporting that 98% of physicians would not consider warfarin if a patient had a high risk of falling [40]. Despite this, evidence suggests that a predisposition to falls should not be considered an automatic contraindication to anticoagulation therapy [66, 67]. In a recent study, ManSonHing *et al.* used a Markov decision analytic model to ascertain the ideal therapy for elderly patients with AF who are at risk of falling. They found that, for a patient with an average risk of stroke from AF (5% per year), it would require the patient to fall roughly 300 times per year for the risks of anticoagulant therapy to outweigh its benefits, in terms of intracranial bleeding [66]. The mean number of falls sustained annually by elderly individuals who fall is, however, only 1.81 [72]. The same study also highlights that the risk of incurring other significant injuries from falls, such as fractures, is far higher than the risk of intracranial bleeding [66].

Our review suggests therefore, that both a risk of falls and a risk of bleeding are *disproportionate* barriers to anticoagulation.

The meaning of the term 'risk of falls' was not congruent between all studies. Some gave little detail as to the level of risk, or whether the hypothetical patient in question had fallen in the past and how often. In practice this difference would be considered extremely important when assessing a patient's suitability for anticoagulation, and should be taken into account. Similarly, the exact meaning of the term 'bleeding risk' was not provided by all studies. Indeed, many methods of calculating bleeding risk, such as the HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalised ratio, Elderly (>65 years), Drugs/alcohol concomitantly) score, include elderly age as a factor [75].

Evidence is less clear about the risk and benefits of anticoagulation in patients with cognitive impairment, alcoholism and a patient's ability to comply with treatment. These patients are usually excluded from clinical trials assessing the risks and benefits of anticoagulation in AF and, consequently, sound clinical judgement is required in these cases [68]. In addition to this, the exact meaning of 'cognitive impairment' was not stated by some studies, making it difficult to draw firm conclusions.

Other research in the field

To the best of our knowledge, this is the only systematic review of perceived barriers to anticoagulation which aims to identify the importance of the particular barriers to its prescription, rather than quantify the extent of its under-utilisation. As mentioned in the introduction, some work has been done in an attempt to identify to what extent warfarin is under-utilised, and a systematic review of this evidence has been carried out [69].

Relevance of the review

In 2009 the NHS published a document named Guidance on Risk Assessment and Stroke Prevention in Atrial Fibrillation (GRASP-AF) [17]. This risk stratification tool aids GPs with clinical decision-making regarding anticoagulant therapy for AF. The tool aims to identify those patients with AF who, according to their calculated $CHADS_2$ score, qualify for warfarin therapy and yet are not receiving it. However, the tool does not assess these patients' contraindications to warfarin.

Strengths of the review

The search strategy was extensive and the authors believe it to be very unlikely that any relevant published studies were

missed. In addition to this, the inclusion criteria were deliberately broad in order to include all relevant publications from a wide variety of medical specialties and levels of training. The studies in the review also span the entirety of the two decades from when warfarin as stroke prevention was introduced until the present day.

Limitations of the review

Only studies that were available in the English language were selected. All unpublished data were excluded from the review, leading to the possibility of publication bias. It is hoped that this bias will be minimal however, as the studies under review focus on opinions rather than positive or negative results, which should mean that publication bias is unlikely.

Only studies published after 1989 were included in the review as this was the year of publication of the first large randomised controlled trial comparing oral anticoagulation with placebo in the prevention of stroke in patients with chronic AF [7]. Despite this, some of the earliest studies included in the review may still have been conducted at a time when anticoagulation was not as extensively understood as it is now, which means that attitudes expressed in these studies may not reflect our current understanding.

Limitations of included studies

The results of this review are based upon physicians' self-reported practice and thus may not reflect actual practice with regard to warfarin therapy. Furthermore, the low response rate in some of the studies limits generalisability.

Methodological quality

The quality assessment included in the review suggests that, in general, the studies were carried out well. Therefore, we do not feel that variations in the quality of the evidence influence the results of this review.

Implications for future research

Further work needs to be done to increase rates of anticoagulation, and future guidelines should specifically address the barriers described in this review. The need for more clearly defined guidelines is a view that is shared by the latest Cochrane review of oral anticoagulation for stroke prevention [70].

The GRASP-AF initiative, is undoubtedly a step in the right direction, however its use should be extended for use in all specialties in which patients with AF are cared for. The efficacy of the GRASP-AF tool is, as yet, unknown, as it has been a relatively recent introduction, and audit will be important to assess this.

Conclusion

Physicians report that age is a significant barrier to anticoagulation, despite good evidence of its effectiveness in older people. The risk of falls and bleeding risk were also found to be disproportionate barriers to anticoagulation when compared with guidelines [6, 64, 66, 67].

The discrepancies highlighted in this systematic review are likely to be a significant part of why up to 40% of patients in the UK who would benefit from anticoagulation therapy are not receiving it [17].

Key points

- This review has found that advanced age is an important barrier to the prescription of warfarin, despite guidelines attempting to promote the opposite.
- A patient's bleeding risk and falls risk are also disproportionate barriers to warfarin therapy.
- Further studies are required to determine how best to overcome the barriers highlighted here.

Conflicts of interest

None declared.

Supplementary data

Supplementary data mentioned in the text is available to subscribers in *Age and Ageing* online.

References

Owing to the large number of references, only 30 are listed below and are represented by bold type throughout the text. The full list can be found as *Age and Ageing* online.

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Received 12 April 2011; accepted in revised form 26 May 2011

Patient Preference and Adherence

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REVIEW

Current issues in patient adherence and persistence: focus on anticoagulants for the treatment and prevention of thromboembolism

This article was published in the following Dove Press journal:
Patient Preference and Adherence
10 March 2010
Number of times this article has been viewed

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Abstract: Warfarin therapy reduces morbidity and mortality related to thromboembolism. Yet adherence to long-term warfarin therapy remains challenging due to the risks of anticoagulant-associated complications and the burden of monitoring. The aim of this paper is to review determinants of adherence and persistence on long-term anticoagulant therapy for atrial fibrillation and venous thromboembolism. We evaluate what the current literature reveals about the impact of warfarin on quality of life, examine warfarin trial data for patterns of adherence, and summarize known risk factors for warfarin discontinuation. Studies suggest only modest adverse effects of warfarin on quality of life, but highlight the variability of individual lifestyle experiences of patients on warfarin. Interestingly, clinical trials comparing anticoagulant adherence to alternatives (such as aspirin) show that discontinuation rates on warfarin are not consistently higher than in control arms. Observational studies link a number of risk factors to warfarin non-adherence including younger age, male sex, lower stroke risk, poor cognitive function, poverty, and higher educational attainment. In addition to differentiating the relative impact of warfarin-associated complications (such as bleeding) versus the lifestyle burdens of warfarin monitoring on adherence, future investigation should focus on optimizing patient education and enhancing models of physician–patient shared-decision making around anticoagulation.

Keywords: anticoagulation, warfarin, adherence, persistence, thromboembolism

Introduction

Therapy with vitamin K antagonists such as warfarin is highly effective in reducing morbidity and mortality related to thromboembolism. Numerous trials have demonstrated a clear benefit to treating patients with atrial fibrillation and consensus guidelines now recommend routine anticoagulation in many patient groups with atrial fibrillation.[1,2] Similarly, some guidelines have advocated for indefinite anticoagulation in certain subsets of patients with venous thromboembolism.[3] At the same time, recent efforts to enhance patient safety have identified anticoagulants as "high risk" medications,[4] the proper use of which requires particular scrutiny to maximize clinical safety.[5] Despite data supporting the use of long-term anticoagulation in a number of patients and increases in physician prescription of appropriate anticoagulant therapy,[6,7] maintaining patient adherence on long-term warfarin therapy remains a significant challenge due to the risks of anticoagulant-associated bleeding complications and the burdens of frequent monitoring and dose-adjustment. Moreover, provider concerns around patient compliance with anticoagulant regimens likely prevent more widespread adoption of indicated anticoagulation therapy.[8]

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The aim of this paper is to review known determinants of patient adherence and persistence on long-term anticoagulant therapy for atrial fibrillation and venous thromboembolism. We evaluate what the current literature reveals about the impact of warfarin use on quality of life, evaluate existing clinical data to identify patterns of patient adherence to warfarin, and summarize what is known about the major risk factors that influence warfarin discontinuation.

Common indications for long-term anticoagulation with warfarin

Prolonged warfarin therapy is indicated in a number of clinical scenarios other than atrial fibrillation and venous thromboembolism, including for prosthetic heart valves.[2] However, clinical application of available guidelines for atrial fibrillation and venous thromboembolism remains somewhat unique in that patient preference and values are emphasized as important contributors to the decision to begin and maintain warfarin therapy.[1,3] Also, physicians demonstrate reluctance to strictly follow guidelines in atrial fibrillation and venous thromboembolism in part due to the perceived barriers to warfarin success in their patients as well as recognition that guidelines around appropriate anticoagulation are difficult to generalize to all patients.[8–10] In other words, indefinite warfarin use in atrial fibrillation and venous thromboembolism can be viewed by some patients and clinicians as more optional and subject to ongoing comparisons of the risks and benefits of therapy. As such, these clinical scenarios offer a unique opportunity to evaluate the way patient behaviors and preferences impact medication adherence.

Atrial fibrillation

Atrial fibrillation is the most common clinically significant arrhythmia, affecting around 2.5 million people in the United States – a number bound to rise dramatically as the population ages in coming decades.[11,12] Atrial fibrillation is an important independent risk factor for stroke, accounting for 15% of all strokes in the US and up to 36% of all strokes occurring in patients 80 to 89 years old.[13] Overall, atrial fibrillation confers a 4- 5-fold increase in ischemic stroke risk, and patients left untreated for atrial fibrillation face a 4.5% risk per year of suffering a stroke.[14,15]

Numerous well-designed clinical trials demonstrate that oral vitamin K antagonists such as warfarin sodium substantially reduce the risk of atrial fibrillation-related stroke, such that treating only 32 patients with atrial fibrillation prevents 1 stroke.[16–21] Moreover, adjusted-dose warfarin is superior to available alternative treatment options, such as anti-platelet therapy with clopidogrel and aspirin.[1] Based on the cumulative clinical trial data weighing the benefit of stroke prevention versus the risk of adverse effects from warfarin such as bleeding, consensus opinion recommends long-term (lifelong) warfarin treatment (goal INR 2.0–3.0) in patients with additional risk factors for stroke, such as previous stroke, older age, hypertension, diabetes mellitus, and congestive heart failure.[1]

Venous thromboembolism

Clinically significant venous thromboembolism, particularly deep vein thrombosis (DVT) and pulmonary embolism (PE), represents a considerable public health concern with an annual incidence of about 100 per 100,000 in the general population[22–24] and with PE causing up to 200,000 deaths annually in the US.[25] Randomized trials have clearly demonstrated that at least 3 months of warfarin is more effective in preventing recurrent venous thromboembolism than shorter durations. However, certain patient sub-groups, such as those with active cancer or idiopathic venous thromboembolism, have higher rates of recurrent venous thromboembolism and thus may benefit from life-long anticoagulation.[26,27] At the same time, the benefits of reducing venous thromboembolism recurrence risk must be balanced with an increased bleeding risk and may be strongly influenced by patient preference.[3] Although several promising strategies have been developed to help estimate a person's risk for venous thromboembolism recurrence, there remains no validated risk scheme that can help clinicians risk-stratify patients to appropriate duration of anticoagulation therapy.[10,28,29]

The 8th American College of Chest Physicians Consensus Guidelines currently recommend indefinite anticoagulation in the following patient subgroups: (1) patients with a first unprovoked proximal DVT without risk factors for bleeding and for whom adequate anticoagulant monitoring is achievable, (2) patients with a second unprovoked DVT, (3) patients with concomitant cancer.[3]

Translating evidence-based recommendations into the clinical setting

Despite evidence supporting long-term anticoagulant therapy in certain patients, multiple factors, including the necessity of frequent international normalized ratio (INR) monitoring and drug-drug and diet interactions make the translation of evidence-based recommendations into "real-life" challenging.[1,9] Clearly, tight warfarin control within a narrow therapeutic range is an important practical consideration

since supratherapeutic INRs (especially >4.0) raise the risk of severe bleeding complications such as intracranial hemorrhage.[18,30–32] Likewise, warfarin under-dosing puts patients at significant risk for thromboembolism and stroke.[33,34] Despite the importance of maintaining warfarin in a therapeutic range, nearly one-half of patients with atrial fibrillation who had stroke despite intention-to-treat with warfarin had inadequate anticoagulation (INR < 1.5) and 30% were not actively taking warfarin at the time of their stroke.[35] Data suggest that patients maintain a target INR level only about 50% of the time[35] and that as many as 22%–33% of patients newly started on warfarin for atrial fibrillation discontinue therapy within the first year of treatment.[36–39]

Clearly, the appropriate translation of evidence-based recommendations to the real world remains a challenge. Because many patients benefit from appropriate lifelong anticoagulation with warfarin, insights into adherence and reasons for discontinuation have critical implications for improving the quality of anticoagulant care.

Impact of long-term warfarin therapy on quality of life

Warfarin has a narrow therapeutic window, requiring frequent blood tests and dose-adjustments.[40] Warfarin effects also may vary in response to changes in diet and other medications. The challenges in maintaining warfarin in an appropriate therapeutic-range combined with increased risk of both major and minor bleeding may contribute to difficulties in convincing patients to take chronic warfarin as well as remain compliant with recommended treatment and monitoring. Despite methodologic challenges when attempting to formally quantify quality of life,[41] studies have generally challenged assumptions that long-term warfarin therapy significantly and negatively impacts patient quality of life. Warfarin appears to have at most a modest impact on quality of life, and studies suggest a wide range of interpatient variability of quality of life experiences on warfarin, supporting the merit of incorporating individual patient preferences into warfarin treatment decisions.

Health-related quality of life can be estimated as a subjective measure of how physical impediments as well as psychological and emotional discomfort impact a person's day-to-day life. A medication's net impact on a patient's quality of life can be thought of as a balance between the potential side effects of a medication, the burden of complying with an appropriate dose of the medication, and the medication's ability to prevent the targeted adverse health outcome.[42]

Qualitative studies and patient interviews have identified several domains that come into play when considering the impact of long-term warfarin therapy on quality of life (Table 1). These include the inconvenience of taking the medication, inconvenience of frequent blood monitoring, perceived efficacy of the medication, perceived safety of the medication, anxiety related to potential and actual side effects of the medication, patient autonomy, the quality of information given to patients by physicians and shared decision making before starting the medication, symptom alleviation (or prevention), and impact of the medication on physical activities.[43] In qualitative studies, the most commonly cited difficulties for patients on long-term warfarin include the burden of regular clinic visits, dietary and alcohol restrictions, and worrying about side effects and drug-drug interactions.[44]

However, attempts to formally quantify the effects of warfarin on quality of life have found relatively small effects even when compared to medications (such as aspirin) that do not require the monitoring and restrictions of warfarin. This may be related in part to the value patients place on the potential of warfarin to prevent adverse health outcomes (especially debilitating stroke) over the risk of adverse drug effects or inconvenience of the drug regimen.[45] Physicians, in fact, may tend to over-emphasize the impact of long-term warfarin on quality of life, and many have speculated that mismatched expectations between physician and patient perceptions of risks, benefits, and lifestyle burden of long-term warfarin may have important implications in under-prescribing and medication compliance patterns.[8,42,44,46]

Patients demonstrate considerable variability in their quality of life preferences regarding warfarin therapy for stroke prevention. One study interviewed patients with atrial fibrillation to quantify the impact of stroke using a time-tradeoff method and found that 83% considered a

Table 1 Factors that may influence quality of life for patients taking warfarin

Inconvenience of taking the medication
Inconvenience of frequent blood monitoring and clinic visits
Perceived efficacy of the medication in preventing adverse outcomes (ie, stroke)
Anxiety related to potential and actual side effects of the medication
Anxiety about potential drug-drug interactions
Extent of shared decision making between the physician and patient when starting the medication
Quality of information given to patients by physicians
Impact of the medication on physical activities
Dietary and alcohol restrictions

major stroke to be equal or worse than death.[41] However, about 10% of patients estimated that the same type of stroke would decrease their quality of life by less than 50%. These patients also generally considered stroke prophylaxis with warfarin to have nearly no negative impact on their quality of life overall, and about the same as using aspirin for stroke prevention. However, 16% of patients estimated their quality of life on warfarin so low that treatment with aspirin alone would actually be preferred in terms of quality-adjusted life expectancy. Acknowledging that indirect measurements of quality of life, such as by using time-tradeoff estimation, are artificial and difficult to apply to actual patient experience, this study indicates that individual patient preference is likely to play a role in ultimate adherence to a given prophylaxis regimen.

Only one major randomized controlled trial has examined in detail the impact of long-term warfarin therapy on quality of life.[47] This trial randomized patients with non-rheumatic atrial fibrillation to adjusted-dose warfarin versus control. The study followed patients for over two years and regularly assessed quality of life with validated scales measuring overall functioning, well-being, and health perceptions. Of patients taking warfarin in the study, only 11% of patients agreed that "taking warfarin restricts my life-style," 22% said "I worry a lot about the side effects of warfarin," and 3% agreed "I would be more physically active if I did not take warfarin." Overall, no significant differences in global quality-of-life were found between warfarin and non-warfarin treated patients. However, the study noted that bleeding complications resulted in worsened adverse health perceptions and distress.

Studies of elderly patients (>75 years) in the United Kingdom used a validated version of the short form (SF)-36 to measure quality of life before and 6 months after starting warfarin therapy for atrial fibrillation and failed to demonstrate a negative quality of life impact from warfarin, regardless of length of warfarin therapy.[42,48] In another study, structured interviews of 21 older patients (average age 74 years) with atrial fibrillation on warfarin explored patients' experiences within four domains including "impact on daily life" and "patient satisfaction," finding that for the most part, warfarin was well tolerated and did not pose heavy additional burdens or lifestyle changes; in fact, quality of life appeared to be more influenced by the patient's underlying comorbid conditions.[44] At the same time, the study acknowledged a wide range in the perceived impact of warfarin therapy, where ~25% of patients stated that adhering to warfarin has at least some negative impact on their daily life. Locadia et al studied quality of life differences among younger patients (average age 60 years) treated with three versus 6 months of warfarin for deep venous thrombosis.[49] Similar to studies in patients with atrial fibrillation, there was no difference in quality of life between the two groups at 6 months. Even among young (average age 51 years), indigent, minority patients studied at two Bronx anticoagulation clinics, only 19% of patients on warfarin reported limitations in their daily life.[50]

While available data argue against attributing a significant negative quality of life impact to long-term warfarin therapy, all of the studies have limitations. For one, we do not know whether quality of life would have been more negatively impacted in patients who were not selected to start warfarin; similarly, little is known about quality of life changes in patients who discontinued warfarin. Most studies were of patients who already elected to take warfarin, individuals who may be at baseline more compliant or agreeable to chronic therapy. Greater variability in quality of life may be more likely in unselected patients.[46,51] Also, for the most part, studies have evaluated older patients and potentially lack generalizability to younger patients who might experience a more pronounced quality of life detriment when forced to limit activities (like sports) to prevent bleeding.[47] Finally, the impact of experienced side effects (ie, bleeding), even if minor, likely plays a significant role in determining patient's quality of life while taking warfarin and needs a more robust assessment in future quality of life analyses.

Several anticoagulation-specific quality of life measurement tools have been developed in recent years with the goal of better measuring nuances related to long-term anticoagulation therapy effects on quality of life.[43,52,53] Future studies using these tools, especially given the development of novel therapies that do not require the monitoring and dose-adjustment burdens of warfarin,[43,53] may uncover important details of how quality of life issues interact with patient experiences on long-term anticoagulation.

Adherence to anticoagulation in clinical trial settings

Randomized clinical trials that randomly assign patients to either warfarin or an alternative agent can help illuminate the risk of non-adherence related to warfarin, independent of potential confounding factors that affect the validity of observational studies. Because patients are randomly assigned to either warfarin or an alternative, risk factors that may be related to adherence should be equally allocated.

The majority of warfarin trials have been non-blinded, where only patients randomized to warfarin undergo regular INR testing. In these studies, both medication side-effects and the burdens of monitoring may be factors contributing to non-adherence.

The original clinical trials comparing oral anticoagulants to placebo or aspirin did not consistently demonstrate a compliance difference between the two arms. Some trials reported higher rates of discontinuation in patients randomized to oral anticoagulants[16,21] while others showed no difference.[17–19,55]

The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE W) trial randomized patients to oral anticoagulation or clopidogrel plus aspirin.[54] The cumulative risk of permanent discontinuation was only 7.8% for oral anticoagulation versus 13.8% for clopidogrel plus aspirin. In comparison, the Birmingham Atrial Fibrillation Trial of the Aged (BAFTA) study found that elderly patients were more likely to discontinue warfarin than aspirin therapy.[20] After a mean follow-up period of 2.7 years, 33% of individuals randomized to warfarin discontinued therapy, compared to 24% of patients randomized to aspirin. Notably, discontinuation rates were relatively high in both arms and it is possible that the burdens of warfarin monitoring weighed more heavily in elderly patients.

Newer anticoagulants, such as oral direct thrombin inhibitors and Factor Xa inhibitors may become promising alternatives to warfarin and have the advantage of fixed oral dosing without routine INR measurements. The Stroke Prevention using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III trial randomized patients to open-label warfarin versus ximelagatran, a direct thrombin inhibitor.[55] Although ximelagatran was taken twice daily at fixed doses and did not require routine INR monitoring, 18% prematurely discontinued ximelagatran while 14% discontinued warfarin. The double-blinded SPORTIF V trial, where patients randomized to ximelagatran had sham INR testing to mimic on-warfarin treatment, found no significant difference in the proportion of patients who chose to stop therapy (10.6% in the warfarin arm versus 10.0% in the ximelagatran arm).[56] The recent Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial compared the oral direct thrombin inhibitor dabigatran to warfarin and showed 16.6% discontinued warfarin at 2 years while 21.0% discontinued fixed dose dabigatran.[57] In a subsequent randomized trial comparing warfarin to dabigatran for treatment of acute DVT, treatment was stopped in 1.6% of patients on dabigatran for non-adherence compared to 2.8% of patients on warfarin, though the study was not designed to evaluate adherence rates.[58]

In summary, discontinuation and non-adherence rates on warfarin are not consistently higher than in control arms of randomized clinical trials, although elderly patients may be more likely to discontinue warfarin than aspirin. Extrapolating these findings to general clinical care must be done cautiously since randomized trials tend to recruit highly motivated participants who may be more compliant than unselected populations. Additionally, randomized trials have frequent monitoring and follow-up related to the study, which may lead to a higher adherence rate than in general clinical care. Data from observational studies are therefore useful to examine risk factors for non-adherence in real-world settings.

Risk factors for poor adherence to warfarin therapy

Large proportions of patients in whom warfarin therapy is indicated do not take warfarin, particularly for atrial fibrillation.[59–61] While the reasons for undertreatment are multiple, the failure to initiate warfarin therapy is responsible for a large percentage of underuse.[6,9,62–64] At the same time, data suggest that even in patients appropriately initiated on warfarin therapy, many struggle to maintain adherence over the long term.[38–40,65] Although as described above, there are challenges in quantifying the negative impact of warfarin on quality of life, several risk factors for non-adherence to warfarin have been identified, including younger age, male sex, low overall stroke risk, poor cognitive function, poverty, homelessness, and higher educational attainment (Table 2). Continuing to study and uncover contributing risk factors for non-adherence is important due to the correlation of poor adherence to lower proportions of time spent in therapeutic INR ranges[65–68] as well as to worse morbidity and mortality.[69]

Table 2 Factors associated with poor adherence to warfarin therapy

Younger age
Male sex
Low overall stroke risk
Poor cognitive function
Poverty
Homelessness
Higher educational attainment
Employment
Reluctant receptivity of medical information

Preliminary data from the Anticoagulation and Risk factors in Atrial Fibrillation (ATRIA) Study suggest that over one in four patients newly started on warfarin therapy for atrial fibrillation discontinue therapy within 1 year.[70] These results are consistent with data from clinical trials as discussed above showing a 22% discontinuation in the first year and 33% during a mean study period of 2.7 years in patients randomized to warfarin versus alternative agents,[37,39] as well as an observational study demonstrating that 26% of patients older than 79 years newly started on warfarin had stopped therapy within the first year.[38] Although a high frequency of hemorrhagic events partially explained the significant discontinuation rate in one study,[38] discontinuation rates were large even in studies without many major bleeding episodes.[37,70]

Despite the higher risk of hemorrhagic complications in elderly patients, studies have found younger age to be a risk factor for poor warfarin adherence.[36,71] Men and patients with fewer risk factors for stroke also appear to have lower warfarin adherence rates.[36,64,71]

The INR Adherence and Genetics (IN-RANGE) study examined the prevalence and risk factors of inconsistent warfarin use.[72,73] Using electronic pill bottle caps to monitor patient adherence over 32 weeks, 92% had at least one missed or extra bottle opening and 36% missed more than 20% of the prescribed bottle openings. Analysis of the IN-RANGE data linked poor adherence to several risk factors, including education beyond high school and being actively employed, but also to lower mental health functioning and poor cognitive functioning.[74]

In terms of educational attainment, the IN-RANGE findings are consistent with previous case-control data,[71] possibly because higher education may correspond to patient confidence in independent decision making or decreased trust in physicians. Fang et al showed that although limited health literacy was associated with deficits in warfarin-related knowledge, knowledge and literacy levels were not significantly associated with self-reported adherence or INR control.[75] Active employment has been found to be a risk factor for poor adherence for both anticoagulation as well as other diseases,[67,76] possibly because employed patients may have greater competing time interests. While employment may be linked to poor adherence, so might extreme poverty, as data from an underserved urban population demonstrate an association with higher self-reported adherence in individuals with an annual income greater than $10,000.[50]

While race has been implicated as an independent risk factor for adherence of certain medications, such as anti-hypertensive medications,[77–79] few studies have looked at the impact of race on adherence to warfarin regimens. Case-control data suggest a trend where non-compliant cases were more likely to be non-white.[71] There is evidence that some warfarin related racial disparities exist, including worse INR testing frequency among African-American and Hispanic patients[80] and increased likelihood of African-Americans having subtherapeutic INRs.[81] However, none of these studies demonstrated a difference in adherence based on race, and further studies are needed to understand the interaction, if any.

Investigation into psychosocial determinants specific to warfarin adherence has been limited, but evaluation of medically ill patients in general has identified multiple associated factors including depressive symptoms, perceived lack of social support, poor cognitive function, and poor health related quality of life.[82–85] In a study of patients on warfarin for non-valvular atrial fibrillation, patients with presumed psychosocial risk factors for non-adherence, in particular substance abuse, had increased risk for adverse medical outcomes, though adherence rates were not directly assessed.[83] Johnston et al found that only 9.7% of studied Medicaid patients with new atrial fibrillation filled a prescription for warfarin within 30 days of diagnosis.[62] In this cohort, alcohol and drug abuse, psychiatric disease, homelessness, and lack of caregiver support were inversely related to warfarin use, though the study could not differentiate between patients who were given a prescription and failed to fill it versus those who never received a prescription. Cognitive functioning has inconsistent associations with adherence, but such studies are likely to be confounded by caregiver involvement.[84,85]

In addition to psychosocial determinants of warfarin use, a few studies have investigated attitudinal correlates to warfarin adherence. A study of patients in an academic anticoagulation clinic evaluated self-reported compliance and found that in addition to being homeless, non-married, and having a higher pill-burden, patients' perceptions of barriers to taking warfarin correlated to worse compliance.[86] Barriers measured in this case included the perception of taking too many pills, the perception that taking warfarin increases worry about bad health outcomes, and the perception that taking warfarin increases bruising and bleeding. Qualitative data also hint at the potential impact of high pill burden as a perceived barrier warfarin adherence.[44] In another analysis, Cruess et al found trends linking several attitudinal assessment scores with warfarin non-adherence.[87] Of these, higher "Information Discomfort," specifically a measure of "patient reluctance to hear information about their medical

conditions and treatments," was independently associated with poor adherence.

In summary, patients often struggle to maintain adherence with warfarin regimens, potentially leading to more difficult INR control and increasing the risk for adverse health outcomes.[72] Multiple risk factors seem to predispose patients to inconsistent warfarin use. Among demographic factors, younger age and male sex confer worse compliance, while elderly patients may be among the most adherent groups. In terms of medical comorbidities, a lower risk of stroke confers worse adherence as does poor cognitive functioning. Indirect data suggest that multiple comorbidities and the associated high pill burden may enhance perceived barriers to warfarin adherence among patients. Hemorrhagic events on warfarin surely influence future drug persistence, but questions about the exact relationship of non-adherence to bleeding and the relative weight of minor versus major bleeding events needs further evaluation. Those with higher educational attainment are less likely to demonstrate warfarin adherence as are those currently employed, though the reasons for this are not clear. Homelessness, poverty, and lack of social support are associated with lower adherence. Finally, attitudinal factors including the perception of barriers to compliance and reluctant receptivity of information related to medical conditions may play an important role in determining adherence.

Ultimately, the determinants of warfarin adherence in an individual patient probably exist as a complex matrix of interacting factors. Awareness of these factors and development of strategies to overcome their influence represent potentially important ways to improve not just initiation of warfarin therapy, but also the *persistence* of that therapy.

Conclusion and future investigations

Anticoagulant use will likely increase as the national and worldwide population ages in coming decades. As more patients are initiated on warfarin therapy and novel anticoagulant agents are developed, further studies are needed to elucidate the complex interaction of various factors contributing to patient adherence and persistence on anticoagulation. It remains unclear whether monitoring burdens significantly affect subsequent persistence on therapy independent of the associated activity limitations and bleeding complications of warfarin. Measuring the relative impact of warfarin therapy on quality of life is challenging. Newer classes of oral anticoagulants including direct thrombin inhibitors and factor Xa inhibitors offer the promise of predictable pharmacokinetics and more specific factor targeting that will limit the need for monitoring and may have quality of life advantages over warfarin.[88] Interestingly, a recent randomized trial comparing oral warfarin to the oral direct thrombin inhibitor dabigatran demonstrated that dabigatran was as good as warfarin at 6 months in preventing recurrent venous thromboemolism, and shared a similar safety profile, but did not require laboratory monitoring.[58] The study did not directly address quality of life differences. As these new drugs continue evaluation and development, quality of life measurement tools that are specific to anticoagulant therapy will be important when comparing the efficacy of these agents with warfarin.[43]

Clinicians likely influence persistence as well, as patients are more likely to remain on anticoagulation if they have multiple thromboembolic risk factors. Although major bleeding events on anticoagulation are relatively uncommon, minor bleeds may significantly affect both clinician and patient perceptions of the risk of therapy, and thus, subsequent persistence.

Strict adherence to anticoagulant regimens is important to maximize the time spent in a therapeutic anticoagulation intensity. In certain patient populations, such as those who have impaired cognition, interventions such as monthly medication organizers,[89] interactive voice response systems,[90] compliance-linked financial incentives,[91] and at-home warfarin self-management programs,[92,93] have shown promise in improving adherence.

Attempts to enhance adherence and persistence in individual patients must prioritize patient preference and tailor treatment options appropriately. Evidence highlights a dramatic interpatient variability around perceptions and preferences for antithrombotic prophylaxis,[41] as well as the problematic nature of physician assumptions about patient preferences.[43] While patient knowledge about warfarin therapy seems a logical target for shaping patient perceptions of warfarin, anticoagulation education and health literacy alone have not proven to independently predict adherence.[75] Further exploration of the type and best delivery mode for that information will help shape education strategies in the future.[94,95] Furthermore, it must be understood that in addition to overt preferences, more subtle patient attitudes – such as perceived adherence barriers[86] and lack of receptivity to medical information[87] – may need to be addressed for successful adherence. As such, future investigation should focus on enhancing models of patient-physician shared decision making around anticoagulation.[46]

Disclosures

The authors declare no conflicts of interest.

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RISK FACTORS & CURRENT RISK ASSESSMENT TOOLS

There are many different risk factors identified for both stroke and bleeding; however, many risk assessment tools only look at anticoagulated patients, younger patients, trial cohorts, etc. Ideal risk assessment tools will reduce subjectivity and produce confident, patient-tailored decisions. Bleeding has also not historically been considered as a determinant for use of anticoagulants. Part of the challenge for this roundtable is to determine if the current bleeding risk tools are adequate for health care practitioners and the patients they treat. Additionally, are there other risk factors or markers for risk—like plasma von Willebrand factor (vWF)—that should be considered when making assessments?

Stroke Risk Assessment

$CHADS_2$ Score and Stroke Rate

Letter	Clinical Characteristic*	Points Awarded
C	Congestive heart failure	1
H	Hypertension	1
A	Age ≥75	1
D	Diabetes mellitus	1
S_2	Stroke/TIA/TE	2
	Maximum score	6

TIA = transient ischemic attack; TE = thromboembolism
0 points = low risk
1 point = intermediate risk
2 or more points = high risk
Annual Adjusted Stroke Rate
0 points = 1.9%
1 point = 2.8%
2 points = 4%
3 points = 5.9%
4 points = 8.5%
5 points = 12.5%
6 points = 18.2%

CHA_2DS_2-VaSc Score and Stroke Rate

Letter	Clinical Characteristic	Points Awarded
C	Congestive heart failure/LV dysfunction	1
H	Hypertension	1
A_2	Age ≥75	2
D	Diabetes mellitus	1
S_2	Stroke/TIA/TE	2
V	Vascular disease	1
A	Age 65 – 74	1
Sc	Sex category (i.e. female sex)	1
	Maximum score	9

LV = left ventricular; TE = thromboembolism; vascular disease = prior myocardial infarction, peripheral artery disease, or aortic plaque
0 points = low risk
1 point = intermediate risk
2 or more points = high risk
Annual Adjusted Stroke Rate
0 points = 0%
1 point = 1.3%
2 points = 2.2%
3 points = 3.2%
4 points = 4.0%
5 points = 6.7%
6 points = 9.8%
7 points = 9.6%
8 points = 6.7%
9 points = 15.2%

Curr Atheroscler Rep (2011) 13:290–297
DOI 10.1007/s11883-011-0188-x

Prediction of Stroke Risk in Atrial Fibrillation, Prevention of Stroke in Atrial Fibrillation, and the Impact of Long-Term Monitoring for Detecting Atrial Fibrillation

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Published online: 7 June 2011

Abstract Atrial fibrillation (AF) is a large public health problem that affects about 1% of the population in the United States. It confers an increased risk for stroke and thromboembolism, but the stroke risk is not equal in all patients. Further refinement in stratifying stroke risk in patients with AF will help in properly directing therapy for AF patients while minimizing adverse events. Warfarin is the first-line treatment for stroke reduction in patients with AF, but many new drugs are on the horizon that will significantly change practice. New and improved cardiac monitoring techniques and devices will help with detection of AF in those at risk for stroke and will assist in assessing which patients will most benefit from anticoagulation.

Keywords Atrial fibrillation · Stroke

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. AF is present in 1% of the US population and is expected to affect up to 15 million patients by 2050 [1]. It confers a high risk for stroke and thromboembolism (approximately 4% per year) and accounts for 15% of ischemic strokes [2]. This stroke risk is not equal in all patients. Although oral anticoagulant therapy with warfarin remains the mainstay therapy for stroke reduction in AF, many new agents and techniques will soon be available for the management of stroke risk in AF. Improvements in cardiac monitoring have yielded improved detection of AF and quantification of AF burden, which may help better individualize therapy for AF.

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Prediction of Stroke Risk in Atrial Fibrillation

The identification of stroke risk in atrial fibrillation (AF) is an important but elusive goal. It is particularly important to be able to separate low-risk patients who do not need oral anticoagulant therapy (OAC) from intermediate- and high-risk patients who will generally benefit. Analysis from prior trials has consistently identified four independent risk factors for stroke in AF: prior stroke or transient ischemic attack (TIA), advanced age, hypertension, and diabetes [3]. Prior cerebral ischemia has been shown to be a very significant predictor of future stroke, conferring a risk of at least 5% per year. Left ventricular (LV) dysfunction or history of congestive heart failure has also been associated with increasing stroke risk, but is not as robust as the four core risk factors [3].

The CHADS2 score remains the cornerstone of risk stratifying patients with AF for stroke. It was initially derived from the combination of prior stroke prediction schemes. The Atrial Fibrillation Investigators (AFI) scheme was derived from a pooled analysis from the control groups of five trials to identify independent risk factors for stroke. The Stroke Prevention in Atrial Fibrillation (SPAF) scheme was based on a retrospective analysis of risk factors from aspirin-treated groups. The CHADS2 scoring algorithm assigns one point for congestive heart failure, one point for

hypertension, one point for age >75 years, one point for diabetes mellitus, and two points for history of prior stroke or TIA [4]. Currently, patients with a score of zero are considered low risk, a score of 1 is intermediate risk, and a score of 2 to 6 is considered to be associated with a high risk for developing a stroke. The CHADS2 score was prospectively validated in a cohort of Medicare beneficiaries. It is modestly effective in risk stratifying patient in AF. The primary advantage of the CHADS2 score is its simplicity in categorizing patients into different groups that warrant anticoagulation [5•].

Other AF stroke risk stratification schemes include the Framingham score, the 2006 American College of Cardiology (ACC)/American Heart Association (AHA)/European Society of Cardiology (ESC) AF guidelines, the 8th American College of Chest Physicians (ACCP) guidelines, the United Kingdom National Institute for Health and Clinical Excellence (NICE) guidelines, and the CHA2DS2-VASc [5]. They are all based on similar risk factors and are described in Table 1. They all perform equivalently when applied to large cohorts of patients with AF with a c-statistic of around 0.6, depending on the study [5•]. The c-statistic is equivalent to the area under a receiver-operating characteristic (ROC) curve. A c-statistic of 1 indicates perfect prediction of risk by model and a c-statistic of 0.5 indicates zero ability to predict risk.

Other clinical risk factors for stroke in AF are less well validated or not as robust. Female gender is thought to be predictive of stroke. Also, peripheral vascular disease, coronary artery disease, and history of prior myocardial infarction (MI) have also been shown to have some utility in selected patient to predict risk of future stroke in AF [5•, 6].

The newly published CHA2DS2-VASc scheme has incorporated these risk factors to better stratify the intermediate-risk patients and refine the low-risk population that does not need any antithrombotic therapy. The new system modifies the original CHADS2 score by giving 2 points for age > 75 years, and one point for age 65–74 years, history of vascular disease (prior MI, peripheral arterial disease, or aortic atheroma), and female gender (Table 2). This was validated against the Euro Heart Survey on AF. It showed a marginal improvement over the original CHADS2 score in stroke predication. Its primary advantage is that its low-risk cohort had zero strokes and the CHA2DS2-VASc patients with a score of 1 had a 0.6% rate of stroke

Table 1 Stroke risk stratification schema for atrial fibrillation

Risk scheme	Low risk	Intermediate risk	High risk
CHADS2	Score 0	Score 1	Score 2–6
Framingham (2003) Age 0–10 points Female Sex 6 points Hypertension 0–4 points TIA/Stroke Hx 6 points Diabetes 5 points	Score 0–7	Score 8–15	Score 16–31
NICE guidelines (2006)	Age<65 years with no moderate/high-risk factors	Age≥65 years with no high-risk factors Age<75 years with hypertension, diabetes, or vascular disease	Previous stroke or TIA or thromboembolic event Age≥75 years with hypertension, diabetes, or vascular disease, clinical evidence of valve disease or heart failure, or impaired left ventricular function
ACC/AHA/ESC guidelines (2006)	No risk factors	Age≥75 years, or hypertension, or heart failure, or LVEF≤35%, or diabetes	Previous stroke, TIA or embolism, or≥2 moderate risk factors: age≥75 years, hypertension, heart failure, LVEF≤35%, diabetes
Eighth ACCP guidelines (2008)	No risk factors	Age>75 years, or hypertension, or moderately or severely impaired LVEF and/or heart failure, or diabetes	Previous stroke, TIA or embolism, or≥2 moderate risk factors: age≥75 years, hypertension, moderately or severely impaired LVEF and/or heart failure, diabetes
CHA2DS2-VASc (2009) ESC guidelines (2010)	No risk factors	One combination risk factor: heart failure/ LVEF≤40%, hypertension, diabetes, vascular disease, female gender, age 65–74 years	Previous stroke, TIA or embolism, or age≥75 years y, or≥2 combination risk factors: heart failure/ LVEF <40%, hypertension, diabetes, vascular disease, female gender, age 65–74 years

LVEF left ventricular ejection fraction, *TIA* transient ischemic attack.

Table 2 Observed stroke rates between CHADS2 and CHA2DS2-VASc

	Patients, *n*	Adjusted stroke rate, *%/year*
CHADS2 score		
0	120	1.9
1	463	2.8
2	523	4.0
3	337	5.9
4	220	8.5
5	65	12.5
6	5	18.2
CHA2DS2-VASc score		
0	1	0
1	422	1.3
2	1230	2.2
3	1730	3.2
4	1718	4.0
5	1159	6.7
6	679	9.8
7	294	9.6
8	82	6.7
9	14	15.2

[5•]. The CHA2DS2-VASc score has been included in the 2010 ESC guidelines on management of AF [7].

Risk stratification for AF patients also includes assessment of their bleeding risk. Historically, it has been difficult to assess an individual patient's stroke risk. Many of the same factors that predict increased bleeding risk also predict increased stroke risk, making it difficult to discriminate which patients are too high risk for OAC. Recently, the HAS-BLED criteria for identifying bleeding risk were introduced. A value of one point is given for hypertension (systolic blood pressure [SBP]>160 mm Hg), abnormal renal or liver function, stroke, bleeding history or predisposition, labile International Normalized Ratio (INR) (therapeutic < 60% of the time), older age (> 65 years), or drugs (platelet inhibitors, nonsteroidal anti-inflammatory drugs [NSAIDs], or concomitant alcohol use). A score of 0 is considered low risk, 1 to 2 is intermediate risk, and > 2 is high risk [8•]. According to the criteria, OAC should be reconsidered in AF patients if the HAS-BLED score is greater than the CHADS2 score. The HAS-BLED criteria are also included in the ESC guidelines on management of AF.

Many other risks factors for stroke in AF have been identified. Left atrial appendage clot, severe spontaneous echo contrast, or an emptying velocity < 20 cm/s are risk factors for thromboembolism. LV dysfunction (ejection fraction [EF]<40%), and aortic atheroma are all independent echocardiographic risk factors for stroke [9]. Numerous inflammatory markers and hypercoagulable markers are elevated in AF. Elevated C-reactive protein (CRP) levels have been shown to be an independent predictor of stroke in AF [10]. Also, recent studies have shown that certain genetic variants (polymorphisms of chromosome 4q25 and 16q22) are associated with increased stroke risk in AF [11, 12].

Prevention of Stroke in Atrial Fibrillation

OAC with vitamin K antagonists is the mainstay of stroke prevention in AF. Warfarin results in an approximate 60% reduction of stroke in randomized controlled trials, with an average absolute 3% reduction of thromboembolic events [13]. This effect has been consistent across multiple trials and different populations. It is associated with an increase in the rate of major bleeding episodes, especially in older trials (0.3–0.5% for absolute increase for major bleeding and 0.2% increase in intracranial hemorrhage) [13]. The benefits of OAC extend to elderly patients (> 75 years), which were shown in the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) trials that compared aspirin to Coumadin (Bristol-Myers/Squibb, New York, NY) [14]. All major guidelines recommend OAC with a goal INR of 2 to 3 for patients with a CHADS2 score of ≥ 2.

Patients with a CHADS2 score of 1 are intermediate risk. Traditionally, guidelines have suggested warfarin or ASA for these patients. Analysis of the older randomized data and cohort data suggested that the bleeding risk on warfarin negated the reduction in ischemic stroke in patients with a CHADS2 score of 1 [15]. However, more recent data, as reflected in the ACCP and ESC guidelines, suggest that patients with a CHADS2 score of 1 benefit from warfarin. In the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE W) trial, patients with a CHADS2 score of 1 had a reduction of ischemic stroke from 1.25% per year in the aspirin-clopidogrel arm versus 0.43% per year in the warfarin arm [16]. A recent retrospective analysis of a Korean cohort of patients with a CHADS2 score of 1 showed a 20.9% stroke rate in the no therapy cohort, 10.7% in the antiplatelet group, and 4.2% in the warfarin cohort [17]. A similar French study showed an 8.4% event rate in warfarin arm and a 17.9% rate in the non-warfarin arm [18]. The primary event driving the outcome in this study was death and not stroke. Both trials showed a low incidence of major bleeding that did not negate the benefit of OAC.

Aspirin has been recommended for low- to intermediate-risk patients with AF. Aspirin has been shown in pooled analysis to have about a 20% relative risk reduction for stroke in the AF population [19]. Recent analysis has emphasized that aspirin's benefit is derived from the 325-mg dose and not from lower doses [20]. The BAFTA trial showed

that warfarin was superior to aspirin in elderly patients [14]. This was without an increased risk of major bleeding. The Warfarin vs Aspirin for Stroke Prevention in Octogenarians with Atrial Fibrillation (WASPO) trial also showed a higher rate of adverse events with aspirin versus warfarin [21]. A Japanese aspirin versus control trial showed no benefit of aspirin (dose 150–200 mg) in the prevention of stroke in AF. It also showed a marginal increase in major bleeding episodes (1.7% vs 0.4% for placebo; $P=0.10$) [20]. This 1.7% bleeding rate is similar to the warfarin arms of BAFTA and ACTIVE W. Given these data, newer guidelines are leaning toward use of OAC in intermediate-risk AF patients.

Clopidogrel has been studied in for use in AF stroke prevention and was recently added to the 2011 update to the ACC/AHA/HRS AF management guidelines. In the ACTIVE A trial, aspirin plus clopidogrel was superior to aspirin alone in reducing major vascular events (6.8% per year vs 7.6% per year) for patients deemed unable to take warfarin. This finding is driven by a reduction in strokes in the clopidogrel plus aspirin arm (2.4% per year vs 3.3% per year) [22•]. This occurred at the expense of increased major bleeding episodes (2.0% vs 1.3%). In ACTIVE W, clopidogrel plus aspirin was inferior to warfarin in the prevention of vascular events (3.93% to 5.60%; $P=0.0003$.) In addition, clopidogrel plus ASA was associated with an increased risk of bleeding episodes (15.4% vs 13.2%; $P<0.001$) [23].

An important component to stroke reduction and maximizing outcomes in AF with warfarin is adequate monitoring to maintain patients in the target therapeutic range (INR 2.0–3.0). Data have suggested that incremental stroke reduction benefit starts to plateau around an INR of 1.8 to 2.0, and the increased risk for intracranial hemorrhage and major bleeding begins to significantly increase with INR>3.0 to 3.5 [24]. Maximizing the amount of time in the therapeutic range has been shown to improve patient outcomes. A recent analysis showed that patients who spent more than 70% of the time with an INR between 2.0 and 3.0 had a significantly reduced rate of stroke and mortality, and those who spent < 30% with an INR between 2.0 and 3.0 had a trend toward worse outcome versus control patients not taking warfarin [25]. Specialized warfarin clinics have been shown to improve control of INRs, and although home INR testing slightly improved INR control, it did not improve outcomes [26]. Pharmacogenetic management of warfarin may help enhance warfarin control in the future, especially during initiation of warfarin, when adverse events are most common [27].

Dabigatran (Pradaxa; Boehringer Ingelheim, Ridgefield, CT) is a new oral anticoagulant that has been recently approved by the US Food and Drug Administration (FDA) at a dose of 150 mg twice daily for management of stroke risk in AF. It was extensively studied for prevention of venous thromboembolism (VTE) before the RE-LY trial demonstrated its efficacy in prevention of thromboembolism in AF. The RE-LY trial randomized patients with AF and at least an intermediate stroke risk to warfarin or dabigatran (110 mg or 150 mg twice daily). The primary outcome was stroke or systemic embolus. The trial showed that 110 mg of dabigatran twice daily was noninferior to warfarin (event rate of 1.53% per year vs 1.69 per year; $P<0.001$ for non-inferiority). Dabigatran at 150 mg twice daily was superior to warfarin (event rate of 1.11%; $P<0.001$ for superiority). The dabigatran 110-mg group had a significantly lower risk of major bleeding than the warfarin group (3.36% vs 2.71%; $P=0.003$), and the dabigatran 150-mg dose group had a similar major bleeding rate (3.1%). Both doses of dabigatran had a significant reduction in intracerebral hemorrhage (0.7% warfarin, 0.3% dabigatran 150 mg, and 0.2% dabigatran 110 mg.) There was also a trend toward lower mortality in the dabigatran-treated patients. However, there was a slight increase in the incidence of myocardial infarction that reached marginal significance with dabigatran at 150 mg twice daily (0.5% vs 0.7%; $P=0.048$) [28••].

Dabigatran is an oral direct thrombin (IIa) inhibitor (DTI). It blocks thrombin-mediated generation of fibrin from fibrinogen and prevents the thrombin-mediated activation of factors V, VIII, XI, and XIII. It is 80% renally excreted, and has a half-life of 12–17 h. There is a dose adjustment to 75 mg twice daily for a creatinine clearance of 15–30 mL/min. Dabigatran reaches peak effect in 2–3 h. It does not need to be monitored. At therapeutic doses it raises the activated partial thromboplastin time (aPTT), but the aPTT does not provide a precise measurement of anticoagulant activity, especially at high doses of dabigatran. A thrombin clotting time (TT) is very sensitive for detecting dabigatran activity. However, because the reagents for the test are not standardized between laboratories TT cannot be used to precisely monitor the effect or overdose of dabigatran. A Hemoclot Thrombin inhibitor assay (Hyphen BioMed, Neuville-sur-Oise, France) is a standardized TT assay that allows for a direct assessment of direct thrombin inhibitor (DTI) activity. Precise measurement of dabigatran levels can be determined with this test. The ecarin clotting time (ECT) measures thrombin generation, thus directly measuring DTI effect. However, it is currently mostly a research tool. At this time aPTT or TT can be used to verify DTI presence, but these tests do not have the precision to predict anticoagulant effect like an INR does for warfarin [29].

In cases of overdose or life-threatening bleeding, there is no specific antidote for dabigatran or any other DTI. Activated charcoal can be given to inhibit absorption, and hemodialysis can remove dabigatran from the blood. Recombinant factor VII (rFVIIa [NovoSeven; NovoNordisk, Bagsvaerd, Denmark) has been shown in some reports to be able to reverse the effects of DTI; however, it may take several doses,

depending on the clearance of dabigatran. Prothrombin complex concentrates (PCCs) contains various vitamin K-dependent factors. They also have potential to reverse DTI effect and have been shown in animal models to reverse dabigatran [29].

Rivaroxaban (Xarelto; Bayer Schering Pharma, Berlin, German) is a direct factor Xa inhibitor. Factor Xa is at the confluence of the intrinsic and extrinsic pathways and facilitates the conversion of prothrombin (factor II) to thrombin (factor IIa). Two thirds of the compound is metabolized by the liver and one third is cleared by the kidneys. It has been extensively studied in the prevention of venous thromboembolism, and an FDA advisory panel recommended its approval for prevention of VTE. The Rocket-AF (Randomized, Double-Blind Study Comparing Once Daily Oral Rivaroxaban With Adjusted-Dose Oral Warfarin for the Prevention of Stroke in Subjects With Non-Valvular Atrial Fibrillation) trial was a randomized, double-blinded comparison of rivaroxaban 20 mg daily (15 mg for a creatinine clearance of 30–49 mL/min) against dose-adjusted warfarin in patients with more than two risk factors for stroke or a history of thromboembolism. This high-risk population had an average CHADS2 score of 3.5. The primary endpoint was stroke and non–central nervous system embolism. Rivaroxaban was shown to be non-inferior to warfarin, with an event rate of 1.71% per year (rivaroxaban) versus 2.16% per year (warfarin) ($P<0.001$). A prespecified secondary on-treatment analysis showed rivaroxaban to be superior warfarin (event rate 1.70% per year vs 2.15 per year [$P=0.015$]). Major bleeding and adverse events were similar between groups. Intracranial hemorrhage (0.49 vs 0.74 [$P=0.0149$]) and fatal bleeding (0.24 vs 0.48; $P=0.003$) was significantly lower in the rivaroxaban group. The time in therapeutic range was 57.8%; however, the outcomes of trial were consistent, even the subgroup of patients with good INR control [30].

Apixaban is a reversible direct factor Xa inhibitor with a high oral bioavailability, rapid onset, and a half-life of about 12 h. It is 75% CYP3A4 metabolized and 25% renally excreted. It also has been studied in prevention of venous thromboembolism. In the Apixaban Versus Acetylsalicylic acid (ASA) to Prevent Strokes (AVERROES) trial, apixaban 5 mg twice daily was compared to aspirin (81–364 mg) for prevention of stroke in AF patients who were not suitable candidates for warfarin. The average CHADS score was 2.1. The primary outcome was the incidence of stroke or systemic embolic event. The trial was stopped early and the results were presented at the 2010 ESC Congress. The primary event rate was 4.0% per year on aspirin and 1.7% per year on apixaban ($P=0.000004$). Major hemorrhage was 1.2% per year on aspirin and 1.5% per year on apixaban ($P=0.330$). Intracerebral hemorrhage was 0.4% per year on apixaban and 0.3% per year in the aspirin group ($P=0.79$). There was a trend toward decreased mortality with apixaban over aspirin (3.4% vs 4.4%; $P=0.07$). The Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation (ARISTOTLE) trial is an ongoing study comparing apixaban to warfarin for AF stroke prevention [31].

Edoxaban and betrixaban are also direct Factor Xa inhibitors in development. Edoxaban 30 mg daily and 60 mg daily will be compared against warfarin in the phase 3 ENGAGE-TIMI 48 trial [32]. Betrixaban is almost completely hepatically metabolized and is in phase 2 development [32]. It is being developed with a Factor Xa reversal agent PRT064445 [33].

Tecafarin is a vitamin K antagonist like Coumadin. It is not metabolized by the cytochrome P450 system and should be easier to dose than warfarin. A recent dosing study of 64 patients showed that patients had a time in therapeutic range of 71% while on tecarfarin versus 59% when taking warfarin [34] (Fig. 1).

Left atrial appendage (LAA) occlusion has been proposed as an alternative to anticoagulation for patients with AF. Up to 90% of thromboembolic events in AF are thought to originate from the LAA [35]. LAA occlusion has been performed surgically using various techniques. Outcomes from surgical

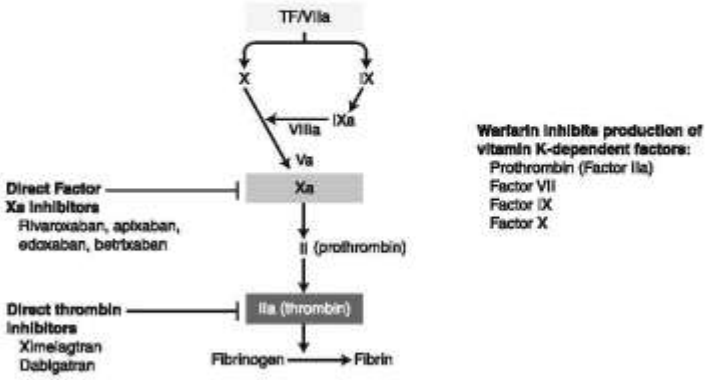

Fig. 1 Sites of action of standard and experimental anticoagulants for atrial fibrillation

LAA occlusion have never been systemically studied, and frequently (30–50%) the occlusion is incomplete due to the variable nature of LAA anatomy and technique used [35]. Percutaneous LAA occlusion has been studied, and devices are in advanced clinical trials. The Watchman device (Atritech, Plymouth, MN) was studied in the Embolic Protection in Patients with Atrial Fibrillation (PROTECT-AF) study. It randomized patients to warfarin or LAA occlusion. The device patients took warfarin for at least 45 days post-implant. The Watchman device was noninferior to warfarin in the prevention of all strokes (hemorrhagic or ischemic). However, there was a significant increase in adverse events (mostly procedural-related pericardial effusion) [36•]. The percutaneous left atrial appendage transcatheter occlusion (PLAATO) device has been studied in patients who were not candidates for warfarin. The 5-year follow-up data showed a 3.8% yearly rate of stroke, which was lower than the 6.6% stroke risk predicted by the CHADS2 score for the cohort. Both studies showed a good success rates with LAA closure [37].

Maintaining sinus rhythm may also reduce stroke risk. Data from the Stroke Prevention in Atrial Fibrillation (SPAF) trials showed that paroxysmal and persistent AF had similar stroke rates (3.2% paroxysmal per year vs 3.3% with persistent AF). However, analysis from the Stroke Prevention using Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III and SPORTIF V trials showed a stroke rate of 1.73% per year for persistent AF and a 0.93% per year for paroxysmal AF (P=0.037) [38]. Also, recent data from a meta-analysis of trials for dronedarone showed a stroke rate of 1.2% in the dronedarone-treated group and 1.8% in the placebo group (P=0.027%) [39]. Data from follow-up of patients who underwent AF ablation suggest that those in sinus rhythm post- ablation have a very low risk of stroke even after anticoagulation is stopped [40]. However, the data are nonrandomized and all major guidelines recommend continuing anticoagulation for all AF patients with a high risk for stroke regardless of whether sinus rhythm is restored.

Hypertension is an important risk factor for stroke in AF. Control of systolic blood pressure has been shown to significantly reduce the rate of stroke in patients with AF. This has been particularly shown with angiotensin receptor blockers and angiotensin-converting enzyme inhibitors [41, 42].

Impact of Long-Term Monitoring for Detecting Atrial Fibrillation

AF can frequently be paroxysmal and asymptomatic. Twenty-five percent of patients can have episodes of AF that are asymptomatic and undetected on routine monitoring. Many patients present with stroke as their first symptom of AF, and 4% of strokes are associated with newly diagnosed AF [43]. The stroke prevention guidelines recommend screening for AF by checking the pulse during blood pressure monitoring and obtaining electrocardiograms (ECG) in patients older than 65 years of age. A recent study showed the utility of a novel blood pressure monitor in detecting AF during routine checks [44].

Multiple recent studies have shown the utility of ECG monitoring of stroke patients to diagnose AF. Routine telemetry during inpatient admission can diagnose AF in about 5% of patients who present with a new stroke. A Holter monitor can confirm paroxysmal AF in up to 10% of patients who present with new stroke or TIA patients and a sinus rhythm ECG [45]. A study of patients with cryptogenic stroke showed that 30-day event monitors detected AF in 20% of patients when ECG and inpatient telemetry were negative for AF [46]. A transtelephonic ECG monitoring study showed a 9.2% yield in the detection of AF in a cryptogenic stroke population [47]. A majority of patients that are newly diagnosed with AF post-stroke have the AF detected more than 48 h after presentation for stroke. It appears to be cost effective to perform long-term ECG monitoring, especially in patients with risk factors for AF (hypertension, elderly, left atrial dilation, or high burden of Premature atrial contractions) [48]. Currently, trials are testing the utility of implantable loop recorders for detecting AF in cryptogenic stroke.

Implantable cardiac devices now have the capability of detecting atrial fibrillation and atrial high rate episodes, and quantifying AF burden in individual patients. This allows the detection of asymptomatic AF in many patients. In the TRENDS study, a threshold duration of 5.5 h AF per month conferred an increased stroke risk for that given month [49•]. Another study showed that combining the amount of AF burden detected from implanted cardiac devices with clinical risk stratification helped identify patients at higher risk for stroke who would benefit from OAC [50]. The ongoing Impact of Medical Subspecialty on Patient Compliance to Treatment (IMPACT) study is examining whether early detection and treatment of AF with remote device monitoring compared with standard care will reduce stroke rates.

Conclusions

Atrial fibrillation remains a large public health problem. Further refinement in stratifying stroke risk in patients with AF will help in properly directing therapy for AF patients while minimizing adverse events. Although warfarin is the primary option for OAC for patients with AF, many new drugs are on the horizon that will significantly change

practice. New and improved monitoring techniques and devices will help with detection of AF in those at risk for stroke and will assist in assessing which patients will most benefit from anticoagulation.

Disclosure The authors report no potential conflicts of interest relevant to this article.

Conflicts of Interest None

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- • Of importance
- •• Of major importance

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CME Available

Comparison of 12 Risk Stratification Schemes to Predict Stroke in Patients With Nonvalvular Atrial Fibrillation

Stroke Risk in Atrial Fibrillation Working Group*

Background and Purpose—More than a dozen schemes for stratifying stroke risk in patients with nonvalvular atrial fibrillation have been published. Differences among these schemes lead to inconsistent stroke risk estimates for many atrial fibrillation patients, resulting in confusion among clinicians and nonuniform use of anticoagulation.

Methods—Twelve published schemes stratifying stroke risk in patients with nonvalvular atrial fibrillation are analyzed, and observed stroke rates in independent test cohorts are compared with predicted risk status.

Results—Seven schemes were based directly on event-rate analyses, whereas 5 resulted from expert consensus. Four considered only clinical features, whereas 7 schemes included echocardiographic variables. The number of variables per scheme ranged from 4 to 8 (median, 6). The most frequently included features were previous stroke/TIA (100% of schemes), patient age (83%), hypertension (83%), and diabetes (83%), and 8 additional variables were included in ≥1 schemes. Based on published test cohorts, all 8 tested schemes stratified stroke risk, but the absolute stroke rates varied widely. Observed rates for those categorized as low risk ranged from 0% to 2.3% per year and those categorized as high risk ranged from 2.5% to 7.9% per year. When applied to the same cohorts, the fractions of patients categorized by the different schemes as low risk varied from 9% to 49% and those categorized by the different schemes as high-risk varied from 11% to 77%.

Conclusions—There are substantial, clinically relevant differences among published schemes designed to stratify stroke risk in patients with atrial fibrillation. Additional research to identify an optimum scheme for primary prevention and subsequent standardization of recommendations may lead to more uniform selection of patients for anticoagulant prophylaxis. (***Stroke*. 2008;39:1901-1910.)**

Key Words: atrial fibrillation ■ clinical prediction rules ■ risk factors ■ stroke

The absolute risk of stroke varies widely among patients with atrial fibrillation depending on patient age and other clinical features. Estimating stroke risk is a critical first step when balancing the potential benefits and risks of chronic antithrombotic therapy for stroke prevention. Multiple stroke risk stratification schemes for atrial fibrillation patients have been proposed based on various combinations of clinical and echocardiographic predictors.[1] Although there is considerable overlap, differences alter the predicted risk status of hundreds of thousands of atrial fibrillation patients,[2–4] contributing to the inconsistent use of anticoagulation.[5]

Here, we compare 12 published schemes that stratify stroke risk in patients with nonvalvular atrial fibrillation.[6–17] The key features, the distribution of atrial fibrillation patients classified into different risk strata, and the stroke rates in test cohorts are analyzed for each scheme.

Materials and Methods

Twelve stroke risk stratification schemes were selected for inclusion based on publication in peer-reviewed English language journals from 1994 to mid 2007, beginning with the landmark Atrial Fibrillation Investigators initial analysis.[6] Schemes were identified through a computerized literature search using OVID software combining the key term "atrial fibrillation" with (separately) "risk factor" and "risk stratification." Recent review articles and a recent systematic review of independent predictors of stroke in atrial fibrillation patients[1] were also canvassed. Schemes were included if they sought to predict all stroke, ischemic stroke, or a combination of stroke, systemic embolism, or TIA in patients with nonvalvular atrial fibrillation not receiving oral anticoagulation; schemes assessing stroke in patients receiving antiplatelet therapy were included. Included reports must have explicitly proposed risk strata using ≥1 clinical or echocardiographic features and must have linked the strata to recommendations for antithrombotic prophylaxis; those assessing stroke risk factors but without proposing a specific risk stratification scheme were not considered. For schemes generated by expert groups that were serially revised, only the most recent version was included. For example, only the most recent version of the American College of Cardiology/American Heart Association/European Society of Cardiology guideline was included,[11] and an earlier iteration was not considered.[18] The single exception was inclusion of both the 2001 version[13] and the 2004 revision[16] of the American College of Chest Physicians consensus statement because the earlier scheme has been tested in 2 independent cohorts. Studies reporting the performance of specific risk stratification schemes in independent

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Received August 22, 2007; final revision received October 10, 2007; accepted October 19, 2007.
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Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.107.501825**

Table 1. Stroke Risk Stratification Schemes for Patients With Atrial Fibrillation

Study (Year of Publication)	Derivation*	Event Type	Risk Strata	Types of Variables	During Aspirin Rx
Atrial Fibrillation Investigators (1994) (6)†	Multivariate RCT 108 events	IS	High/moderate/low	Clinical	No
Stroke Prevention in Atrial Fibrillation Investigators (1995) (7)	Multivariate RCT 73 events	IS+SE	High/moderate/low	Clinical+echo	Yes
European Atrial Fibrillation Trial Study Group (1995) (8)‡	Multivariate RCT 78 events	S	High/moderate/low	Clinical+CT	No
Atrial Fibrillation Investigators (1998) (9)	Multivariate RCT 78 events	IS	Multiple	Clinical+echo	No
Stroke Prevention in Atrial Fibrillation Investigators (1999) (10)	Multivariate RCT 130 events	IS	High/moderate/low	Clinical+echo	Yes
CHADS2 (2001) (12)	Expert consensus	IS+TIA	Multiple	Clinical	Both
American College of Chest Physicians (2001) (13)	Expert consensus	NS	High/moderate/low	Clinical+echo	NS
Framingham Heart Study (2003) (15)	Multivariate ES 83 events	S	Multiple	Clinical	Both
Van Walraven et al (2003) (14)	Recursive partitioning RCT 103 events	S+TIA	High-moderate/low	Clinical	Yes
American College of Chest Physicians (2004) (16)	Expert consensus	NS	High/moderate/low	Clinical+echo	NS
Birmingham/NICE (UK) (2006) (17)	Expert consensus	IS+SE	High/moderate/low	Clinical+echo	NS
ACC/AHA/ESC Guidelines (2006) (11)	Expert consensus	IS+SE	High/moderate/low	Clinical+echo	NS

ACC/AHA/ESC indicates American College of Cardiology/American Heart Association/European Society of Cardiology; CHADS2, congestive heart failure, hypertension, age, diabetes, secondary prevention; CT, brain computed tomograms; echo, echocardiographic; ES, epidemiological study; IS, ischemic stroke; multivariate, multivariate analysis of a derivation cohort; NICE, National Institute for Clinical Excellence; NS, not specified; RCT, randomized clinical trial; Rx, treatment; S, all stroke; SE, non-CNS systemic emboli.

Expert opinion was generally based on synthesis of multiple previous studies of independent predictors (1).

*Multivariate RCT implies multivariate analysis of non-anticoagulated participants in randomized clinical trials (not that patients were randomized on the basis of risk factors).

†The original publication presents two levels of risk: high and low; subsequently most experts have extrapolated into 3 risk tiers, with patients 65 years old or older without other risk factors as moderate risk.

‡All participants had recent stroke or TIA.

populations of nonanticoagulated patients with atrial fibrillation (including those receiving antiplatelet agents) comprised the 11 test cohorts.[2,12,15,17,19–26]

The stratification schemes were applied to a stratified random sample of 1000 patients was selected from Stroke Prevention in Atrial Fibrillation III participants[22,23] to compare the relative distribution of risk strata. This sample included 40% women and a 10% prevalence of previous stroke/TIA; 2 years were added to each participant's age to increase the mean age of this cohort to 72 years, closer to that of a large outpatient atrial fibrillation population[3,26] and pooled participants in clinical trials.[14]

Results

Seven of the 12 schemes were based on event-rate analyses of stroke predictors in a derivation cohort,[6–10,14,15] whereas the remainder originated from consensus of expert panels (Table 1).[11–13,16,17] Two investigator groups published 2 schemes each. In one instance, this was because of addition of echocardiographic variables to a previously published clinical scheme,[6,9] and in the other, analysis of a separate larger cohort given aspirin modified an earlier multivariate analysis of stroke predictors in the absence of antithrombotic therapy.[7,10] Four schemes included only clinical features, whereas 7 schemes also considered transthoracic echocardiographic variables (Table 1). One scheme stratified risk among atrial fibrillation patients with recent stroke or TIA and included results of brain CT.[8]

The schemes varied substantially in complexity: the number of variables ranged[6,11,17] from 4 to 8, with a median of 6 (Table 2). The most frequent elements were previous stroke/TIA (100%), age (83%), hypertension (83%), and diabetes (83%; Table 3). Heart failure (50%), left ventricular systolic dysfunction (50%), and systolic blood pressure (42%) were the next most frequent; coronary artery disease (33%) and female sex (25%) were included in a minority of schemes (Table 3). Schemes varied in whether they used age and systolic blood pressure as continuous or ordered categorical variables and, in the latter case, different age thresholds were used (eg, 65 vs 75 years).

Stroke rates associated with specific risk strata were assessed in independent test cohorts for 8 of the schemes, whereas for the remaining 4 schemes no test cohorts were identified (Table 4). The characteristics of patients in the 11 test cohorts varied widely, from an elderly hospital discharge cohort (mean age, 81 years) with a 25% prevalence of previous stroke/TIA,[12] to a younger outpatient-based cohort (mean age, 72 years), with a 8% prevalence of previous stroke/TIA.[24,26] Two of the test cohorts were restricted to primary prevention.[2,20] Mean observation duration ranged from 1.2 years[12] to 5.3 years,[21] with a median of 2.0 years. Two schemes[7,12] were evaluated in 6 independent test cohorts,[6,13–17] 1 in 5, and the remaining 5 in 1 or 2. In some

Table 2. Summary of 12 Stroke Risk Stratification Schemes

	Derivation Cohort			
	% of Cohort	N of Events	Event Rates, %/yr (95% CI)	Independent Testing
Atrial Fibrillation Investigators (AFI) 1994 (6)				
Age <65 yr				Pearce et al (2)
No risk factors (low risk)	15	3	1.0 (0.3–3.1)	Gage et al (12)
HTN, DM, previous stroke/TIA (high risk)	17	16	4.9 (3.0–8.1)	Wang et al (15)*
Age 65–75 yr				Gage et al (20)
No risk factors (moderate risk)	20	16	4.3 (2.7–7.1)	Fang et al (26)
HTN, DM, previous stroke/TIA (high risk)	27	27	5.7 (3.9–8.3)	
Age >75 yr				
No risk factors (high risk)	11	6	3.5 (1.6–7.7)	
HTN, DM, previous stroke/TIA (high risk)	9	13	8.1 (4.7–13.9)	
Stroke Prevention in Atrial Fibrillation Investigators (SPAF) III, 1995 (7)				
High risk	48	55	5.9 (4.5–7.8)	Feinberg et al (21)
Previous thromboembolism				SPAF Investigators (22,23)
Systolic BP >160 mm Hg				Gage et al (12)
Left ventricular dysfunction†				Wang et al (15)*
Women >75 yr				Gage et al (20)
Moderate Risk	23	12	2.8 (1.7–4.7)	Fang et al (26)
HTN, no high risk features				
Low Risk	29	6	1.0 (0.5–2.3)	
No high or moderate risk features				
European Atrial Fibrillation Trial Study Group (1995)‡ (van Latum et al) (8)				
Previous stroke/TIA‡	28	30	NR	None identified
Systolic BP >160 mm Hg	21	20	NR	
Duration of AF >1 yr	57	57	NR	
≥1 infarcts on brain CT	56	51	NR	
Cardiac enlargement on CXR	24	27	NR	
High risk = ≥3 risk factors	30	NR	NR	
Moderate risk=1–2 risk factors	61	NR	NR	
Low risk=No risk factors	9	NR	NR	
Atrial Fibrillation Investigators (AFI) 1998 (9)§				
Age <65 yr				None identified
No clinical risk factors, normal LV (low risk)	15	1	0.8 (0.2–3.0)	
No clinical risk factors, abnormal LV (high risk)	1	1	9.3 (1.3–66)	
≥1 clinical risk factor, normal LV (high risk)	15	8	3.6 (1.8–7.2)	
≥1 clinical risk factor, abnormal LV (high risk)	4	5	9.7 (4.0–23)	
Age 65–75 yr				
No clinical risk factors, normal LV (moderate)	15	8	3.2 (1.6–6.5)	
No clinical risk factors, abnormal LV (high risk)	2	2	8.4 (2.1–33)	
≥1 clinical risk factor, normal LV (high risk)	27	22	4.9 (3.2–7.4)	
≥1 clinical risk factor, abnormal LV (high risk)	4	6	12 (5.3–26)	
Age >75 yr				
No clinical risk factors, normal LV (high risk)	6	0	0 (–)	
No clinical risk factors, abnormal LV (high risk)	1	1	11 (1.4–78)	
≥1 clinical risk factor, normal LV (high risk)	9	12	8.3 (4.7–14.6)	
≥1 clinical risk factor, abnormal LV (high risk)	2	4	20 (7.4–52)	

(Continued)

Table 2. Continued

	Derivation Cohort			
	% of Cohort	N of Events	Event Rates, %/yr (95% CI)	Independent Testing
Stroke Prevention in Atrial Fibrillation Investigators, Aspirin Cohort, 1999 (Hart et al 1999) (10)				
High risk	22	70	7.1 (5.4–9.5)	None identified
Previous stroke/TIA				
Women >75 yr old				
Men >75 yr old+HTN				
Systolic BP >160 mm Hg				
Moderate risk (no high risk features, either of)	37	43	2.6 (1.9–3.6)	
HTN				
DM				
Low risk (no high/moderate risk features)	41	17	0.9 (0.6–1.6)	
CHADS2 (2001) (Gage et al 2001) (12)				
Congestive heart failure,# hypertension,	N/A	N/A	N/A	Gage et al (12)
Age >75 yr, diabetes=1 point each; previous				Go et al (24), Fang et al
Stroke/TIA=2 points				(26), Fang et al (19)
Risk scores range from 0–6 points				Wang et al (15)*
Low risk=0				Gage et al (20)
Moderate risk=1–2				Lip et al (17)
High risk ≥3				Healey et al (25)
American College of Chest Physicians (ACCP) 2001 (Albers et al 2001) (13)				
High risk (any of)	N/A	N/A	N/A	Pearce et al (2)
Previous thromboembolism				Gage et al (20)
HTN				
HF				
LV dysfunction by echocardiography				
Age >75 yr				
≥2 moderate risk factors				
Moderate risk (any of)	N/A	N/A	N/A	
Age 65–75 yr				
DM				
Coronary artery disease				
Low risk	N/A	N/A	N/A	
No moderate or high risk features				
Framingham Risk Score (Wang et al 2003) (15)				
Age (0–10 points)				Gage et al (20)
Gender (6 points for women)				Fang et al (26)
Systolic BP (0–4 points)				
DM (5 points)				
Previous stroke/TIA (6 points)				
Risk levels estimated for low risk patients				
0–1 points	3	NR	0.0	
0–4 points	14	NR	1.1	
0–7 points	31	NR	1.5	
Van Walraven et al for the Atrial Fibrillation Investigators 2003 (14)				
Low risk if patients do not have	24	~12	0.5 (0.2–1.0)¶	Van Walraven et al (14)
Previous stroke/TIA				Wang et al (15)*

(Continued)

Table 2. Continued

	Derivation Cohort			
	% of Cohort	N of Events	Event Rates, %/yr (95% CI)	Independent Testing
Treated HTN or systolic BP >140				
Angina or previous MI				
DM				
American College of Chest Physicians (ACCP) 2004 (Singer et al 2004) (16)				
High risk (any of)	N/A	N/A	N/A	Fang et al (26)
Previous thromboembolism				
HTN				
HF				
LV dysfunction by echocardiography				
Age >75 yr				
DM				
Moderate risk				
Age 65–75 yr, no high risk features	N/A	N/A	N/A	
Low risk				
Age <65 yr, no high risk features	N/A	N/A	N/A	
Birmingham/ NICE (UK) Criteria (Lip et al 2006) (17)				
High risk	N/A	N/A	N/A	Lip et al (17)
Previous thromboembolism				
Age ≥75 yr plus DM, HTN or vascular disease				
HF or abnormal LV function by echo	N/A	N/A	N/A	
Moderate risk				
Age ≥65 yr, no high risk features				
Age <75 yr plus one of DM, HTN, or vascular disease	N/A	N/A	N/A	
Low risk				
Age <65 yr with no moderate or high risk features				
ACC/AHA/ESC Guidelines 2006 (Fuster et al 2006) (11)				
High risk	N/A	N/A	N/A	None identified
Previous thromboembolism				
≥1 moderate risk feature	N/A	N/A	N/A	
Moderate risk				
Age ≥75 yr				
HF				
HTN				
DM				
LV ejection fraction ≤35% or fractional shortening <25%	N/A	N/A	N/A	
Low risk‖				
No moderate or high risk features				

AF indicates atrial fibrillation; BP, blood pressure; DM, diabetes; HF, heart; HTN, history of hypertension; LV, left ventricular; N/A, not applicable; NR, not reported; TEE, transesophageal echocardiography; ACC/AHA/ESC, American College of Cardiology/American Heart Association/European Society of Cardiology.

*Testing only the low-risk criteria with a small, uncertain number of events.

†Recent (≈3 months) clinical congestive heart failure or left ventricular fractional shortening ≤25% by M-mode echocardiography.

‡All participants had recent stroke or TIA. Event rates reported only for the combination of stroke, systemic embolism, myocardial infarction, and vascular death (not for stroke alone). Previous stroke/TIA pertains to cerebral ischemia before the qualifying event.

§Clinical risk factors are previous stroke/TIA, history of hypertension, and diabetes mellitus. Abnormal LV means moderate-to-severe systolic dysfunction by 2-dimensional echocardiocardiography.

¶For stroke events only.

‖"Less well-validated" risk factors were female sex, coronary artery disease and age 65 to 75 years. It is unclear whether patient with ≥1 of these should be categorized as moderate risk, although it is stated that antithrombotic therapy with either vitamin K antagonists or aspirin is reasonable depending on bleeding risks, ability to safely sustain anticoagulation and patient preferences.

#"Recent" heart failure, but widely applied as heart failure without time restriction in testing cohorts.

Table 3. Comparison of Features Included in 12 Risk Stratification Schemes

Study	Age, yr	HTN	DM	Previous Stroke or TIA	Female	Heart Failure	Coronary Artery Disease	Systolic BP	Abnormal LV Function
Atrial Fibrillation Investigators (1994)[8]	≥65	+	+	+					
Stroke Prevention in Atrial Fibrillation Investigators (1995)[7]	>75*	+		++	++*	++		>160	++
European Atrial Fibrillation Trial Investigators (1995)[9]†				+				>160	
Atrial Fibrillation Investigators (1998)[6]	>65	+	+	+					+
Stroke Prevention in Atrial Fibrillation Investigators (1999)[10]	>75‡	+	+	++	++‡			>160	
CHADS2 (2001)[12]	≥75	+	+	++		+			
American College of Chest Physicians (2001)[13]	≥65 >75	++	+	++		++	+		++
Framingham Heart Study (2003)[15]	+§		+	+	+			+	
van Walraven et al (2003)[14]		+	+	+			+	+	
American College of Chest Physicians (2004)[16]	≥65 >75	++	++	++		++			++
Birmingham/NICE (UK) (2006)[17]	≥65	+	+	++		++	+		++
ACC/AHA/ESC Guidelines (2006)[11]¶	≥75	+	+	++	¶	+	¶		+
Overall frequency	83%	83%	83%	100%	25%	50%	25%	42%	50%

See Table 2 for specific schemes.

+ indicates included in risk stratification; ++, heavily weighted or indicative of high rather than moderate risk.

*Stroke risk was classified as high in women >75 years, but not elderly men or younger women.

†All participants had recent stroke or TIA. Three additional risk factors unique to this scheme not included in the Table: cardiomegaly on chest x-ray, ischemic stroke on brain CT, and duration of atrial fibrillation >1 year.

‡Stroke risk was classified as high in all women >75 years old and men >75 years old with hypertension, but not younger women or elderly men without hypertension.

§In the Framingham scheme, age was divided into 11 strata.

¶Age ≥65 years, being female, and coronary artery disease were stated to be "less validated or weaker risk factors."

test cohorts, echocardiographic assessment of left ventricular function was not available and clinical heart failure was substituted; in other test cohorts, a history of hypertension was substituted for measured systolic blood pressure >160 mm Hg[12,15,20,26] compromising assessment.[7]

In the test cohorts all of the schemes predicted rank order of stroke risk (Table 4). Stroke rates in patients categorized as being at low risk ranged from 0% to 2.3% per year.[15,17] For example, patients classified as being at low risk based on the CHADS2 scheme[12] had observed stroke rates ranging from 0.5% per year (95% CI, 0.3 to 0.8)[26] to 1.9% per year (95% CI, 1.2 to 3.0),[12] although TIAs were combined with stroke outcomes in the latter study. Patients classified as being at high risk had observed stroke rates varying from 2.5% per year[26] to 7.9% per year.[23]

Comparisons of different schemes in a common test cohort are limited to a handful of studies (supplemental Table I, available online at http://stroke.ahajournals.org)[7,12,15,17,20,26,28] and sometimes are compromised by substitution of some features for others (eg, heart failure for left ventricular systolic dysfunction; history of hypertension for systolic blood pressure >160 mm Hg). When compared in this fashion, the proportions of patients categorized as being at low risk varied between schemes from 12% (stroke rate 0.1% per year) to 37% (stroke rate 0.9% per year) and those as being at high risk varied between schemes from 16% (stroke rate 4.0% per year) to 80% (stroke rate 2.5% per year).[26]

In the representative cohort of atrial fibrillation patients, the mean age was 72 years, 40% were women, and prevalences of hypertension, diabetes, heart failure, systolic blood pressure >160 mm Hg, coronary artery disease, and previous stroke/TIA were 56%, 15%, 29%, 12%, 24%, and 10%, respectively. Applying each scheme to the representative cohort (Figure), the fraction of patients categorized as being at low risk ranged from 7% to 42%. Assuming 2.8 million Americans with atrial fibrillation, application of different schemes would result in up to 980 000 more or fewer patients categorized as being at low risk.

Discussion

These 12 schemes for stratifying atrial fibrillation patients according to stroke risk reflect the spectrum of choices facing clinicians. Nearly all include previous stroke/TIA, age, hypertension, and diabetes as clinical predictors of stroke. However, the fraction of patients categorized as being at low risk and high risk varies 5- to 7-fold among schemes, and this contributes to inconsistent recommendations for anticoagulation for hundreds of thousands of patients with atrial fibrillation. "The widespread nonsystematic production of guidelines" [for anticoagulant treatment in atrial fibrillation] has led to considerable variation with implications for the quality of care and clinical decision making."[29] Little has changed

Table 4. Independent Testing of 12 Stroke Risk Stratification Schemes

Study	Test Cohort (N, Mean Age, 2°PVT, Type)	High-Risk Event Rate, 95% CI (% of Cohort)	Moderate-Risk Event Rate, 95% CI (% of Cohort)	Low-Risk Event Rate, 95% CI (% of Cohort)
Atrial Fibrillation Investigators (1994)[6]				
Gage et al[12]*	1733, 81 yr, 25%, HDC	5.4 (4.2–6.5); NR	2.2 (1.1–3.5); NR	NR
Gage et al[24]†	2014, ~72 yr 0%, RCT	3.5 (2.7–4.5); 50%	1.7 (1.1–2.5); 39%	0.9 (0.3–2.3); 12%
Wang et al[25]‡	705, 75 yr, 14%, ES	NR	NR	0.9 (NR); 6%
Pearce et al[2]	1073, 68 yr, 0%, RCT	NR	NR	0.3 (0.0–2.3); 15%
Fang et al[26]	5588, 72 yr, 8%, PC	2.5 (NR); 62%	2.1 (NR); 25%	0.2 (NR); 13%
Stroke Prevention in Atrial Fibrillation Investigators (1995)[7]				
Gage et al[12]	1733, 81 yr, 25%, HDC	5.7 (4.4–7.0); NR	3.3 (1.7–5.2); NR	1.5 (0.5–2.8); NR
Gage et al[24]†	2014, ~72 yr, 0%, RCT	3.6 (2.7–4.7); 44%	2.7 (1.8–4.0); 23%	1.1 (0.7–1.8); 33%
Wang et al[25]‡	705, 75 yr, 14%, ES	NR	NR	2.3 (NR)†; 17%
SPAF Investigators[22,27]	1413, 69 yr, 15%, RCT	7.9 (5.9–10.6); 37%	3.6 (2.5–5.2); 29%	1.1 (0.6–2.0); 34%
Feinberg et al[21]	259, 74 yr, 7%, ES	3.7 (2.1–5.8); 45%	2.0 (0.7–4.7); 24%	1.7 (0.6–3.8); 31%
Fang et al[26]#	5588, 72 yr, 8%, PC	3.2 (NR); 44%	1.7 (NR); 29%	0.9 (NR); 28%
European Atrial Fibrillation Trial Investigators (1995)[8]	None identified	…	…	…
Atrial Fibrillation Investigators (1998) (9)	None identified	…	…	…
Stroke Prevention in Atrial Fibrillation Investigators (1999)[10]	None identified	…	…	…
CHADS2 (2001)[17]		3–6 points	1–2 points§	0 points
Gage et al[12]*	1733, 81 yr, 25%, HDC	7.6 (NR); 36%	3.4 (NR); 57%	1.9 (1.2–3.0); 7%
Gage et al[24]†	2014,~72 yr, 0%, RCT	5.3 (3.3–8.4); 11%	2.7 (2.2–3.4); 66%	0.8 (0.4–1.7); 23%
Go et al,[28]	5089, 71 yr, 4%, PC	5.6 (NR); 20%	2.1 (NR); 57%	0.5 (0.3–0.8); 22%
Wang et al[25]‡	705, 75 yr, 14%, ES	NR	NR	1.7% (NR); 10%
Lip et al[17]¶	994, 69 yr, 13%, RCT	7.0 (3.9–11); 18%	2.7 (1.8–3.9); 56%	0.7 (0.1–1.6); 26%
Healey et al[25]‖	3335,70 yr, 15%, RCT	3.6 (NR); 27%	1.6(NR); 70%	NA; NA
Nieuwlaat et al[5]	4564, ~70 yr, NR, PC	NR (NR); 22%	NR (NR); 60%	NR (NR); 18%
American College of Chest Physicians (2001)[11]				
Gage et al[24]†	2014,~72 yr, 0%, RCT	3.0 (2.5–3.8); 77%	1.0 (0.4–2.2); 15%	0.5 (0.1–2.2); 9%
Pearce et al[2]†	1073, 68 yr, 0%, RCT	3.5 (2.6–4.7); 66%	1.2 (0.5–2.8); 20%	0.3 (0.1–2.5); 14%
Nieuwlaat et al[5]	3580,~70 yr, ~13%, PC	NR (NR); 82%	NR (NR); 7%	NR (NR); 11%
Framingham Heart Study (2003)[15]				
Gage et al[24]†	2014,~72 yr, 0%, RCT	4.2 (2.8–6.1); 16%	3.2 (2.4–4.3); 35%	1.4 (1.0–2.1); 49%
Fang et al[26]	5588, 72 yr, 8%, PC	4.0 (NR); 16%	2.5 (NR); 47%	0.9 (NR); 37%

(Continued)

Table 4. Continued

Study	Test Cohort (N, Mean Age, 2°PVT Type)	High-Risk Event Rate, 95% CI (% of Cohort)	Moderate-Risk Event Rate, 95% CI (% of Cohort)	Low-Risk Event Rate, 95% CI, (% of Cohort)
van Walraven et al (2003)[14]				
van Walraven et al[14]	840, 70 yr, 3%, RCT	NR	NR	1.1 (NR); ~22%**
Wang et al[15]‡	705, 75 yr, 14%, ES	NR	NR	1.9 (NR); 16%
American College of Chest Physicians (2004)[16]				
Fang et al[21]	5588, 72 yr, 8%, PC	2.5 (NR); 80%	0.9 (NR); 8%	0.1 (NR); 12%
Birmingham/NICE (UK) (2006)[17]				
Lip et al[17]¶	994, 69 yr, 13%, RCT	5.8 (3.7–8.3); 34%	2.0 (1.2–2.9); 55%	0 (–); 11%
ACC/AHA/ESC Guidelines (2006)[11]	None identified	...	...	...

2°PVT indicates fraction with previous stroke/TIA; ES, epidemiological study; HDC, hospital discharge cohort; NA, not applicable; NR, not reported; PC, prospective cohort; RCT, randomized clinical trial; SPAF, Stroke Prevention in Atrial Fibrillation.

*24% (23/94) of outcome events were TIAs, so stroke rates were ~ 25% lower than the rates provided in the Table. LV fractional shortening and systolic blood pressure (2 high-risk features in the SPAF 1995 scheme) were not available in the data set; hence, participants were classified based on incomplete information that would shift high-risk patients into the moderate risk category.

†High risk rates are for primary prevention (i.e. excluding patients with previous stroke/TIA); for Gage et al(20) echocardiographic data were not available, and hence the variable "abnormal left ventricular systolic function" could not be included from the Stroke Prevention in Atrial Fibrillation Investigators (1995) scheme and the American College of Chest Physicians (2001) scheme; "recent heart failure" could not be assessed, and heart failure was used.

‡Point estimate reported without CI based on a small number of stroke events for AFI 1994 and CHADS2; echocardiographic LV dysfunction was not considered in the SPAF 1995 scheme.

§Rates/frequencies for CHADS2 score=1 are: Go et al (24) 1.5%/yr (1.2–1.9) including ischemic strokes and systemic emboli per 32%; Gage et al (12) 2.8%/yr (2.0–3.8) including strokes and TIAs per 27%; Gage et al (20) 2.2%/yr (1.6–3.1) per 37%; Healey et al (25) 1.2%/yr (NR) per 36%. In a UK outpatient cohort of 234 atrial fibrillation patients undergoing echocardiography, the frequency of CHADS2=0 was 24% (27).

¶Approximately half of test cohort overlapped the test cohort of Gage et al (20).

||All received clopidogrel and aspirin. CHADS2=0 were excluded unless peripheral vascular disease was present.

**Reported event rate for the validation cohort differs between abstract (1.1) and text (0.9); CI difficult to estimate precisely from figure 4.

#Systolic blood pressures were not available to identify high-risk patients.

since this statement appeared a decade ago, and in the meantime additional schemes and guidelines have proliferated.

Authorities on clinical prediction rules advocate independent testing before their general clinical application.[30–32] Several schemes have not been tested to characterize their predictive accuracy and hence cannot be compared, directly or indirectly, to others. The duration of follow-up in most derivation and validation cohorts averages 1 to 2 years, and the enduring predictive value of risk stratification schemes for longer periods is often unknown, requiring periodic reassessment of risk. The contribution of individual variables to risk stratification schemes has not been well-defined. For example, heart failure appeared in half the schemes, but this

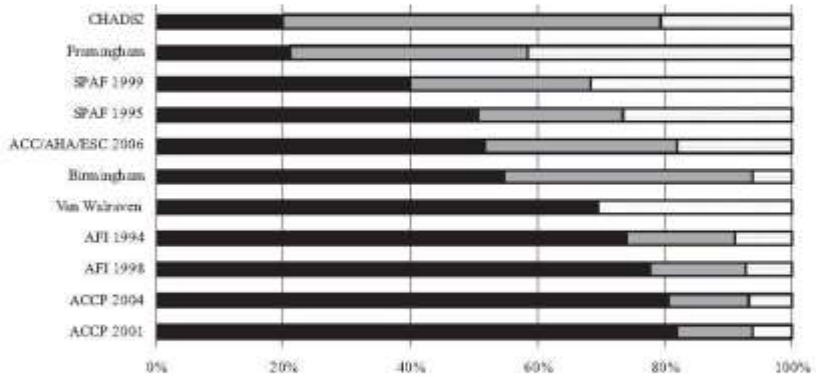

Figure. Relative distribution of patients predicted to have high (black), moderate (gray), and low (white) stroke risk by applying different risk stratification schemes to a representative cohort of atrial fibrillation patients. The mean age was 72 years and the frequencies of female sex, hypertension, diabetes, heart failure, systolic blood pressure >160 mm Hg, coronary artery disease, and previous stroke/TIA were 40%, 56%, 15%, 29%, 12%, 24%, and 10%, respectively. For the Framingham Heart Study criteria,[18] high risk was considered ≥14 points, moderate risk was 8 to 13 points, and low risk was ≤7 points. For Van Walraven et al,[14] there are only 2 risk strata: low risk and combined moderate and high risk. Because the European Atrial Fibrillation Trial criteria were intended to apply to patients with recent previous stroke/TIA, it is not included.[8] See Table 2 for study abbreviations.

clinical feature has not been validated as an independent predictor of stroke in atrial fibrillation patients.[1] Criteria used for diagnosis of heart failure have not been uniform in these studies, and the contribution of this variable to risk stratification is, therefore, unclear. The stroke risk attributable to hypertension in atrial fibrillation patients is likely to vary depending on its severity and treatment,[33] confounding application of this prevalent risk factor. Previous stroke or TIA is the most powerful risk factor[1] and, by itself, drives the successful identification of high-risk patients, regardless of the presence of other risk factors in all except 2 schemes.[12,15] The predictive value of these schemes for primary prevention (ie, for patients without previous stroke or TIA) is a more important, albeit more difficult, problem.[20]

Stroke rates in recent clinical trials[34–37] involving atrial fibrillation patients appear lower than in clinical trials completed 15 years ago.[6] Better control of blood pressure may contribute to lower stroke rates among patients with a history of hypertension,[38,39] because even modest blood pressure lowering has a substantial favorable impact on the risk of vascular events.[33] Whether absolute stroke rates among those stratified as being at high risk by any scheme are lower now than they were 10 to 15 years ago is uncertain.[34,40] In short, secular trends in stroke rates among atrial fibrillation patients may confound accurate risk prediction.

At the core of existing schemes are 4 features that have been independently and consistently associated with stroke in atrial fibrillation patients: previous stroke or TIA, hypertension, advanced age, and diabetes.[1] Other risk factors included in several schemes (eg, coronary artery disease, heart failure, female sex) have not been validated as consistent independent predictors of stroke in atrial fibrillation patients.[1,19,25] Additional possible independent predictors that are not included in current schemes (eg, estrogen replacement therapy associated with higher stroke risk, regular alcohol consumption with reduced stroke risk) have been identified,[10] but these have not been sufficiently investigated to justify application in clinical practice. The additional discriminatory power of biomarkers of thrombosis and inflammation are an area of active research.[17]

Comparison of the predictive power of available schemes with subsequent stroke in a single cohort of atrial fibrillation patients of adequate size and with a full range of variables is not currently available, and the optimal risk stratification scheme cannot be determined from existing data. The proportion of patients categorized as being at low, moderate, or high risk by a scheme will vary depending on the composition of the patient cohort to which it is applied, ie, the proportions of primary versus secondary prevention cases, proportions of elderly patients with multiple risk factors versus younger individuals with few risk factors, and the availability of echocardiographic data. Considering the inherent difficulty in distinguishing patients with stroke risk of 1% per year versus 4% per year (a determining difference regarding recommendations to anticoagulate in most guidelines), it is surprising, perhaps, that the existing schemes appear able to do so, albeit with differing results at the individual patient level.

We surveyed a scattered and complex literature on stroke risk stratification for patients with atrial fibrillation to bring its strengths and limitations into focus. We do not address the threshold of absolute stroke risk for which anticoagulation is warranted, because this depends on additional considerations, including estimated bleeding risk during anticoagulation,[41] access to quality anticoagulation monitoring, and patient preferences and values.[42] Several million people with atrial fibrillation now receive chronic anticoagulation to prevent stroke. Additional research to identify more discriminating and accurate risk models around which standard recommendations could be developed would encourage more uniform use of antithrombotic agents and would likely lead to better patient outcomes.

Appendix

Stroke Risk in Atrial Fibrillation Work Group

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Disclosures

Dr Hart has served on data monitoring committees of clinical trials involving patients with atrial fibrillation sponsored by Astellas Pharmaceuticals, Sanofi-Aventis Pharmaceuticals, and Biotroniks, Inc.

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Moving the Tipping Point

The Decision to Anticoagulate Patients With Atrial Fibrillation

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Background—The rate of ischemic stroke associated with traditional risk factors for patients with atrial fibrillation has declined over the past 2 decades. Furthermore, new and potentially safer anticoagulants are on the horizon. Thus, the balance between risk factors for stroke and benefit of anticoagulation may be shifting.

Methods and Results—The Markov state transition decision model was used to analyze the $CHADS_2$ score, above which anticoagulation is preferred, first using the stroke rate predicted for the $CHADS_2$ derivation cohort, and then using the stroke rate from the more contemporary AnTicoagulation and Risk Factors In Atrial Fibrillation cohort for any $CHADS_2$ score. The base case was a 69-year-old man with atrial fibrillation. Interventions included oral anticoagulant therapy with warfarin or a hypothetical "new and safer" anticoagulant (based on dabigatran), no antithrombotic therapy, or aspirin. Warfarin is preferred above a stroke rate of 1.7% per year, whereas aspirin is preferred at lower rates of stroke. Anticoagulation with warfarin is preferred even for a score of 0 using the higher rates of the older $CHADS_2$ derivation cohort. Using more contemporary and lower estimates of stroke risk raises the threshold for use of warfarin to a $CHADS_2$ score ≥ 2. However, anticoagulation with a "new, safer" agent, modeled on the results of the Randomized Evaluation of Long-Term Anticoagulation Therapy trial of dabigatran, leads to a lowering of the threshold for anticoagulation to a stroke rate of 0.9% per year.

Conclusions—Use of a more contemporary estimate of stroke risk shifts the "tipping point," such that anticoagulation is preferred at a higher $CHADS_2$ score, reducing the number of patients for whom anticoagulation is recommended. The introduction of "new, safer" agents, however, would shift the tipping point in the opposite direction. ***(Circ Cardiovasc Qual Outcomes.* 2011;4:14-21.)**

Key Words: anticoagulants ■ atrial fibrillation ■ health services research ■ stroke prevention ■ decision analysis

The increased use of warfarin anticoagulation for prevention of thromboembolic stroke in patients with atrial fibrillation (AF) has produced substantial benefits, but has also resulted in an estimated quintupling of the incidence of warfarin-associated intracerebral hemorrhage (ICH).[1] Warfarin-associated ICH now comprises roughly 20% of all ICH. Furthermore, among patients with ICH, warfarin is associated with a doubling in the case fatality rate at 3 months and an increase in poor neurological outcomes.[2] There is suggestive evidence that the risk-adjusted incidence of ischemic stroke in patients with AF has declined over the past 2 decades, perhaps in response to more aggressive treatment of underlying risk factors, such as hypertension and hyperlipidemia.[3–10] As a result, the balance between the risk and benefit of anticoagulation therapy in patients with nonvalvular AF may be shifting.

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The most recent guidelines from the American College of Chest Physicians on antithrombotic therapy focus on stroke risk (Appendix Table 1).[9] Using the $CHADS_2$ criteria[11] for stroke risk stratification, these guidelines recommend oral anticoagulant therapy for patients with a $CHADS_2$ score ≥ 2 and consideration of either warfarin or aspirin for those with a $CHADS_2$ score of 1. Bleeding risk is not explicitly considered, although these recommendations assume that the patient is not at high risk for bleeding, and that good control of anticoagulation will occur. Guidelines from the American College of Cardiology/American Heart Association/European Society of Cardiology are essentially the same.[12] Adding the consideration of bleeding risk, which may vary from patient to patient,[13] the spectrum of decision-making for anticoagulant therapy in patients with AF can be schematized, as shown in Appendix Figure 1. Patients at lower risk of stroke and at high risk of bleeding should not receive oral anticoagulant therapy; patients at higher risk of stroke and at low risk of bleeding should receive anticoagulant therapy. The more difficult decisions lie in the middle where the risks of stroke

Received June 25, 2010; accepted October 29, 2010.

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The online-only Data Supplement is available at http://circoutcomes.ahajournals.org/cgi/content/full/CIRCOUTCOMES.110.958108/DC1.

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Circ Cardiovasc Qual Outcomes **is available at http://circoutcomes.ahajournals.org** **DOI: 10.1161/CIRCOUTCOMES.110.958108**

and bleeding are more closely balanced. Here lies the so-called "tipping point."

Our goal was to revisit the tipping point in light of more contemporary data suggesting a declining stroke risk for any of the typically defined risk factors, by constructing a decision analytic model examining strategies of oral anticoagulant therapy with warfarin, no antithrombotic therapy, and aspirin across a range of values for risk of ischemic stroke. We also wished to explore how the future availability in the United States of new, potentially safer anticoagulants, such as the direct thrombin inhibitor dabigatran, or the multiple direct factor Xa inhibitors in advanced development would impact the "tipping point" for anticoagulant therapy.

WHAT IS KNOWN

- The rate of stroke in patients with atrial fibrillation has declined over the past 2 decades.
- New and potentially safer anticoagulant medications are on the horizon.
- Thus, the balance between risk factors for stroke and benefit of anticoagulation may be shifting.

WHAT THE STUDY ADDS

- Tools in use to predict stroke risk may overestimate this risk, and thus result in recommendations for blood thinning therapy for some patients who may not require such treatment. The $CHADS_2$ score is one such tool.
- Using more recent estimates of stroke risk shifts the "tipping point," such that anticoagulation is preferred at a higher $CHADS_2$ score (ie, higher stroke risk), reducing the number of patients for whom anticoagulation is recommended.
- The introduction of "new, safer" agents, however, would shift the tipping point in the opposite direction.

Methods

Review of Data

Risk of Ischemic Stroke

There are a number of risk stratification schemes that have been developed to predict ischemic stroke risk in AF patients.[11,14–17] One of the more widely used is $CHADS_2$,[11] which assigns 1 point for each of the following risk factors for patients with AF: congestive heart failure, hypertension, age ≥75 years, and diabetes. Two points are assigned for a history of stroke or transient ischemic attack. A $CHADS_2$ score of 2 (or 4% per year risk of stroke) roughly corresponds to the "average" patient not taking warfarin in the pooled analyses of AF trials.[16] In a more contemporary study of 13 559 adults with nonvalvular AF receiving care within the Kaiser Permanente system of Northern California, rates of stroke among patients not taking warfarin were significantly lower.[5] Although the derivation cohort for $CHADS_2$ reported stroke rates ranging from 1.9% to 18.2% per year for scores between 0 and 6, stroke rates ranged between 0.36% and 6.10% per year in the AnTicoagulation and Risk Factors In Atrial Fibrillation (ATRIA) cohort for patients not receiving warfarin (Appendix Table 2).

Major Bleeding Events in Patients Receiving Anticoagulant Therapy

We stratified major bleeding events into intracerebral hemorrhage, subdural hematoma, and extracranial bleeding. In a study of the ATRIA cohort, examining the net benefit of warfarin in AF, patients between 65 and 74 years of age had a 0.12% per year rate of intracranial hemorrhage off warfarin and a 0.44% per year rate on warfarin.[5] Approximately 47% of these patients had intracerebral hemorrhages. Furthermore, roughly 50% of these patients were taking aspirin.[18] After correcting for these factors, the annual rate of intracerebral hemorrhage in patients not receiving warfarin was 0.05%, and 0.21% in those receiving warfarin (relative hazard, 4.07). These were used for the base case values. Neurological outcomes (Table 1) were obtained from a study of 435 patients with warfarin intracerebral hemorrhage.[2] A meta-analysis evaluating the effects of antiplatelet therapy in patients at high risk for vascular events, the Antithrombotic Trialists' Collaboration, reported an odds ratio of 1.22 (95% confidence interval [CI], 1.03 to 1.44) for fatal or nonfatal hemorrhagic stroke in patients receiving aspirin.[19] This estimate is consistent with other summary analyses indicating that the incremental risk of hemorrhagic stroke in patients taking aspirin is small.[20]

In the ATRIA study noted above, 34% of patients with intracranial hemorrhages had subdural hematomas. Correcting for aspirin use, subdural hematomas occurred at an annual rate of 0.027% in patients not receiving warfarin and 0.0015% in those receiving warfarin.[5] This is consistent with rates of subdural hematomas on warfarin described in other studies.[16,21,22] The mortality associated with anticoagulant-related subdural hematoma is roughly 27%.[23]

In 16 trials examining the use of anticoagulant and antiplatelet agents for the prevention of stroke, the relative risk for major extracranial hemorrhage in patients receiving anticoagulant therapy was 2.4, resulting in an average rate of 1.4% per year for trial participants taking warfarin.[24,25] In a large cohort study of 13 559 adults with AF, major extracranial hemorrhages were fatal in 5.1% of patients receiving warfarin.[25] A meta-analysis of 4052 patients with AF receiving either warfarin or aspirin reported a hazard ratio of 2.15 for lethal bleeding among patients receiving warfarin versus aspirin.[26] In the absence of more specific data for mortality of extracranial bleeding among patients receiving aspirin, we calculated a mortality rate of 2.4%.

New, "Safer" Anticoagulants

We used data from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial of the direct thrombin inhibitor dabigatran to describe base case values for both efficacy and bleeding risk for potentially safer and more efficacious novel anticoagulants. In sensitivity analyses, we explored how changes in either the efficacy or safety of such new agents would affect the "tipping point." In RE-LY, the 150 mg dose of dabigatran was found to be more effective than warfarin in preventing ischemic stroke (relative risk, 0.76; 95% CI, 0.60 to 0.98).[27] In addition, the relative risk of intracranial bleeding was 0.40 (95% CI, 0.27 to 0.60) compared with warfarin. The risk of extracranial bleeding was 1.07 (95% CI, 0.92 to 1.25). Of note, the absolute event rate for intracranial bleeding in patients receiving warfarin in this study was quite high, 0.74% per year, almost double the rate seen in other studies.[5,18,28] Therefore, as a more conservative estimate for the relative risk of intracranial bleeding in patients receiving the new "safer" oral anticoagulant compared with warfarin, we hypothesized that the bleeding risk should be similar to that of an "ideal" agent, such as warfarin that was never out of the therapeutic range. In a study describing the odds of intracranial hemorrhage as a function of INR, 22% of bleeds occurred in patients with an INR ≥3.6, meaning that 78% of such bleeds occurred when patients were within the therapeutic range.[29] Therefore, in our model we calculated the risk of intracranial hemorrhage associated with the new "safer" agent to be 0.78 times the intracranial hemorrhage risk of warfarin. In addition, a high proportion of patients (11.3%) had significant gastrointestinal side effects. We attempted to capture some of these issues by assigning a slightly lower quality of life to the hypothetical new, "safer" agent of 0.99.

Decision Analytic Model

We developed a 28-state Markov state transition decision model to explore outcomes of the 4 strategies: (1) anticoagulate with warfarin;

Table 1. Data Required in the Analysis: Probabilities, Rates, and Quality of Life

Parameter				Value
Annual rate of ischemic stroke (untreated)				0.023 (5)
$CHADS_2=2$ (ATRIA cohort)				
Efficacy of treatment				
With warfarin				0.68 (16)
With aspirin				0.21 (44)
Probable outcome of ischemic stroke				
Death				0.16 (45)
Permanent sequelae				0.44 (16, 46)
With severe disability				0.69 (16, 46)
With mild disability				0.31 (16, 46)
Good recovery				0.40 (16, 46)
Annual rate of bleeding event (untreated)				
ICH				0.0005 (5, 18)
Subdural hematoma				0.00027 (5, 16, 47)
Extracranial				0.006 (24, 25)
Location of Hemorrhage	Lobar ICH	Deep ICH	Subdural Hematoma	Extracranial
Relative hazard of bleeding				
Warfarin	4.1 (5, 18)	4.1 (5, 18)	5.5 (5, 21, 49)	2.4 (24)
Aspirin	1.2 (20, 48)	1.2 (20, 48)	2.0 (50)	1.08 (24)
Probable outcome from bleed (without warfarin/with warfarin)*	(2)	(2)		
Death	0.19/0.38	0.21/0.41	0.267 (23, 26)	0.024/0.051
Severe long-term disability	0.43/0.43	0.44/0.42	0.07/0.09 (51)	(23, 26)
Mild long-term disability	0.20/0.11	0.19/0.10	0.40/0.50 (51)	
Good recovery	0.19/0.08	0.17/0.07	0.263/0.143	
				Base-Case Value of Quality of Life
Long-term symptoms				
Well				1.0
Well while receiving anticoagulant therapy				0.99 (52)
Severe long-term disability				0.11 (52)
Mild long-term disability				0.76 (52)
Death				0.0
Short-term symptoms				
ICH†				0.79
Ischemic stroke†				0.79
Extracranial bleed‡				0.84
				Base-Case Value of Age-Adjusted Annual Excess Mortality
Stroke with long-term disability			0.08 (53)	

*Assume outcomes of bleeding events for aspirin-treated patients are the same as for untreated patients.

†Assume quality of life is 0 for duration of hospitalization. Length of stay for specific cerebrovascular disorders except transient ischemic attack (diagnosis-related group, 14) is 6.4 days.

‡Length of stay for gastrointestinal hemorrhage (diagnosis-related group, 174) is 4.9 days.

(2) anticoagulate with a new, "safer" agent, using dabigatran as the model; (3) treat with aspirin; and (4) no antithrombotic therapy. We used a standard computer program (Decision Maker, Boston, Mass) to build the model, analyze results, and perform sensitivity analyses. Our base case involved a hypothetical 69-year-old man with nonvalvular AF who had no contraindications to warfarin therapy. During each monthly cycle, patients face a chance of stroke and hemorrhage, either of which may lead to death, significant neurological sequelae, or symptom resolution. The simulation is run for the entire life expectancy of the hypothetical cohort of similar patients. Base case values for model parameters are summarized in Table 1 and the decision tree Figure and modeling details provided in appendix Figure 2 and accompanying text.

Results

Results of the base case analysis for a 69-year-old man with nonvalvular AF with a $CHADS_2$ score of 2, corresponding to

Table 2. Base Case Analysis

Strategy	Expected Utility (Quality-Adjusted Life-Years)
No antithrombotic therapy	9.11
Aspirin	9.25
Warfarin	9.36
Hypothetical "new and safer" oral anticoagulant, modeled on dabigatran	9.51

Base case was a 69-year-old man with AF (stroke risk, 2.3% per year), corresponding to $CHADS_2$ of 2 in contemporary ATRIA cohort.

an annual ischemic stroke risk of 2.5% in the ATRIA cohort are shown in Table 2. Antithrombotic therapy with warfarin provides a modest gain in quality-adjusted life expectancy compared with either no antithrombotic therapy or aspirin. However, anticoagulation with a new, "safer" agent results in the greatest gain in quality-adjusted life-years.

The question of the "tipping point" is addressed in the following 1-way sensitivity analyses examining outcomes for the strategies in quality-adjusted life-years as a function of the annual rate of ischemic stroke. Figure 1 examines the 3 historically available strategies in the United States: (1) anticoagulation with warfarin; (2) aspirin; and (3) no antithrombotic therapy. Superimposed as a second and third horizontal axis are the $CHADS_2$ risk scores. The top axis shows the association between the $CHADS_2$ scores and the annual stroke rate in the $CHADS_2$ derivation cohort. The bottom-most axis shows annual stroke risk associated with $CHADS_2$ scores in the more contemporary ATRIA cohort.[3] The threshold lines form 3 regions. To the left, at lowest rates of stroke (<0.2% per year), no anticoagulant therapy is preferred. To the far right, at stroke rates greater than 1.7% per year, anticoagulation with warfarin is best. In the small region between 0.2% and 1.7% per year, aspirin is preferred. With reference to the scores in the $CHADS_2$ derivation cohort, anticoagulation with warfarin is reasonable for patients with a score ≥0. Using a more contemporary estimate of stroke risk for any $CHADS_2$ score (lower horizontal axis of Figure 1), our results suggest that patients with a score of zero or 1 should receive aspirin, whereas those with scores of 2 or greater should receive anticoagulation with warfarin. It should be noted that the magnitude of the differences in expected utility between the 3 strategies at low stroke rates (below 1.7% per year) is quite small. Therefore, patient-to-patient variability in either bleeding risk or preferences for outcomes could alter the optimal therapy in this region. The overall impact of the declining risk of ischemic stroke for any $CHADS_2$ score was to shift the "tipping" point so that a higher $CHADS_2$ score is needed to "justify" anticoagulant therapy.

We next examined how the use of a new, "safer" anticoagulant would affect the tipping point at which anticoagulant therapy is preferred over no anticoagulant therapy. As shown in Figure 2, the threshold for ischemic stroke risk above which anticoagulant therapy with a hypothetical new, "safer" agent is preferred over aspirin is lower (>0.9% per year). In fact, this threshold is near a $CHADS_2$ score of 1, given the more contemporary assignment of stroke risk (ie, the bottom-most axis).

Figure 3 depicts a 3-way sensitivity analysis examining the relative hazard of intracerebral hemorrhage (new, "safer"

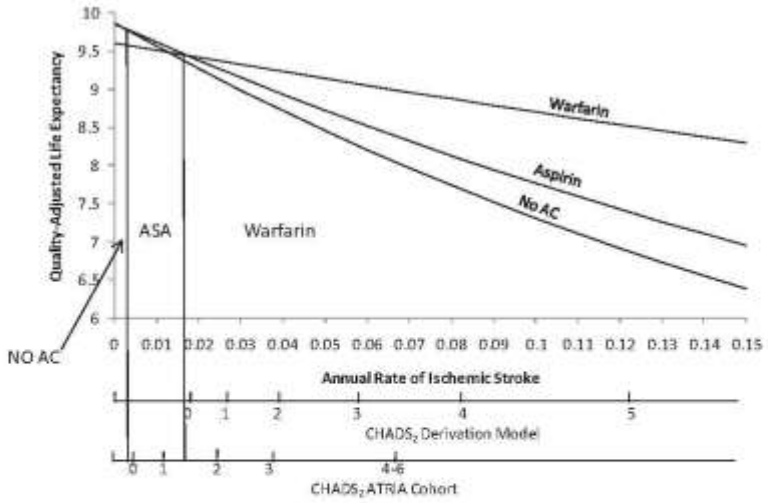

Figure 1. One-way sensitivity analysis: Annual rate of ischemic stroke. Quality-adjusted life expectancy for each of the 3 strategies (warfarin, aspirin, and no antithrombotic therapy) is shown as a function of the annual rate of ischemic stroke ranging from 0 to 0.15 per year. There are 2 secondary horizontal axes showing the corresponding $CHADS_2$ scores. The upper secondary axis uses the $CHADS_2$ derivation cohort (see Appendix Table 2), whereas the lower axis maps the $CHADS_2$ predictors to the annual stroke rate found in the more contemporary ATRIA cohort. The threshold lines divide the decision space into 3 regions. To the far left, at low rates of ischemic stroke (<0.2% per year), no antithrombotic therapy is best, whereas to the far right at stroke rates greater than 1.7% per year, anticoagulation with warfarin is best. There is a small region between these 2 thresholds in which aspirin use is preferred. Using more contemporary data for stroke risk (bottommost horizontal axis), anticoagulation is only preferred at a higher $CHADS_2$ score (≥2), compared with stroke risk predicted by the $CHADS_2$ derivation model (top secondary horizontal axis), for which warfarin is preferred even with a $CHADS_2$ score less than 0.

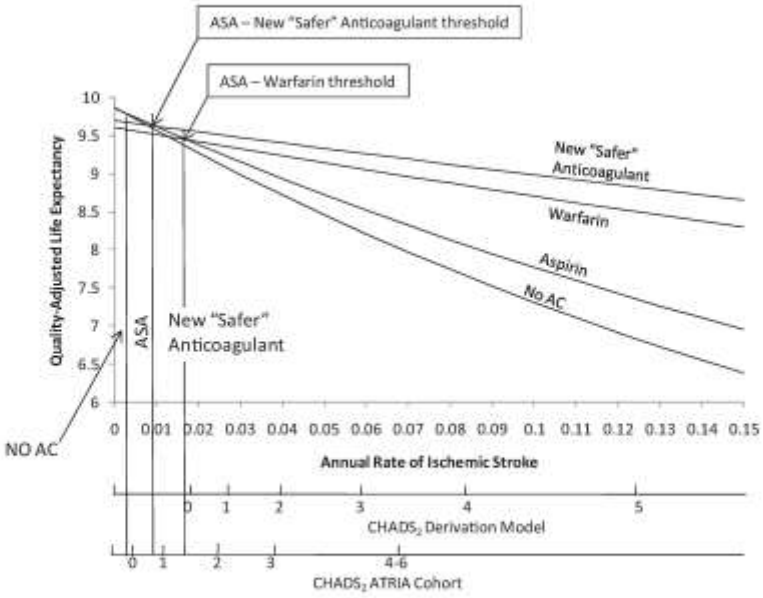

Figure 2. One-way sensitivity analysis: Annual rate of ischemic stroke with addition of anticoagulation with a new, "safer" anticoagulant. The axes are the same as in Figure 1. With the addition of a new, "safer" agent as another option for anticoagulation, the "tipping point" above which the risk and outcomes of ischemic stroke outweigh the risk and outcomes of major hemorrhage shifts to the left. Anticoagulation with the new drug is preferred at annual stroke rates above 0.9% per year ($CHADS_2$ score <0 in the derivation model; and CHADS2 score of ≥1 using the ATRIA data).

anticoagulant versus warfarin) on the horizontal axis, and the relative hazard of ischemic stroke (new, "safer" anticoagulant versus warfarin) on the vertical axis, for 3 different values of quality of life while taking the new anticoagulant (0.98, 0.99, and 1.0). The base case values are shown as an ellipse, demarked by the 95% CIs (from the RE-LY study) around the 2 relative hazards on the *x* and *y* axes. For a patient with a $CHADS_2$ score of 2, the base case ellipse falls within the region in which anticoagulation with the new, "safer" agent is preferred, even if the quality of life on this drug is 0.99 (eg, the same as the quality of life while taking warfarin). If the quality of life on this new agent is lower, for example, 0.98, the outer edge of the ellipse falls within the region in which warfarin is best. Should other hypothetical new oral anticoagulants be developed with greater efficacy and lower hemorrhage risk (toward the bottom left of the Figure), the gain in quality-adjusted life-years would become even greater.

Discussion

Our analysis suggests that the "tipping point," the threshold of ischemic stroke risk below which anticoagulant therapy should be withheld and above which anticoagulant therapy

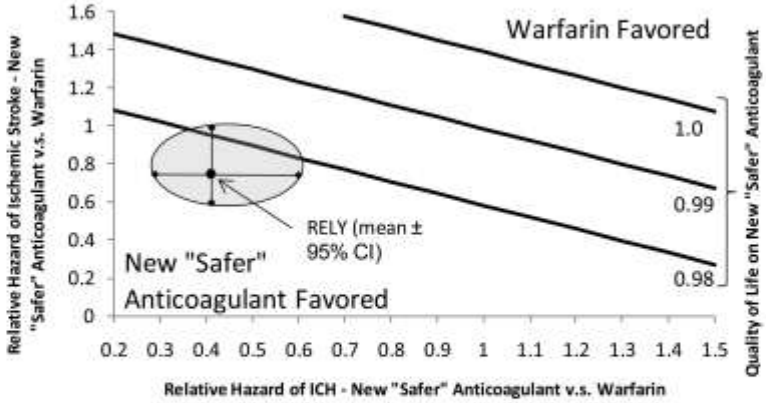

Figure 3. Three-way sensitivity analysis: Relative hazard of intracerebral hemorrhage and relative hazard of ischemic stroke (new, "safer" anticoagulant versus warfarin) and quality of life. The decision space is divided into 2 regions. At the lower left, where the relative hazards of ICH and ischemic stroke while receiving the new, "safer" anticoagulant versus warfarin are low, the new agent is preferred. At the upper right, where the relative hazards of these events is high, warfarin is preferred. Three threshold lines are shown for varying quality of life while taking the new anticoagulant (0.98, 0.99, and 1.0). If the new anticoagulant has no detrimental impact on quality of life (eg, quality of life of 1.0), then the region in which it is favored is largest. As the quality of life while taking the new anticoagulant decreases, the size of this region becomes smaller. The ellipse demonstrating the base case values for the relative hazards of ICH and ischemic stroke, along with their 95% CIs, falls within the region in which the new anticoagulant is preferred if the quality of life while taking this new agent is 0.99 or greater. Hypothetical new and safer agents characterized by higher efficacy and lower bleeding risk (lower left corner) would be preferred over warfarin.

should be prescribed, has changed. The risk of ischemic stroke in nonvalvular AF appears to have declined, perhaps as a result of more aggressive control of blood pressure and lipid levels.[3–7] Indeed, our analysis using a more contemporary cohort of patients with AF from the ATRIA study suggests that the threshold has shifted such that the balance of risk and benefit afforded by anticoagulation tips in favor of warfarin at a higher $CHADS_2$ score than in the past. Specifically, anticoagulation with warfarin is preferred for patients with a $CHADS_2$ score of 2 or more. Aspirin is preferred among patients with $CHADS_2$ scores of zero or 1. No antithrombotic therapy is only preferable among those at close to no risk of ischemic stroke. However, the magnitude of gain between aspirin and either no antithrombotic therapy or warfarin at low $CHADS_2$ scores is small. Therefore, patient-specific differences in bleeding risk or preferences for health outcomes, along with statistical uncertainty in parameter estimates, may affect the strength of this result. Furthermore, the magnitude of gain from warfarin increases as the annual rate of ischemic stroke increases above the threshold. Current American College of Chest Physicians and American College of Cardiology/American Heart Association/European Heart Society guidelines suggest either warfarin (grade 1A) or aspirin (grade 1B) for patients with a $CHADS_2$ score of 1 and warfarin for patients with scores of 2 or more (grade 1A).[9] Although results of our decision analysis suggest that warfarin may have been preferred above a $CHADS_2$ score of zero, based on older estimates of ischemic stroke risk, this is not congruent with older guidelines. Perhaps older guidelines were a bit too conservative about warfarin use, given data available at the time, but our analysis would suggest that current guidelines are now appropriate given the decreasing risk of ischemic stroke.

It also is important to note that whereas the $CHADS_2$ score is categorical (a patient cannot have a score of 1.5, for instance), risk progresses in a continuous fashion. Therefore, it is difficult to interpret thresholds that fall between $CHADS_2$ scores. Furthermore, the annual rate of stroke associated with each $CHADS_2$ score has associated uncertainty (see Appendix Table 2).

A modification of $CHADS_2$ has recently been proposed to incorporate additional stroke risk factors. This CHA_2DS_2-VASc scheme has been incorporated into the European Society of Cardiology guidelines, although there is no formal evidence that it is superior to $CHADS_2$.[30] Appendix Figure 3 demonstrates the addition of the CHA_2DS_2-VASc to the threshold analysis. Indeed, the limited precision of available risk prediction tools remains a major barrier to patient-specific decision-making for stroke prevention in nonvalvular AF. Although we have used the $CHADS_2$ algorithm to highlight the secular change in ischemic stroke risk associated with patient-specific risk factors, the overall quality of prediction rules for ischemic stroke is mediocre.[8] An assessment of 5 of the major stroke risk stratification schemes for patients with AF ($CHADS_2$, Atrial Fibrillation Investigators, Stroke Prevention in AF, and Framingham indices, and the 7th American College of Chest Physicians guidelines) demonstrated receiver operating characteristic areas between 0.56 to 0.62, indicating poor discrimination.[31] Similarly, assessment of the CHA_2DS_2-VASc in a verification cohort (Euro Heart Survey patients) yielded a c-statistic of 0.61, highlighting the need for better stroke prediction models.[30] In particular, our analysis demonstrates the importance of being able to identify patients at very low risk of ischemic stroke who in fact might be best served by no antithrombotic therapy. Furthermore, there are no formal models estimating risk of ICH, although a variety of determinants of such risk has been identified.[18,32–42] To make better, patient-tailored decisions and recommendations regarding anticoagulant therapy for AF patients, new and more robust prediction tools will need to be developed for both ischemic stroke and ICH risk. A goal of these improved risk prediction tools would be to accurately move predicted risks away from threshold values, allowing more confident decisions.

The introduction of novel anticoagulants, such as dabigatran, which appear to be more efficacious while leading to lower risks of intracranial hemorrhage, expands the number of individuals for whom anticoagulation can be recommended compared with warfarin. Indeed, use of a more effective and safer anticoagulant also shifts the tipping point, such that anticoagulation with such an agent may be preferred over either warfarin or aspirin for patients with a $CHADS_2$ score of 1. We have used data from RE-LY describing the efficacy, safety, and side-effect profile of dabigatran to characterize a prototypical new and safer anticoagulant. However, the very positive findings from the RE-LY trial may deteriorate in real world use.

Our decision analytic framework also can be used to model other new or novel therapies. For instance, for patients in whom vitamin K antagonists may not be suitable (poor anticipated compliance with INR measurement or dosage adjustment), the addition of clopidogrel to aspirin was examined in the ACTIVE-A trial.[43] They found the combination of the 2 drugs had a relative hazard of 0.72 (95% CI, 0.62 to 9.83) for stroke and 1.57 (95% CI, 1.29 to 1.92) for major hemorrhage compared with aspirin alone. Examining these 2 strategies in our model, the combination antiplatelet regimen would be preferred for patients with a stroke risk greater than 0.4% per year, and the magnitude of the gain would increase as the patient-specific stroke risk increased. However, if a new and "safer" oral anticoagulant were also available, how might it compare with the combination antiplatelet regimen? Using the same base case assumptions from our previous analysis, we found that the new, "safer" oral anticoagulant would be preferred above a stroke risk of 1.3% per year, aspirin would be preferred for stroke risk below 0.4% per year, whereas combination antiplatelet therapy would be preferred for stroke risks in between these 2 thresholds. Nonpharmacological interventions for appropriate patients, such as catheter ablation or the Maze procedure, also could be examined using this analytic framework.

In summary, secular trends in the risk of ischemic stroke as reflected in ATRIA appear to have shifted the "tipping point" in favor of withholding anticoagulant therapy from patients who might have received it in the past based on their $CHADS_2$ scores. However, as new, safer anticoagulants become available, the "tipping point" will shift again in the opposite direction. With the proliferation of new anticoagu-

lants and antithrombotic therapies, along with nonpharmacological interventions for AF, and the improbability of clinical trials performing head-to-head comparisons of these treatments, a decision analytic framework can be used to examine new treatments as data become available. Finally, it is clear that the biggest barrier to personalized decision-making for patients with AF remains the limited discriminating ability of available tools for predicting risk of thromboembolic stroke and hemorrhage.

Sources of Funding

Dr Eckman was supported by The National Center for Research Resources, The National Institute of Diabetes and Digestive and Kidney Diseases, The National Heart, Lung, and Blood Institute, and the National Library of Medicine. Dr Singer was supported by the Eliot B. and Edith C. Shoolman fund of the Massachusetts General Hospital, and The National Heart, Lung, and Blood Institute. Dr Rosand was supported by National Institutes of Neurological Disorders and Stroke. The funding sources listed had no role in the design or implementation of the study or in the decision to seek publication.

Disclosures

Dr Eckman has consulted for Savient Pharmaceuticals and has received research support from Gilead Sciences, Inc. Dr Singer has consulted for Boehringer Ingelheim, Daiichi Sankyo, Inc, Bayer Healthcare, Johnson & Johnson, Inc, Merck and Co, and Sanofi Aventis, Inc, and has received research support from Daiichi Sankyo Inc.

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Validation of the Essen Stroke Risk Score and the Stroke Prognosis Instrument II in Chinese Patients

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Background and Purpose—Little was known about the predictive accuracy of the Essen Stroke Risk Score and the Stroke Prognostic Instrument II in Chinese patients with stroke.

Methods—We evaluated the predictive accuracy of both Essen Stroke Risk Score and Stroke Prognostic Instrument II scores for both recurrent stroke and combined vascular events using data from a prospective cohort of 11 384 patients with acute ischemic stroke and transient ischemic attack admitted to 132 urban hospitals throughout China.

Results—The cumulative 1-year event rates were 16% (95% CI, 15%–16%) for recurrent stroke and 18% (95% CI, 18%–19%) for combined vascular events. Both event rates were significantly higher in patients with transient ischemic attack and increased significantly from lower to higher Essen Stroke Risk Score and Stroke Prognostic Instrument II categories. Essen Stroke Risk Score and Stroke Prognostic Instrument II had similar predictive accuracies for each study outcome.

Conclusions—In Chinese patients with ischemic stroke or transient ischemic attack, both Essen Stroke Risk Score and Stroke Prognostic Instrument II scores are equally able to stratify the risk of recurrent stroke and combined vascular events. **(*Stroke*. 2011;42:3619-3620.)**

Key Words: Essen Stroke Risk Score ■ ischemic stroke ■ Stroke Prognostic Instrument II ■ transient ischemic attack

Recurrent stroke and subsequent cardiac events after stroke are major contributors to disability and mortality for stroke victims.[1] Identification of those patients at high risk of recurrent stroke and/or cardiac events is critically important for both inpatient management and outpatient care. Several predictive scores have been developed to help stratify the risk of recurrent stroke and/or cardiac events for patients with transient ischemic attack (TIA) and ischemic stroke, including the Essen Stroke Risk Score (ESRS) and the Stroke Prognostic Instrument II (SPI-II) score. Although both ESRS and SPI-II have been validated in Western populations,[2,3] the performance of these scores has not been examined in large Chinese stroke patient populations.

Methods

Data for patients with TIA or ischemic stroke from the China National Stroke Registry (CNSR) were used in this report. The design, rationale, and baseline information of CNSR has been described previously.[4] In brief, CNSR was a nationwide prospective hospital-based cohort study of consecutive patients with stroke aged ≥18 years admitted to 132 hospitals within 14 days after the onset of symptoms between September 2007 and August 2008 in China. Stroke and TIA were defined based on World Health Organization criteria.[5] Except for TIA, all the diagnoses were confirmed by brain CT or MRI. Detailed baseline data were abstracted prospectively using paper-based registry forms. Patients or their authorized proxies were contacted by telephone 3, 6, and 12 months after symptom onset. The study was approved by the central Institutional Review Board at Beijing Tiantan Hospital. Written informed consent was obtained from the patient or his or her legally authorized representative.

The study outcomes were recurrent stroke and combined vascular event. A recurrent stroke was defined as a newly diagnosed stroke in a patient in whom the initial symptoms had substantially or fully recovered. A combined vascular event was defined as any event including recurrent stroke, myocardial infarction, or cardiovascular death.

Statistical Analysis

Proportions were used for categorical variables; mean with SD were used for continuous/score variables. Chi-square tests were used to compare categorical variables; Student *t* test was used for continuous/score variables. The cumulative event rates and the corresponding 95% CIs of outcomes were calculated based on a binomial distribution. We estimated the discrimination of ESRS and SPI-II to predict 1-year cumulative recurrent stroke and combined vascular event using the area under the curve by c-statistic. We used 1000 bootstrap samples to estimate the 95% CI for each c-statistic. All tests were 2-tailed, and $P<0.05$ was considered statistically significant. All analyses were conducted using SAS 9.1.

Results

There were 11 384 eligible patients with TIA (1061) or ischemic stroke (10 323) in our analysis, after excluding 1381 (10.5%) patients with a history of atrial fibrillation and 851 (7.0%) patients without follow-up. The patients with and without

Received April 25, 2011; final revision received June 29, 2011; accepted July 19, 2011.

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The online-only Data Supplement is available at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.111.624148/-/DC1.

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***Stroke* is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.111.624148**

Table 1. Twelve-Month Cumulative Rates for Recurrent Stroke and Combined Vascular Events Stratified by the ESRS or SPI-II Categories

	Recurrent Stroke				Combined Vascular Events			
	IS		TIA		IS		TIA	
	No.	Percent (95% CI)	No.	Percent (95% CI)	No.	Percent (95% CI)	No.	Percent (95% CI)
ESRS								
0–2	5193	12 (11–13)	652	16 (13–19)	5193	13 (12–14)	652	18 (15–21)
3–9	5130	20 (19–21)	409	21 (17–25)	5130	23 (22–24)	409	24 (20–28)
SPI-II								
0–3	3243	10 (9–11)	678	15 (12–18)	3243	11 (10–12)	678	17 (14–20)
4–7	4625	16 (15–17)	341	22 (18–27)	4625	19 (18–20)	341	26 (21–31)
8–15	2455	23 (21–25)	42	24 (12–39)	2455	26 (24–28)	42	29 (16–45)
Total	10 323	16 (15–17)	1061	18 (15–20)	10 323	18 (17–19)	1061	20 (18–23)

ESRS indicates Essen Stroke Risk Score; SPI-II, Stroke Prognosis Instrument II; IS, ischemic stroke; TIA, transient ischemic attack; CI, confidence interval.

complete follow-up were comparable in terms of the prevalence of baseline risk factors and clinical characteristics (Supplemental Table; http://stroke.ahajournals.org).

The cumulative 1-year event rates were 16% (95% CI, 15%–16%) for recurrent stroke and 18% (95% CI, 18%–19%) for combined vascular event. Both event rates were significantly higher in TIA, especially for patients in lower ESRS and SPI-II score categories compared with patients with ischemic stroke. In addition, both event rates increased significantly for patients from lower to higher ESRS and SPI-II score categories (Table 1).

ESRS and SPI-II scores had similar predictive accuracy for either recurrent stroke or cumulative vascular events, and there were no statistically significant differences in area under the curve values for each outcome using either ESRS or SPI-II score (Table 2).

Discussion

Our results showed that both ESRS and SPI-II scores were equally able to stratify the risk of recurrent stroke and combined vascular events in a Chinese stroke population and the area under the curve values were similar to a recent study in German patients with stroke.[2] These scores may help the clinicians to identify the patients at high risk of recurrent stroke and/or cardiac events and raise the awareness of managing risk factors for both inpatient treatment and outpatient care. However, the relatively low accuracy may raise concerns for the usefulness of these 2 predictive scores in individual treatment decisions and secondary prevention.

There were limitations in this study. The study sites were selected from urban areas and may represent the institutes having better inpatient and outpatient care; the rates for recurrent stroke and cardiac events may be underestimated. In addition, some of the cardiovascular deaths may be misdiagnosed. Because the analysis was performed only in patients who completed the 1-year follow-up, there may be potential biases in estimation of event rates and calculation of prediction accuracies.

Table 2. Predictive Accuracy of ESRS and SPI-II Scores

	Recurrent Stroke		Combined Vascular Events	
	AUC	95% CI	AUC	95% CI
ESRS				
IS	0.60	0.57–0.61	0.60	0.59–0.62
TIA	0.57	0.52–0.62	0.56	0.52–0.61
All patients	0.59	0.58–0.60	0.60	0.59–0.61
SPI-II				
IS	0.60	0.58–0.62	0.61	0.59–0.62
TIA	0.58	0.54–0.63	0.59	0.55–0.63
All patients	0.59	0.58–0.61	0.60	0.58–0.61

ESRS indicates Essen Stroke Risk Score; SPI-II, Stroke Prognosis Instrument II; AUC, area under the curve; IS, ischemic attack; TIA, transient ischemic attack; CI, confidence interval.

Sources of Funding

This study was funded by the Ministry of Science and Technology and the Ministry of Health of the People's Republic of China (grant no. 2008ZX09312-008 and 2009CB521905).

Disclosures

None.

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Bleeding Risk Assessment

HAS-BLED Score & Bleeding Rate

Letter	Clinical Characteristic	Points Awarded
H	Hypertension	1
A	Abnormal renal &/or liver function (1 point each)	1 or 2
S	Stroke history	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (age ≥ 65)	1
D	Drugs or alcohol (1 point each)	1 or 2
	Maximum score	9

Hypertension = systolic BP≥160 mmHg; Abnormal renal function = presence of chronic dialysis or renal transplantation or serum creatinine≥200µmol/L; Abnormal liver function = chronic hepatitis disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin>2x upper limit of normal, in association with AST/ALP/ALP>3x upper limit normal, etc.); Bleeding = previous bleeding history or predisposition to bleeding (e.g. bleeding diathesis, anemia, etc.); Labile INRs = unstable/high INRs or poor time in therapeutic range (e.g. <60%); Drugs or alcohol = concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatories, or alcohol abuse, etc.; INR = international normalized ratio

Annual Adjusted Bleeding Rate

0 points = 1.13%
1 point = 1.02%
2 points = 1.88%
3 points = 3.74%
4 points = 8.70%
5 points = 12.50%
Any score = 1.56%

ATRIA Score & Bleeding Rate

	Clinical Characteristic	Points Awarded
	Anemia	3
	Severe renal disease	3
	Age ≥ 75	2
	Bleeding history	1
	Hypertension	1
	Maximum score	10

Severe renal disease = glomerular filtration rate <30ml/min or dialysis-dependent
ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation
0 – 3 points = low risk
4 points = intermediate risk
5 – 10 points = high risk

Annual Adjusted Bleeding Rate

0 – 3 points = 0.8%
4 points = 2.6%
≥ 5 points = 5.8%

HEMORR$_2$HAGES Score & Bleeding Rate

	Clinical Characteristic	Points Awarded
H	Hepatic or renal disease	1
E	Ethanol abuse	1
M	Malignancy	1
O	Older (age >75)	1
R	Reduced platelet count or fxn	1
R	Rebleeding risk	2
H	Hypertension (uncontrolled)	1
A	Anemia	1
G	Genetic factors	1
E	Excessive fall risk*	1
S	Stroke	1
	Maximum score	12

*Including neuropsychiatric disease
0 – 1 points = low risk
2 – 3 points = intermediate risk
≥4 points = high risk
Annual Adjusted Bleeding Rate
0 points = 1.9%
1 point = 2.5%
2 points = 5.3%
3 points = 8.4%
4 points = 10.4%
≥ 5 points = 12.3%

Outpatient Bleeding Risk Index (OBRI) & Bleeding Rate

	Clinical Characteristic	Points Awarded
	Age ≥ 65 years	1
	History of GI bleeding	1
	History of stroke	1
	One or more comorbid conditions	1
	Maximum score	4

Comorbid conditions = recent MI, anemia (hematocrit <30%), renal impairment (creatinine level >1.5mg/dL), or diabetes mellitus
0 points = low risk
1 – 2 points = intermediate risk
≥3 points = high risk

Bleeding risk assessment and management in atrial fibrillation patients

Executive Summary# of a Position Document from the European Heart Rhythm Association [EHRA], endorsed by the European Society of Cardiology [ESC] Working Group on Thrombosis

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Summary

In this executive summary of a Consensus Document from the European Heart Rhythm Association, endorsed by the European Society of Cardiology Working Group on Thrombosis, we comprehensively review the published evidence and propose a consensus on bleeding risk assessments in atrial fibrillation (AF) patients. The main aim of the document was to summarise 'best practice' in dealing with bleeding risk in AF patients when approaching antithrombotic therapy, by addressing the epidemiology and size of the problem, and review established bleeding risk factors. We also summarise definitions of bleeding in the published literature. Patient values and preferences balancing the risk of bleeding against thromboembolism as well as the prognostic implications of bleeding are reviewed. We also provide an overview of published bleeding risk stratification and bleeding risk schema. Brief discussion of special situations (e.g. periablation, peri-devices such as implantable cardioverter defibrillators [ICD] or pacemakers, presentation with acute coronary syndromes and/or requiring percutanous coronary interventions/stents and bridging therapy) is made, as well as a discussion of the prevention of bleeds and managing bleeding complications. Finally, this document puts forwards consensus statements that may help to define evidence gaps and assist in everyday clinical practice.

Keywords

Bleeding, oral anticoagulation, atrial fibrillation, risk assessment

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Received: October 5, 2011
Accepted after minor revision: October 27, 2011
Prepublished online: November 2, 2011
doi:10.1160/TH11-10-0690
Thromb Haemost 2011; 106: 997–1011

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The full version of this document has been published in Europace 2011; 13: 723–460.

1. Introduction and scope

Prevention of stroke and thromboembolism is one of the main therapeutic goals in atrial fibrillation (AF) (1, 2). Oral anticoagulation (OAC) is highly effective in preventing ischaemic strokes in patients with AF and conveys a clear net clinical benefit despite a potential risk for major bleeding events (3).

Current OAC in common use are essentially the vitamin K antagonists (VKA), most often warfarin or acenocoumarol or phenprocoumon, which are dose-adjusted to achieve an international normalised ratio (INR) of 2.0–3.0 (2). The VKA have many limitations, including a significant inter- and intra-patient variability of effective dose, and various food and drug interactions. New OAC, broadly divided into two categories, the oral direct thrombin inhibitors and the oral direct factor Xa inhibitors, are in advanced clinical development, and may offer alternative therapies to patients who suffer from the limitations and dis-utility associated with VKA (4). Indirect comparisons show how well these new OAC may perform relative to VKA, aspirin-clopidogrel combination therapy, aspirin monotherapy or placebo (5).

Anticoagulant therapy with VKA carries a risk for bleeding, including severe bleeding events, but the clinical benefit of OAC clearly outweighs the risk of OAC therapy, especially in patients at high risk for stroke: indeed, bleeding events are 5–8 times less likely than ischaemic strokes reported among AF patients from trials and registry data (6).

Estimation of the stroke risk in an individual patient with AF can be achieved using easily applicable clinical stroke risk estimators such as the $CHADS_2$ score (7) and an increasingly more refined score that considers additional stroke risk factors, the CHA_2DS_2-VASC score (2, 8, 9).

Despite the clear net clinical benefit of OAC in AF patients at risk for stroke, major bleeding events, especially intracranial bleeds, may be devastating when they do occur (3). The decision for OAC should therefore be based on a careful assessment of both stroke risk and bleeding risk. Clinical scores for bleeding risk estimation are much less well validated than stroke risk scales and the estimation of bleeding risk is rendered difficult as many of the known factors that increase bleeding risk overlap with stroke risk factors, and many factors that increase bleeding risk are transient, such as variable INR values, operations, vascular procedures, and drug-drug or food-drug interactions.

This is an executive summary of a Consensus Document from the European Heart Rhythm Association (EHRA), endorsed by the European Society of Cardiology (ESC) Working Group on Thrombosis, where we comprehensively review the published evidence and propose a consensus on bleeding risk assessments in AF patients. The full document has been published in *Europace* (10) and includes systematic reviews of the evidence/data pertaining to bleeding risk in AF patients.

2. Systematic review of evidence/data

2.1 Epidemiology and size of the problem of bleeding risk in AF

OAC therapy greatly reduces the risk of stroke in AF and the clinical dilemma faced by physicians and patients is anticoagulant-related haemorrhage, which increases with age. The reported rate of intracranial haemorrhage has increased markedly with expanded use of anticoagulants in older adults, often with AF as the primary indication (11). Perceived bleeding risk and older age are potent negative predictors of receiving warfarin and partly explain the reported low rates of warfarin use in clinical practice (12, 13). The risk of both haemorrhage (and stroke) are highest when AF is newly diagnosed and during the initiation of anticoagulant medication (14). One recent randomised trial did not suggest that OAC naïve status conferred a disadvantage in relation to efficacy and bleeding endpoints (15).

Reported rates of major bleeding among individuals with AF taking oral VKA vary widely ranging from 1.3% to 7.2% per year (16–35) (►Table 1). These disparate rates reflect the wide variability in patient characteristics studied and the methodology employed. The early trials in AF that established the efficacy of warfarin excluded almost 90% of individuals screened (16). Trial participants may be selected, based on a lower bleeding risk profile and higher likelihood of adherence. Thus, bleeding rates reported from randomised trials will often be lower than in clinical practice.

More recent randomised controlled trials designed to evaluate the safety and efficacy of new anti-thrombotic agents have tried to include substantial numbers of patients without prior exposure to anticoagulation since these individuals are at high risk for bleeding and thromboembolism (15).

Observational studies are also subject to selection bias and methodological differences. The proportion of patients within the defined AF population taking warfarin should be recorded, which reflects individual physician judgment of VKA candidacy or eligibility which is often subjective. However, prospective registries that require written informed consent for participation are less likely to enrol the more acutely ill, medically complex, or frail individuals, and may underestimate the bleeding that occurs in routine care. Indeed, rates reported from these studies are lower than rates of haemorrhage on warfarin from recent studies (15, 22–24) that have enrolled older individuals and more first-time takers of warfarin (warfarin naïve) (36, 37).

Available data suggest that strokes in AF patients are more severe than other types of stroke, and more often result in permanent disability or death than in non-AF stroke (38). Given the severity of these presumably ischaemic strokes, determination of a bleeding risk threshold that would justify withholding anticoagulant therapy is difficult. One recent real-world analysis using nationwide cohort data reported that there was a *negative* net clinical benefit balancing ischaemic stroke against intracranial haemorrhage (ICH) for warfarin treatment, only in 'truly low risk' patients with AF (39); of note, the net clinical benefit was more positive in patients at high bleeding risk, and the absolute benefit in reducing stroke with warfarin would outweigh the small increase in ICH with warfarin.

2.2 Definitions of bleeding

The incidence of bleeding with OAC varies widely in published studies, reflecting differences in study design, patient populations and quality of monitoring. There are also diverse classifications of bleeding events (major, life-threatening and minor) adopted in each study. For example, many differences are found in the various definitions for the decrease in haemoglobin (Hb) level required for a bleed to be considered as 'major' (40).

Heterogeneous definitions are frequently observed in the trials assessing the benefits of antithrombotic drugs in acute coronary syndromes (ACS), with the TIMI (Thrombolysis in Myocardial Infarction) and GUSTO being the two bleeding definitions most commonly used in trials on ACS (41–51). Different definitions are also used in studies on patients with other clinical conditions (25, 27, 33, 46, 52–58) (see ►Suppl. Table 1 available online at www.thrombosis-online.com). The Academic Research Consortium has

Table 1: Annual rates of major haemorrhage among patients taking warfarin.

Study	Year pub.	Population (n)	Major haemorrhage, %/year	ICH, %/year	New to warfarin, %	Age, mean
Randomised Trials						
AFI [16]	1994	AF (n=3691)	1.3	0.3	100	69
SPAF II[17] (2 age strata)	1994	AF (n=715) AF (n=385)	1.7 4.2	0.5 1.8	100 100	NR 80
AFFIRM[18]	2002	AF (n=4060)	2.0	0.6	NR	70
SPORTIF III [19]	2003	AF (n=3407)	2.2	0.4	27	70
SPORTIF V [20]	2005	AF (n=3422)	3.4	0.1	15	72
ACTIVE W [21]	2006	AF (n=6706)	2.2	NR	23	71
RE-LY [22]	2009	AF (n=18006)	3.4	0.74	51	72
ROCKET-AF [23]	2011	AF (n=14264)	3.5	0.7	37	73
ARISTOTLE [24]	2011	AF (n=18201)	3.1	0.8	43	70
Inception Cohort						
Landefeld [25]	1989	All (n=565)	7.4	1.3	100	61
Steffensen[26]	1997	All (n=682)	6.0	1.3	100	59F/66M
Beyth[27]	1998	All (n=264)	5.0	0.9	100	60
Hylek[28]	2007	AF (n=472)	7.2	2.5	100	77
Pengo[29]	2001	AF (n=433)	Age ≥75: 5.1 Age <75: 1.0	NR	100	68
Non-Inception Cohort (prevalent warfarin use)						
Van der Meer [30]	1993	All (n=6814)	2.7	1.3	NR	66
Fihn[31]	1996	All (n=928)	1.0	1.3	NR	58
ATRIA[32]	2003	AF (n=6320)	1.52	0.46	NR	71
Poli[33]	2009	AF (n=783)	1.4	2.5	NR	75
Rose[34]	2009	AF (n=3396)	1.9	NR	5	74
Poli [35]	2011	AF (n=3015) VTE (n=1078)	1.87	NR	NR	AF 83 (median) VTE 84 (median)

defined bleeding clinical endpoints in coronary stent trials, as shown in ▶Suppl. Table 1c (available online at www.thrombosis-online.com) (43).

Most studies focusing on bleeding events in AF patients have used broadly similar definitions for major bleeding, including the following: fatal, bleeding requiring hospitalisation or transfusion of ≥2 units of packed red blood cells, or bleeding with involvement of a critical site (i.e. intracranial, retroperitoneal, intraspinal, intraocular, pericardial, or atraumatic intra-articular haemorrhage) (44, 45).

The subcommittee on control of anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (ISTH) proposed a definition of bleeding complications in non-surgical patients which was recently revisited (46). Most of the contemporary AF studies have been performed according to this standardised definition. Even the ISTH definition suffers from the inclusion of a wide range of events with variable clinical relevance to the patient, ranging from death or severely life threatening events to 'laboratory indices of bleeding' (2 g/dl Hb drop).

How to interpret major bleeding rates in clinical practice

Clearly, there is a need to record major bleeds in order to assess the safety of a new antithrombotic therapy. However, many of the events that are counted as major bleeds in large trials are clinically less significant: In addition to life-threatening bleeds, events that cause permanent organ damage, and bleeds requiring acute intervention or operation to stabilise the patient, major bleeds also comprise asymptomatic Hb drop of 2 or 3 g/dl combined with a small access site or nasal bleed.

For decision making in clinical practice, it may therefore be helpful to distinguish major bleeding events into clinically relevant major bleeds and clinically less relevant major bleeds. The former would include life-threatening events, symptomatic intracerebral bleeds and other bleeding events resulting in permanent organ damage, and bleeds that require an acute operation to stabilise the patients. Clinically less relevant major bleeds would be less acute events, e.g. an asymptomatic Hb drop associated and bleeding events that result in a temporary cessation of antithrombotic therapy.

Table 2: Factors by which bleeding may negatively impact short- and long-term outcome.

Short, mid and long term prognosis
• Accumulation of risk factors for cardiovascular events in patients with bleeding events
Short and mid term prognosis
• Critical location, e.g. intracranial, pericardial, haemothorax
• Impaired tissue perfusion, e.g. by hypotension, shock, hypoxemia
• Withdrawal of antithrombotic agents, with resultant increased risk of ischaemic complications
• Activation of sympathetic, vasoconstrictive and prothrombotic mechanisms
• Increased cardiac work through increased heart rate and output
• Negative impact of transfusions, especially of older blood
• Prolonged hospitalisation and bed rest, with increased risk of venous thromboembolism

2.3 Prognostic implications of bleeding

Despite the varying clinical impact of different subtypes of "major" bleeds, major bleeding events are associated with a greater risk of death for up to one year compared with non-bleeders, at least in patients with ACS.

The adverse prognosis of patient with bleeding events may stem from the critical location of blood loss (intracranial, pericardial, haemothorax) or to the development of haemorrhagic shock, but also from the negative impact of transfusions and from the frequent discontinuation of antithrombotic therapy, with the ensuing enhanced risk of thromboembolic events. In the short term, reduced tissue oxygenation through declining Hb concentrations, increased cardiac work, haemodynamic compromise, and activation of sympathetic, vasoconstrictive and prothrombotic mechanisms may all contribute to adverse outcomes (►Table 2).

There may also be unfavourable cluster of baseline characteristics, typical of "high risk" patients; indeed, patients with bleeding events are older and with more comorbidities (e.g. renal failure, hypertension, history of prior bleed or stroke) compared to non-bleeders (59). Not surprisingly, the baseline features of patients who bleed largely overlap with those of individuals at high risk of thromboembolic events, thereby denoting a general condition of vascular frailty. Intracranial and spontaneous bleeds carry worse prognosis than procedure-related or extracranial bleeds (59).

2.4 Established bleeding risk factors

Important determinants of bleeding risk include intensity of anticoagulation, management modality and patient characteristics (►Table 3). Drug compliance and maintenance of a therapeutic INR range are other considerations.

Age

Older age, in the majority of studies, has been shown to increase the risk of major haemorrhage. Elderly patients have a two-fold increased risk of bleeding (36), and the relative risk of ICH was 2.5 (95% confidence interval [CI] 2.3–9.4) at age >85 years compared to patients 70–74 years old (37). In the AFFIRM trial (Atrial Fibrillation Follow-up Investigation of Rhythm Management), the risk of major bleeding increased by approximately 5% per year of age (18).

INR range

The most important risk factor for haemorrhage is the intensity of the anticoagulant effect (►Table 3) (37). Studies indicate that with a target INR of >3.0 the incidence of major bleeding is twice as high as in studies with a target INR of 2.0–3.0, at least in some patient groups (52, 60). In patients with prosthetic heart valves, a lower INR target range resulted in a lower frequency of major bleeding and ICH (61). One retrospective analysis of outpatients using warfarin who presented with ICH found that the risk of ICH doubled for each 1 unit increment of the INR (62). Not only the target INR but also the actual individual INR is strongly associated with the risk of bleeding (63).

Anticoagulation control is an important consideration. Among individuals randomised to warfarin in the SPORTIF (Stroke Prevention Using an Oral Direct Thrombin Inhibitor in Atrial Fibrillation) trials, those with Time spent in the therapeutic range (TTR) less than 60% experienced higher rates of major haemorrhage compared to those with TTR greater than 75%, 3.85%/year versus 1.58%/year, $p<0.01$ (64). A similar trend was found in the ACTIVE W (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events) (65).

Structured and well-organised management in specialised anticoagulation clinics, results in higher proportions of patients in the therapeutic target range (66). Point-of-care testing as well as patient self-management did not improve TTR compared with conventional care in one recent large trial (67). Careful INR monitoring by experienced personnel, e.g. in anticoagulation clinics, results in similar rates of bleeding and thrombosis as self-monitoring (66, 68).

Genetic factors affecting VKA metabolism and their antithrombotic effect

Genetic factors have been identified that may affect the risk of bleeding. Common polymorphisms in the cytochrome (CYP) P450 2C9 gene were found to be associated with slow metabolism of VKAs and (possibly) a higher risk of bleeding (69). Other genetic factors that may influence the requirement of VKA are variants in the vitamin K epoxide reductase complex subunit 1 gene (*VKORC1*) (70).

Indeed, the combined analysis of VKORC1, CYP2C9 SNPs, and age may account for more than 50% of the individual variability in the warfarin maintenance dosage, and based on this, prediction

models of warfarin maintenance dosage taking into account these individual parameters have been developed (71). Nonetheless, the clinical relevance of these genetic polymorphisms is still controversial.

Comorbidities including uncontrolled hypertension, hepatic and renal insufficiency

History of bleeding and anaemia are risk factors for subsequent bleeding, being part of various bleeding risk prediction models (see later in the manuscript).

Prior stroke is a potent risk factor for thromboembolic stroke in AF, but it is also a risk factor for ICH. Systolic blood pressure of 140 mmHg or greater has been shown to increase the risk of both haemorrhagic and ischaemic stroke among patients with AF (44, 45, 72). A case-control study in 1,986 patients on VKA showed that renal impairment and hepatic disease each independently more than doubled the risk of bleeding (73). These associations were confirmed in the AFFIRM study, in which hepatic or renal disease conferred a twofold increase in risk (hazard ratio, 1.93; 95% CI, 1.27–2.93); these investigators also found heart failure and diabetes to increase bleeding risk, with hazard ratios of 1.43 and 1.44, respectively (18). However, diabetes has been a less consistent risk factor for bleeding in other overviews (44, 45).

Table 3: Factors affecting bleeding risk when using oral anticoagulant therapy.

Intensity of anticoagulation
Management modality
• usual care versus dedicated anticoagulation clinic or increased monitoring frequency or self management
Patient characteristics
• age
• genetics (may also be assessed by the INR response in the initial period of VKA therapy initiation)
• prior stroke
• history of bleeding
• anaemia
• co-morbidity (hypertension, renal insufficiency, liver disease)
Use of concomitant medication or alcohol
• antiplatelet agents
• NSAIDs
• medication that affects the intensity of anticoagulation
• alcohol abuse

Concomitant medications

The use of concomitant medications, especially antiplatelet drugs, may increase bleeding. Two meta-analyses, comprising 6 trials with a total of 3,874 patients and 10 trials with a total of 5,938 patients, found a relative risk of major bleeding when VKA were combined with aspirin of 2.4 (95% CI 1.2–4.8) and 2.5 (95% CI 1.7–3.7), respectively (74, 75). One nationwide cohort study confirmed the high risk of upper gastro-intestinal bleeding in patients using VKA in combination with aspirin and/or clopidogrel (76, 77). Non-steroidal anti-inflammatory agents (NSAIDs) and alcohol abuse are also associated with an enhanced risk of gastro-intestinal bleeding. The combined use of VKA and NSAID may result in an 11-fold higher risk of hospitalisation for gastro-intestinal bleeding as compared to the general population (77–79). This risk is not significantly lower when using selective inhibitors of cyclo-oxygenase (COX)-2 (78, 79).

The patient's frailty is an important consideration, and biological age rather than calendar age is perhaps a better associate of bleeding risk. Falls may be overstated as a risk factor for bleeding, and based on a Markov decision analysis model, a patient with AF would need to fall 295 times per year for the benefits of stroke prevention with warfarin to be outweighed by the risk of ICH (80).

Implications for clinical practice

Trial data for bleeding may not be representative of the 'real world' situation. In the six pivotal trials that demonstrated the superiority of warfarin over placebo in the prevention of thromboembolic complications in patients with AF, 28,787 patients were screened but only 12.6% of these patients were included in the study (81). As many patients were not included in the clinical trials may have a major impact on the external validity of these trials, in particular regarding safety (81).

Recent trials of stroke prevention in AF have reported rates of major haemorrhage of 3%/year among patients randomised to warfarin (20, 22). Bleeding rates have not differed markedly between open and double-blind trials (81). Rates as high as 7% have been reported in the first year of warfarin therapy among unselected patients with AF in routine practice, especially in the elderly (28). Indeed, warfarin-naïve patients may carry a higher risk for severe bleeding events than other patients.

Systematic reviews (44, 45) have concluded that the following patient characteristics had supporting evidence for being risk factors for anticoagulation-related bleeding complications in AF patients: advanced age, uncontrolled hypertension, history of myocardial infarction or ischaemic heart disease, cerebrovascular disease, anaemia or a history of bleeding, and the concomitant use of other drugs such as antiplatelet agents. The presence of diabetes mellitus, controlled hypertension and gender were not identified as significant risk factors.

Appreciation of bleeding risk factors will help to inform decision making and will also identify higher risk patients for whom management strategies to mitigate bleeding risk should be implemented, for example, by correcting reversible risk factors for bleeding (e.g. uncontrolled blood pressure).

2.6 Bleeding risk stratification and current published bleeding risk schema

Several distinctive clinical prediction rules have been proposed for assessment of the individual risk for bleeding during OAC in patients with AF, based on combination of treatment- and person-associated factors, which may help physicians evaluate the individual risk/benefit ratio of antithrombotic therapy. The characteristics of the available clinical prediction rules specifically addressing AF patients are reported in ▶Table 4 (27, 56, 57, 82, 83).

The modified Outpatient Bleeding Risk Index (mOBRI) (27) has been prospectively derived and validated in patients with different indications for OAC, including AF patients. Another strength of the mOBRI schema was the blinded assessment of bleeding (27). In addition, the settings of anticoagulation control were the primary care physician (27) or a pharmacist-run anticoagulation clinic (55), demonstrating derivation and validation in 'real-life' AF patients.

Whilst all of the clinical prediction rules include age as a risk factor for bleeding, different schemes employ a different cut-off. In the mOBRI (27), age ≥65 years scores one point. Given the advanced age of most AF patients, the majority of the evaluated patients would be attributed at least to the intermediate-risk classification (1–2 points) using the mOBRI, that in the validation cohort (27) was associated with an incidence of major bleeding of 5%, 8% and 12% after three, 12 and 48 months of treatment, respectively. In the independent validation of the mOBRI among elderly AF patients by Aspinall et al. (55), the mOBRI discriminated significantly ($p<0.001$) between those in the intermediate- and high-risk categories for major bleeding.

The remaining prediction schemas have a retrospective design, based on the review of data from the National Registry of Atrial Fibrillation (56), the same Registry plus Medicare data (57), the Euro Heart Survey cohort (82) and the AnTicoagulation and Risk factors in Atrial fibrillation (ATRIA) study (83). The retrospective design of these schemes would be a limitation of their validity since a potential loss of patients with complications in early phase of treatment cannot be excluded.

The $HEMORR_2HAGES$ score (56) considers age >75 years as a condition at risk, also includes factors, such as CYP2C9 single nucleotide polymorphism, that is rarely investigated, while important factors, such as antiplatelet treatment or other co-medication are not included. The rate of patients at high risk of bleeding was 12.0%. The cumulative incidence of major bleeding by risk category in the validation cohort was 2.1%, 5.0% and 8.8% patient-years in the low, intermediate and high risk categories, respectively.

The schema by Shireman et al. (57) incorporates eight risk factors for bleeding, including female gender and an antiplatelet treatment, as well as age. There was a relatively short (90 days) follow-up period and the rate of patients at a high risk was very low (3.4%). This schema requires a complex mathematical calculation to derive the individual patient bleeding risk score, thereby limiting its applicability. In general, some important factors related to bleeding risk, such as poor quality anticoagulation control and the presence of NSAID as concomitant medication (44, 45), have not been included in some of the aforementioned schemas. Reliable ascertainment of aspirin therapy given its non-prescription status is problematic. Moreover, no blinded outcome assessment was conducted and no indication of the setting of anticoagulation control was provided in either the $HEMORR_2HAGES$ (56) or Shireman (57) studies.

More recently a new clinical prediction rule for bleeding risk evaluation in AF patients, HAS-BLED, has been proposed by Pisters et al. (82). The HAS-BLED score demonstrated a good predictive accuracy in the overall cohort (c-statistic 0.72), but performed particularly well in predicting bleeding risk when only antiplatelet therapy (c-statistic 0.91), or no antithrombotic therapy at all (c-statistic 0.85) were used. In the SPORTIF III and V cohorts, the HAS-BLED score was a modest predictor of bleeding events among warfarin-naïve patients at baseline (c-statistic 0.66) and in patients receiving warfarin plus aspirin (c-statistic 0.60) [84]. The HAS-BLED score has also been validated in a large 'real world' nationwide cohort study, with c-statistics nearing 0.8 indicating good predictive value for the HAS-BLED score (85), and has been incorporated into the 2010 ESC guidelines for the management of AF (2) and the Canadian guidelines (86).

The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) score (83) was derived from a cohort of prevalent warfarin users with AF who were randomly divided into a split-sample derivation and validation cohort, and led to a weighted score (which contains elements of the HAS-BLED score) that gives 3 points for anaemia (Hb <13 g/dl in men and <12 g/dl in women), 3 points for severe renal disease (defined as glomerular filtration rate <30 ml/min or dialysis dependent), 2 points for age ≥75 and 1 point each for prior bleeding and hypertension. Thus, this score essentially includes similar components as other scores discussed above, but assigns a weight to the various risk factors (thus, making it more complicated). The c-statistic for the continuous risk score was 0.74, but on collapsing points into a three-category risk index, the annual major haemorrhage rate was 0.8% in the low risk group (0–3 points), 2.6% in medium risk (4 points), and 5.8% in high risk (5–10 points). Limitations are the non-inclusion within the score of uncontrolled blood pressure or concomitant medications (e.g. antiplatelet drugs and NSAID) known to increase bleeding risk with warfarin and its derivation from a selected cohort of prevalent warfarin users.

In summary, the available published bleeding risk prediction rules demonstrate wide differences in the risk factors comprising each schema. Despite the limitations of the available bleeding risk schema, they do offer a starting point for physicians to consider bleeding when initiating and/or continuing long-term oral anticoagulation in AF patients, and this Task Force recommends use of the HAS-BLED score, in keeping with international guideline recommendations (2, 86).

Table 4: Published bleeding risk prediction schemas for patients with atrial fibrillation.

Schema, acronym, author	Ref.	Population [a] Design, [b] n, mean (SD) age, % male; [c] indication for anticoagulation; [d] length of follow-up	Definition of major bleeding Event adjudication	Calculation of risk score	Bleeding risk classification n (%) patients in each risk category	Major bleeding events by risk category in validation cohort, n (%)	Validated in other cohorts
mOBRI Beyth 1998	27	[a] Prospective inception cohort [b] Derivation- n=556, 61 (14); 46.6% Validation- n=264, 60 (16); 47.3% [c] Derivation- Post-op cardiac surgery, mitral valve disease, AF, stroke, TIA, PE, DVT, or other thromboembolism Validation- VTE & cardiac surgery [d] 4 years	Overt bleeding that resulted in the loss of ≥2.0 units in ≤7 days, or was otherwise life-threatening Blinded event adjudication, unaware of bleeding risk factors	Age ≥65 years, previous stroke, GI bleed in last two weeks, ≥1 of the following comorbidities [recent MI, haematocrit <30%, creatinine >1.5 mg/dl, or diabetes mellitus] with 1 point for presence of each risk factor and 0 if absent	Low: 0 Intermediate: 1–2 High: ≥3 Derivation Low: 186 (33.5%) Intermediate: 336 (60.4%) High: 34 (6.1) Validation Low: 80 (30.3) Intermediate: 166 (62.9) High: 18 (6.8)	Cumulative incidence of major bleeding (95% CI) at 3/12/48 months Low: 1 (0–4)/3 (0–8)/ 3 (0–8) Intermediate: 5 (1–8)/8 (3–12)/ 12 (5–19) High: 6 (0–17)/ 30 (0–62)/53 (11–97)	Aspinall 2005 [55]
HEMORR$_2$HAGES Gage 2006	56	[a] Retrospective analysis of NRAF cohort [b] Validation- n=3971, 80.2 (†); 43% [c] AF [d] 3,138 pt-years Bleeding risk factors for schema identified by adaptation of 3 existing bleeding risk schema [mOBRI, SBRPS, plus bleeding risk factors identified in literature [Beyth et al, 2002 [27]	ICD-9-CM codes for major bleeds except those unrelated to antithrombotic therapy †	Hepatic or renal disease, Ethanol abuse, Malignancy, Older (aged >75), Reduced platelet count, Re-bleeding risk, , uncontrolled Hypertension, Anaemia, Genetic factors (CYP 2C9 single nucleotide polymorphisms), Excessive fall risk, previous Stroke/TIA, 1 point for each risk factor present, & 2 points for previous bleed	Low: 0–1 Intermediate: 2–3 High: ≥4 Among those on warfarin (n=1604) Low: 717 (44.7%) Intermediate: 694 (43.3%) High: 193 (12.0%)	Low: 15 (2.1%) Intermediate: 35 (5.0%) High: 17 (8.8%)	
Shireman 2006	57	[a] Retrospective chart review of NRAF cohort and Medicare data [b] Derivation- n=19 875, ≥65 years; 47.5% Validation- n=6511, ≥65 years; 46.9% [c] AF [d] 3 months	Hospitalisation within 90 days of hospital discharge following index AF for GI haemorrhage (diagnosis-related group code 174 or 175) or intracranial haemorrhage (ICD-9 430–432) †	[0.49 x age ≥70] + [0.32 x female gender] + [0.58 x remote bleed] + [0.62 x recent bleed] + [0.71 x alcohol/drug abuse] + [0.27 x diabetes] + [0.86 x anaemia] + [0.32 x antiplatelet] with 1 point for the presence of each condition and 0 if absent	Low: ≤1.07 Intermediate: >1.07 to <2.19 High: ≥2.19 Low: 3889 (59.7%) Intermediate: 2400 (36.9%) High: 222 (3.4%)	Low: 35 (0.9%) Intermediate: 48 (2.0%) High: 12 (5.4%)	
HAS-BLED Pisters 2010	82	[a] Retrospective analysis of Euro Heart Survey cohort [b] Derivation- n=3978 Validation- n=3071, 66.8 (12.8); 59% male [c] AF patients [d] 12 months Bleeding risk factors drawn from Euro Heart Survey cohort and 'historic' bleeding risk factors (OAC, alcohol use & hypertension)	Requiring hospitalisation &/or causing drop of Hb ≥2g/l, need for blood transfusion that was not a haemorrhagic stroke †	Hypertension (uncontrolled SBP>160 mm Hg), Abnormal renal &/or liver function, Stroke, Bleeding history, Labile INR, Elderly (age >65 years), Drugs (antiplatelets/NSAIDS)/concomitant alcohol (≥8units/week), with 1 point for the presence of each risk factor (maximum of 9 points)	Low: 0–1 Intermediate: 2 High: ≥3 Low: 2084 (67.9%) Intermediate: 744 (24.2%) High: 243 (7.9%)	Low: 22 (1.1%) Intermediate: 14 (1.9%) High: 12 (4.9%)	

Table 4: Continued

Schema, acronym, author	Ref.	Population [a] Design, [b] n, mean (SD) age, % male; [c] indication for anticoagulation; [d] length of follow-up	Definition of major bleeding Event adjudication	Calculation of risk score	Bleeding risk classification n (%) patients in each risk category	Major bleeding events by risk category in validation cohort, n (%)	Validated in other cohorts
Fang 2011	83	[a] Retrospective analysis of the ATRIA cohort [b] 9186, † [c] AF patients [d] †	fatal, requiring transfusion of 2 U packed blood cells, or haemorrhage into a critical anatomical site (e.g. intracranial, retroperitoneal) †	Anaemia, severe renal disease (GFR <30 ml/min or dialysis-dependent), age ≥75 years, previous bleed, hypertension, with 1 point each for presence of previous bleed & hypertension, 2 points for age ≥75, and 3 points each for presence of anaemia and renal disease	Low: 0 to 3 Moderate: 4 High: 5 to 10	Low: 0.8% Moderate: 2.6% High: 5.8%	

AF atrial fibrillation; ATRIA AnTicoagulation and Risk factors in Atrial fibrillation; DVT deep vein thrombosis; GFR glomerular filtration rate; GI gastrointestinal; HAS-BLED Hypertension, Abnormal renal &/or liver function, Stroke, Bleeding history, Labile INR, Elderly (age >65 years), Drugs (antiplatelets/NSAIDS)/concomitant alcohol (≥8units/week); Hb haemoglobin; HEMORR;HAGES Hepatic or renal disease, Ethanol abuse, Malignancy, Older (aged >75), Reduced platelet count, Re-bleeding risk, uncontrolled Hypertension, Anaemia, Genetic factors (CYP 2C9 single nucleotide polymorphisms), Excessive fall risk, previous Stroke/TIA; ICD-9-CM International classification of disease- 9th version, clinical modification; ICU intensive/critical care stay; INR international normalised ratio; MI myocardial infarction; mOBRI modified Outpatient Bleeding Risk Index; NRAF National Registry of Atrial Fibrillation; NSAIDs non-steroidal anti-inflammatory drugs; OAC oral anticoagulation; OBRI Outpatient Bleeding Risk Index; PE pulmonary embolism; RCT randomised controlled trial; SBP systolic blood pressure; TIA transient ischaemic attack; VTE venous thromboembolism. † not reported.

2.7 Patient values and preferences

Patients' beliefs about their health, the medications and health-care they receive are important determinants of whether or not they accept recommended treatments and adhere to therapy. Patients often have perceptions about VKA, including the inconvenience of dosing adjustments, the need for daily medication and regular blood tests to monitor INR levels, reduction/abstinence from alcohol, dietary restrictions, the risk of minor and major bleeding, and under-appreciation or lack of knowledge regarding the risk of stroke which may influence their acceptance of warfarin and their ability to maintain good INR control (87–89). On the other hand, patients may feel protected by taking VKA. Thus, patients' preferences and their beliefs about their health are fundamental in determining whether anticoagulant treatment, particularly with warfarin, is adopted in the first place and maintained long-term. Changes in health-care policy emphasise the need to achieve, and benefits of, patient involvement in the management of their own health (90) and incorporation of patients' preferences for anti-thrombotic therapy should be considered in the decision-making process.

To date, various studies have examined patient preferences for antithrombotic therapy in AF patients (91–101) and in patients at high risk of developing AF (102–106), although one study has yet to report its results (106)] (►Suppl. Table 2 available online at www.thrombosis-online.com). A variety of decision aids, such as audio-booklets, decision boards and interactive videos/computer programs have been designed to enable patients to participate in the decision-making process with regard to their antithrombotic therapy, to ensure that treatment choices are consistent with their personal preferences, values, and beliefs. These decision aids provide written, visual and verbal information on the likelihood of clinically important outcomes, such as stroke and major haemorrhage associated with antithrombotic therapy, present the treatment options (currently warfarin, aspirin, or no antithrombotic therapy), and ask patients to indicate their treatment choice (for full details, see full version of this document [10]).

Patients appear to trade off the risks associated with antithrombotic treatment in order to avoid death (105, 107). Overall, these studies appear to suggest that patients place greater emphasis on avoidance of stroke and are willing to accept a higher risk of bleeding to achieve this, although this may represent a lack of patient understanding of the disability associated with major bleeding, particularly ICH. However, it is hard to draw firm conclusions from the available studies as the sample sizes are often small, typically ≤100 patients, and there is significant heterogeneity between the studies (methods employed to elicit preferences, patients' education, risks employed; inclusion of AF patients and those without AF etc).

Further studies need to elicit patient preferences for antithrombotic treatment in warfarin-naïve AF patients, with and without previous stroke, to remove these potential biases. In addition, perceptions of risk can be altered by the way in which information is presented. There is also tremendous disparity in perceptions of the impact of warfarin therapy on the lives of AF patients which may influence the acceptance of such therapy, with many physicians

tending to underestimate the level of patient's satisfaction (108), whereas most patients report that warfarin did not precipitate any significant changes in their day-to-day lives other than minor inconveniences (such as regular blood tests, adjusting warfarin dose, and dietary restrictions) which they are willing to accept.

In summary, patients' preferences for antithrombotic treatment are largely influenced by the type and format of information provided to the patient by the care provider, their level of education and understanding of the consequences of such treatment, and their previous experiences of antithrombotic therapy. Stroke is the most feared complication which patients wish to avoid (described as a 'fate worse than death') but bleeding risk with treatment attenuates the proportion of patients willing to take antithrombotic therapy. Patients need clear, simple, and individualised information on their need for antithrombotic therapy and the potential complications.

2.8 Special situations with additional bleeding risk considerations

Various situations can have important bleeding risk considerations in patients with AF, for example, ablation, devices (implantable cardioverter defibrillator [ICDs], pacemakers), percutaneous coronary interventions (PCI)/stenting, surgical procedures/bridging, etc – for full details, please see full version of this document (10).

Ablation

Catheter ablation carries a small but relevant risk of severe bleeding, associated with vascular access – often with relatively large diameter sheaths -and peri-interventional anticoagulation, increasing when ablation is performed in the left atrium or left ventricle. Interestingly, bleeding events do not appear to be related to pre- and periprocedural antithrombotic therapy (aspirin, VKA, or other). Indeed, bleeding events during or shortly after catheter ablation procedures are largely due to mechanical factors such as vascular access, transseptal puncture, and the ablation lesions themselves. Catheter ablation for AF combines the difficulties related to bleeding (from transseptal puncture, requirement for anticoagulation in many patients) and stroke risk (left atrial lesions, long periods with foreign material in the left atrium, often long endocardial lesions in already diseased atria). The stroke and transient ischaemic attack (TIA) rate is approximately 1% in recent surveys, while bleeding events occur at around 1% for cardiac tamponade and 1–2% for access site bleeds (109, 110). To avoid bleeding complications and to allow rapid adaptation of antithrombotic regimens, a consensus document from EHRA in 2008 recommended stopping warfarin 4–5 days before the ablation procedure and bridging with heparin (110). More recently, uninterrupted OAC is a potential alternative to strategies that use bridging with heparin or low-molecular-weight heparin (LMWH) (111, 112). In summary, recent data suggest that continuation of OAC during catheter ablation procedures for AF may be safe with respect to bleeding events, and help to prevent peri-procedural strokes.

Most guidelines recommend continued anticoagulant therapy for 2–3 months following an AF ablation in all patients regardless of stroke risk factors (2). The optimal duration of this therapy has not been clearly established. Owing to the risk of relapse, the EHRA and ESC guidelines recommend that anticoagulation should be continued long-term as per original indication in subjects with stroke risk factors (2, 113). This is in line with current recommendations for AF and with the observation that AF tends to recur in many patients, including late recurrences in patients after AF ablation.

Peri-devices (ICDs, pacemakers)

It may be necessary to interrupt oral anticoagulant therapy for elective implantation or replacement of a pacemaker or an ICD, although smaller procedures can often be performed without interrupting anticoagulation. In patients with mechanical prosthetic heart valves, it may be appropriate to substitute unfractionated heparin (UFH) or LMWH to prevent thrombosis (114). In patients with AF who do not have mechanical valves, however, based on extrapolation from the annual rate of thromboembolism in patients with non-valvular AF, it was the consensus of the Task Force for the 2010 ESC guidelines that anticoagulation may be interrupted temporarily for procedures that carry a risk of bleeding, such as ICD or pacemaker implantation, without substituting heparin (2). In high-risk patients (particularly those with prior stroke, TIA, or systemic embolism), UFH or LMWH may be administered . In the 2008 ACCP guidelines (114), bridging is "suggested" for patients with $CHADS_2$ score of 3 or 4 (considered at moderate risk of thromboembolism after interruption of antithrombotic therapy) and "recommended" for those with $CHADS_2$ score of 5 or 6 (considered at high risk, i.e.>10% risk per year). It is possible that such operations can in part be performed without interruption of anticoagulation, as for vascular procedures.

In a systematic review of the literature including eight studies on the perioperative management of anticoagulation in patients having implantation of a pacemaker or ICD, a strategy involving bridging anticoagulation with therapeutic-dose heparin was associated with an incidence of pocket haematoma of 12–20%, while a strategy involving perioperative continuation of a coumarin was associated with an incidence of pocket bleeding of 2–7% (115). The incidence of thromboembolic events was 0–1%, irrespective of the perioperative anticoagulation strategy used. In a prospective randomised study including patients with high risk of thromboembolic events in whom 80% had AF, implant of devices while maintaining OAC was as safe as bridging with heparin infusion and allowed a significant reduction of in-hospital stay (116). When drainage systems are used, device implantation appears to be safe and performed without significantly increased risk of clinically relevant haematoma.

Thus, it has been recommended that for such implantations treatment be interrupted pre-operatively and replaced by heparin only if needed (2). If that is not feasible and implantation must be

performed under anticoagulant (whether maintaining OAC or bridging with heparin) and/or antiplatelet therapy (see section *Patients with ACS and/or requiring PCI/stents*), the procedure should be carried out by an experienced operator who will pay close attention to haemostasis.

ACS and coronary angiography/intervention

Several factors associated with coronary angiography or PCI bear an increased bleeding risk in AF patients with a need for oral anticoagulation (for a detailed review see [117]). These include: "triple therapy" using an oral anticoagulant and dual platelet inhibition, most often aspirin and clopidogrel; factors prolonging the duration of combined antithrombotic therapy [e.g. use of drug-eluting stents (DES)]; oral anticoagulation, when compared to non-anticoagulated patients; additional use of a GPIIb/IIIa inhibitor (GPI, e.g. in bailout situations in elective patients or in very high-risk ACS patients); left main or three-vessel disease; older age (e.g. >75 years); female gender; smoking; chronic kidney disease; and high INR value (> 2.6).

Some measures have been undertaken to reduce this increased bleeding risk: radial instead of femoral access was associated with less access site bleeding events in "all-comers" (118, 119). The use of femoral closure devices, although believed to reduce bleeding risk compared to manual compression, was not associated with reduced bleeding events (120).

Due to lack of prospective randomised investigations in this field, a group of European and North American experts recently published recommendations (117, 121), which in the majority are level C, i.e. largely based on expert opinion. The recommendations can be summarised as follows: (i) avoid the use of DES for patients who require triple antithrombotic therapy; (ii) when OAC is given in combination with clopidogrel and/or low-dose aspirin, the intensity must be carefully regulated, with a target INR of 2.0–2.5; and (iii) in case of combined antithrombotic strategies, gastric protection is recommended at least for the duration of combination therapy (122).

2.9 Managing bleeding complications

Management of bleeding consists of measures to preserve adequate circulation, local control (e.g. endoscopic treatment or surgical haemostasis), and proper transfusion procedures. If serious bleeding occurs in a VKA user it may be necessary to reverse the anticoagulant effect of the agent. When interrupting the administration of VKA important differences in the half-lives of the various agents (9 hours for acenocoumarol, 36–42 hours for warfarin, and 90 hours for phenprocoumon, respectively) need to be taken into account (123). There is debate over the best management strategy when a patient on VKA bleeds, given the competing concern for thromboembolic risk. Adequacy of haemostasis and duration of VKA interruption would vary with different patient scenarios (123).

The most straightforward intervention to counteract the effect of VKA is the administration of vitamin K (124–126). There is some debate on the need for vitamin K in the management of a patient with a very high INR but no signs of bleeding. A recent randomised controlled trial did not find any difference in bleeding or other complications in non-bleeding patients with INR values of 4.5 to 10 that were treated with vitamin K or placebo (127, 128). In patients with clinically significant bleeding, administration of vitamin K is crucial to reverse the anticoagulant effect of VKA. Vitamin K can be given orally and intravenously, but the parenteral route has the advantage of a more rapid onset of the treatment (128). After the administration of intravenous vitamin K, the INR will start to drop within 2 hours and will be completely normalised within 12–16 hours (127–129). After oral administration it will take up to 24 hours to normalise the INR. Intramuscular injections of vitamin K should be avoided in patients who are anticoagulated and subcutaneous administration of vitamin K results in a less predictable bioavailability.

When the INR is below 7, a dose range of 2.5–5 mg vitamin K has been advocated, whereas a dose of 5 to 10 mg may be required to correct higher INR. Higher doses of vitamin K are equally effective but may lead to VKA resistance for more than a week, which may hamper long-term management (129).

In case of very serious or even life-threatening bleeding, immediate correction of the INR is essential and can be achieved by the administration of vitamin K-dependent coagulation factors. Theoretically, these factors are present in fresh frozen plasma; however, the amount of plasma that is required to correct the INR is very large, carries the risk of fluid overload, and will probably take hours to administer (130). Therefore, prothrombin complex concentrates (PCCs), most of which containing all vitamin K-dependent coagulation factors, are more useful, and individualised dosing regimens based on INR at presentation and body weight are more effective (131–133). The risk of disseminated intravascular coagulation (DIC) due to traces of activated coagulation factors in PCCs comes from older literature and modern PCCs are not associated with precipitating DIC (134).

3. Left atrial appendage closure

A substantial number of patients eligible for OAC will suffer bleeding complications that may be potentially life-threatening. Patients at high risk of embolic stroke, but with contraindications for OAC are in a need of an alternative strategy that is not associated with long-term bleeding risk. This is particularly true for those after an ICH.

Surgical closure of the left atrial appendage (LAA) has been practiced, and indeed, current guidelines suggest obliteration of the LAA during mitral valve surgery (135). Currently, excision of the LAA at the time of mitral valve surgery is recommended for reduction of future stroke risk. Exclusion of the LAA during coronary artery bypass graft surgery has also been proposed, but with suboptimal results (136).

Consensus statements

General AF populations

- In most patients, thromboembolic rates without anticoagulation are markedly (5- to 8-fold) higher than bleeding rates. Therefore, most patients with AF – including the majority of patients at high bleeding risk – are in need of anticoagulant therapy.
- For AF patients requiring permanent effective anticoagulation, it is recommended that the 2010 ESC Guidelines for the management of patients with AF be applied.
- The bleeding risk with aspirin should be considered as being similar to that with VKA, especially in the elderly.
- Most patients with a high CHA_2DS_2-VASc score benefit from OAC even if their bleeding risk is high. Only in rare patients with a relatively low stroke risk and an extremely increased risk of bleeding may withholding of OAC be considered.
- The assessment of the (long-term) risk of bleeding in the general AF population is recommended.
- In specific AF patients subsets (i.e. post-ablation, post-LAA closure, post-percutaneous coronary intervention/acute coronary syndrome, etc), the assessment of bleeding risk is part of overall management, balancing this risk against the risk of thromboembolic complications
- The HAS-BLED score [Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (> 65), Drugs/alcohol concomitantly] should be considered as a calculation to assess bleeding risk, whereby a score of ≥3 indicates 'high risk' and some caution and regular review is needed, following the initiation of antithrombotic therapy, whether with OAC or antiplatelet drugs.

Periablation

- In many cases, OAC can be continued throughout the ablation procedure.
- Where a bridging strategy is planned, stop VKA 2–5 days before the ablation procedure and bridging therapy with heparin (either LMWH or UFH) until the day before the ablation procedure.
- Peri-procedure anticoagulation: After sheath insertion and transseptal puncture, administration of a bolus of IV heparin (bolus dose empirically 5,000–10,000 U or 50–100 U/kg) followed by continuous infusion of 1,000–1,500 U/h in order to achieve an ACT at least in excess of 300 s that is checked every 30–45 min. At the completion of the procedure, IV heparin is discontinued and sheaths removed when the ACT is sub-therapeutic (<160 s) or if high, reversed by protamine. IV heparin to be resumed for 12–24 h at a maintenance dose of 1000 U/h without a bolus that will maintain aPTT at 60–80 s or at least twice the baseline level. Oral anticoagulation to be resumed the day of the procedure.
- Replace IV heparin with SC LMWH after 12–24 h and reinitiate OAC. Stop LMWH when the target INR 2 is reached.
- Continue therapeutic warfarin for a minimum of 12 weeks after the ablation procedure. Patients have a CHA_2DS_2-VASc score of ≥2 should continue OAC long-term.

Peri-devices (ICD, pacemakers)

- Implant of devices maintaining OAC may be as safe as bridging with heparin infusion and should allow a significant reduction of in-hospital stay.
- In some circumstances, anticoagulant treatment should be interrupted pre-operatively and replaced by heparin.
- If implantation must be performed whilst on anticoagulant (whether maintaining OAC or bridging with heparin infusion) and/or antiplatelet therapy, the procedure should be carried out by an experienced operator who will pay close attention to haemostasis in the area of the generator pocket.

Presentation with ACS and/or requiring PCI/stents

- For antithrombotic therapy management in anticoagulated AF patients presenting with an ACS and/or undergoing PCI/stenting, the recommendations in the 2010 ESC Guidelines for the management of patients with AF or the ESC Thrombosis Working Group Consensus Document should be applied.

The management of bleeding complications

- Appropriate strategies to implement both in the long-term and peri-intervention to prevent bleeding are recommended
- Bleeding risk assessment should be regularly performed, during regular review of the patient. Correctable bleeding risk factors should be managed.

A reasonable alternative may be exclusion of the LAA cavity from the circulation, using either surgical or percutaneous catheter-based procedures (137). The WATCHMAN Left Atrial Appendage System for Embolic PROTECTion in Patients With Atrial Fibrillation (PROTECT AF) study was designed to demonstrate safety, efficacy, and non-inferiority of the WATCHMAN device against chronic warfarin therapy in patients with non-valvular AF who are eligible for long-term OAC (138). An important risk of serious procedural complications was observed (e.g. pericardial tamponade) perhaps related to a learning curve of device implantation. This risk appears to taper a bit with increased operator experience (139). Other devices, such as the AMPLATZER double-disk transseptal occluder, are in development. The available data base is not yet sufficient to define the degree of long-term stroke prevention conferred by this technique.

4. A brief perspective on newer anticoagulants

At the time of writing of this summary, the direct thrombin inhibitor dabigatran is approved for clinical use in the US and in Canada, as well as in Europe. The pharmacokinetics of the drug and its apparent safety compared to warfarin render dabigatran a potentially attractive therapeutic option in patients in need for anticoagulation and at risk for bleeding.

At the lower dose tested (110 mg bid) the rate of intracerebral bleeding events was higher in the VKA group in the RELY trial than in the dabigatran group (22). At the higher tested dose (150 mg bid), dabigatran prevented ischaemic strokes more effectively than VKA. Practical approaches to the management of patients on dabigatran have recently been published, as a consensus document of the Italian Federation of Thrombosis Centers (FCSA) (140).

New data on the efficacy and safety of the oral factor Xa inhibitors, rivaroxaban and apixaban, in comparison to warfarin for stroke prevention in AF, as well as information on their clinical pharmacology, are also available (23, 24, 141–143).

In addition to these long-term benefits, the shorter half-life of direct thrombin or factor Xa antagonists compared to VKA suggests that the management of bleeding complications and the antithrombotic regimen during operations and invasive procedures could become simpler with those substances than with VKA (144). A remaining concern would still be the lack of a specific antidote for these new drugs. One recent small trial in 12 healthy subjects found that the use of PCC 50 IU/kg (Cofact) immediately and completely reverses the anticoagulant effect seen with rivaroxaban (as measured by prothrombin time, endogenous thrombin potential) but had no influence on the anticoagulant effect of dabigatran (increased the activated partial thromboplastin time, ecarin clotting time (ECT), and thrombin time) at the PCC dose used in this study (145). Finally, the use of dabigatran peri-ablation appears safe, with no evidence of thromboembolism and bleeding, in one small reported series (146).

Conflict of interest

G. Y. H. Lip has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer, Biotronik, Portola and Boehringer Ingelheim, and has been on the speakers' bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim and Sanofi-Aventis. F. Andreotti has received consultant or speaker fees from AstraZeneca, Bayer, Bristol-Myers Squibb, Daiichi-Sankyo, Lilly, Pfizer and Servier. L. Fauchier has served as a consultant for Bayer, Medtronic and Sanofi and has received funding for conference travel and educational symposia from Boehringer Ingelheim, Bayer, Boston Scientific, Medtronic and Sanofi-Aventis. K. Huber has received lecture fees for AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Sanofi Aventis, and The Medicines Company. E. Hylek has served on scientific advisory boards for Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Johnson & Johnson, Merck, Pfizer and Ortho-Mc Neil. E. Knight declares no conflict of interest. D. Lane has received research funding and honoraria from various pharmaceutical companies (Boehringer Ingelheim, Bayer Healthcare, Bristol-Myers Squibb and Pfizer) in relation to atrial fibrillation for meetings and educational symposia; she is also a panellist on the revised ACCP Guidelines on Antithrombotic Therapy. M. Levi declares no conflict of interest. F. Marin has received advisory fees from Bayer and Boehringer Ingelheim and research grants from Abbott and Boston Scientific. G. Palareti declares no conflict of interest. P. Kirchhof has received consulting fees and honoraria from 3M Medica, MEDA Pharma, AstraZeneca, Bayer Healthcare, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic, Merck, MSD, Otsuka Pharma, Pfizer/BMS, sanofi-aventis, Servier, Siemens and Takeda; research grants from 3M Medica, MEDA Pharma, Cardiovascular Therapeutics, Medtronic, Omron, Sanofi-Aventis, St. Jude Medical, BMBF, DFG and the EU; and he has received travel support from ESC, EHRA and AFNET.

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Journal of the American College of Cardiology
© 2011 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 58, No. 4, 2011
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.03.031

A New Risk Scheme to Predict Warfarin-Associated Hemorrhage

The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study

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Objectives The purpose of this study was to develop a risk stratification score to predict warfarin-associated hemorrhage.

Background Optimal decision making regarding warfarin use for atrial fibrillation requires estimation of hemorrhage risk.

Methods We followed up 9,186 patients with atrial fibrillation contributing 32,888 person-years of follow-up on warfarin, obtaining data from clinical databases and validating hemorrhage events using medical record review. We used Cox regression models to develop a hemorrhage risk stratification score, selecting candidate variables using bootstrapping approaches. The final model was internally validated by split-sample testing and compared with 6 published hemorrhage risk schemes.

Results We observed 461 first major hemorrhages during follow-up (1.4% annually). Five independent variables were included in the final model and weighted by regression coefficients: anemia (3 points), severe renal disease (e.g., glomerular filtration rate <30 ml/min or dialysis-dependent, 3 points), age ≥75 years (2 points), prior bleeding (1 point), and hypertension (1 point). Major hemorrhage rates ranged from 0.4% (0 points) to 17.3% per year (10 points). Collapsed into a 3-category risk score, major hemorrhage rates were 0.8% for low risk (0 to 3 points), 2.6% for intermediate risk (4 points), and 5.8% for high risk (5 to 10 points). The c-index for the continuous risk score was 0.74 and 0.69 for the 3-category score, higher than in the other risk schemes. There was net reclassification improvement versus all 6 comparators (from 27% to 56%).

Conclusions A simple 5-variable risk score was effective in quantifying the risk of warfarin-associated hemorrhage in a large community-based cohort of patients with atrial fibrillation. (J Am Coll Cardiol 2011;58:395–401) © 2011 by the American College of Cardiology Foundation

Oral anticoagulants such as warfarin can substantially reduce the thromboembolic consequences of atrial fibrillation (1). However, anticoagulant-associated hemorrhage deters many clinicians from prescribing warfarin (2). Accurate risk stratification according to hemorrhage risk would facilitate the anticoagulation decision for individual patients, and could help control for varying hemorrhage risk across different studies or when comparing the safety of various antithrombotic agents. We describe the development and internal validation of a new hemorrhage risk stratification tool and compare its performance to other published hemorrhage risk schemes.

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Manuscript received September 29, 2010; revised manuscript received March 24, 2011, accepted March 29, 2011.

Methods

The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) study followed up 13,559 adults with nonvalvular, nontransient atrial fibrillation enrolled in Kaiser Permanente of Northern California, a large integrated healthcare system. Details of the cohort assembly have been described previously; briefly, subjects were identified by

JACC Vol. 58, No. 4, 2011
July 19, 2011:395–401

Abbreviations and Acronyms

HEMORR$_2$HAGES = hepatic/renal disease, ethanol abuse, malignancy, older age, reduced platelet count, rebleeding risk, hypertension, anemia, genetic factors, excessive fall risk, and stroke

ICD-9 = International Classification of Diseases-Ninth Revision, Clinical Modification

searching clinical databases for International Classification of Diseases-Ninth Revision, Clinical Modification (ICD-9) codes for atrial fibrillation between July 1, 1996, and December 31, 1997, and followed up through September 30, 2003 (3,4). Warfarin exposure was determined using a previously described and validated algorithm based on the number of days supplied per prescription, refill patterns, and intervening international normalized ratio measurements (3). Clinical variables were identified using ICD-9 codes, pharmacy prescriptions, and laboratory databases (3).

We identified 6 published, validated risk stratification schemes developed to predict warfarin-associated hemorrhage (Table 1) and searched for those specific risk factors in the ATRIA study cohort (5-10). Variables unavailable in the ATRIA cohort (e.g., patient genotype) or not directly applicable to atrial fibrillation (e.g., acute pulmonary embolism) were not included as potential variables. Prior bleeding history was defined as any prior outpatient or inpatient ICD-9 diagnosis code of hemorrhage, including by specific organ system (e.g., prior intracranial or gastrointestinal bleeding), in the aggregate (e.g., all-cause prior bleeding), and by timing (within 90 days or >90 days). High fall risk was defined as any prior hospitalization with a discharge diagnosis code indicating mechanical fall that occurred in either the inpatient or outpatient setting.

Clinical laboratory databases were used to identify anemia (hemoglobin <13 g/dl in men and <12 g/dl in women), thrombocytopenia (platelet count <90,000), and renal insufficiency (measured by serum creatinine and estimated glomerular filtration rate) (11). Abnormal laboratory values were considered abnormal from 3 months before to 1 year after the date of the measurement, censored by a preceding or subsequent normal test value. If results were unavailable within the time window, the test was assumed normal based on the assumption that tests would be ordered if there were clinical suspicions.

Clopidogrel and ticlopidine exposure was determined from pharmacy databases, and duration was defined from prescription start date to 2 months after the end of the medication supply. Accurate assessment of aspirin and nonsteroidal anti-inflammatory drugs exposure was not possible since these medications were predominantly obtained without prescription.

Major hemorrhage outcomes. We searched computerized databases for primary discharge ICD-9 codes for extracranial hemorrhages (i.e., gastrointestinal, genitourinary, retroperitoneal) and primary and secondary diagnoses of intracranial hemorrhage, including intracerebral, subarachnoid, or subdural hemorrhages (Online Appendix). Medical charts from potential hemorrhagic events were reviewed by a clinical outcomes committee using a formal study protocol. Only events that occurred during or within 5 days of preceding warfarin exposure were included. Hemorrhages not present on admission that occurred during the hospitalization or as a result of a procedure were excluded. We restricted the analysis to "major hemorrhages," defined as fatal, requiring transfusion of ≥2 U packed blood cells, or hemorrhage into a critical anatomic site (e.g., intracranial, retroperitoneal).

Statistical analyses. All follow-up periods on warfarin were included in the analysis. Cox proportional hazards regression models using time-varying covariates were used to examine the relationships between potential risk factors and hemorrhage outcomes with time origins set at the beginning of each follow-up period. Risk factor values were updated over follow-up with the proviso that no values were changed within 7 days of an endpoint bleeding event.

The cohort was randomly divided into a split-sample "derivation" and "validation" cohort using a 2:1 ratio; models using time-varying covariates were developed in the derivation cohort and performance tested in the validation cohort. Covariates associated with major hemorrhage with a hazard ratio ≥1.5 were considered for potential inclusion in the final multivariable model. Since variable selection procedures may produce unstable results, we applied backward elimination selection on 1,000 bootstrap samples from the derivation set, with ≥0.05 the significance level set for removing a variable. Final model variables were those selected in >50% of bootstrap samples (12). Model discrimination was evaluated using the *c*-index (13), and calibration by the goodness-of-fit test. Variables from the final multivariable Cox regression model were converted to a risk score, with points assigned to each predictor approximately proportional to the magnitude of the regression coefficients rounded to the nearest integer.

The risk score was collapsed into "low," "intermediate," and "high" risk groups based on the observed major hemorrhage rate. Because there are no definitive or clinically determined cut-points for rates of major hemorrhage at which anticoagulation would be universally contraindicated, we chose thresholds in our point score that appeared to optimally aggregate low- and high-risk groups. We then applied the ATRIA study model and 6 other risk schemes using time-varying covariates to the ATRIA cohort to compare model performance using the *c*-index, risk stratification capacity (the proportion of the cohort assigned to clinically meaningful risk categories), and by a recently published extension of the net reclassification improvement metric (14). For net reclassification improvement calculations, all schemes were compared using a low/intermediate/high categorization to provide a common scale. This study was approved by the respective institutional committees on human research boards.

Table 1 Risk Stratification Schemes Used to Predict Warfarin-Associated Hemorrhage

Risk Scheme (Ref. #)/First Author, Year (Ref. #)	Risk Factors	Risk Category	Points	Major Bleeding Rate in Validation Cohorts
Outpatient Bleeding Index (5) Developed in patients newly starting warfarin after hospital discharge	Age ≥65 yrs (1 point) Prior stroke (1 point) Prior GI bleeding (1 point) Recent MI, diabetes mellitus, hematocrit <30%, creatinine >1.5 mg/dl (1 point if any of the above)	Low Intermediate High	0 1–2 3–4	3% at 12 months 8% at 12 months 30% at 12 months
Kuijer et al., 1999 (6) Developed in patients with acute thromboembolism	Age >60 yrs (1.6 points) Female (1.3 points) Malignancy (2.2 points)	Low Intermediate High	0 >0, <3 ≥3	0.6% at 3 months 2% at 3 months 7% at 3 months
Kearon et al., 2003 (7) Developed in patients with acute venous thromboembolism enrolled in clinical trial.† Risk score categories developed and validated by Gage et al. (8)	Age ≥65 yrs (1 point) Prior stroke (1 point) Prior peptic ulcer disease (1 point) Prior GI bleeding (1 point) Creatinine >1.5 mg/dl (1 point) Anemia or thrombocytopenia (1 point) Liver disease (1 point) Diabetes mellitus (1 point) Antiplatelet therapy (1 point)	Low Intermediate High	0–1 2 3 ≥4	2.6 per 100 PY 6.5 per 100 PY 9.3 per 100 PY 15.3 per 100 PY
HEMORR$_2$HAGES Gage et al., 2006 (8) Developed in hospitalized Medicare patients with atrial fibrillation discharged on warfarin	Hepatic or renal disease (1 point) Ethanol abuse (1 point)* Malignancy (1 point) Older age >75 yrs (1 point) Reduced platelet count or function (1 point)* Rebleeding risk (2 points) Hypertension (1 point) Anemia (1 point) Genetic factors (1 point)* Excessive fall risk or neuropsychiatric disease (1 point) Stroke (1 point)	Low Intermediate High	0–1 2–3 ≥4	1.9–2.5 per 100 PY 5.3–8.4 per 100 PY 10.4–12.3 per 100 PY
Shireman et al., 2006 (9) Developed in hospitalized Medicare patients with atrial fibrillation discharged on warfarin	Age ≥70 yrs Female Remote bleeding event Recent bleeding event Alcohol or drug abuse* Diabetes mellitus Anemia (Hct <30% during index hospitalization) Antiplatelet drugs (aspirin, clopidogrel, or ticlodipine at discharge)* Risk score = 0.49 (age ≥70) + 0.32 (female) + 0.58 (remote bleed) + 0.62 (recent bleed) + 0.71 (alcohol/drug abuse) + 0.27 (diabetes) + 0.86 (anemia) + 0.32 (antiplatelet use)	Low Intermediate High	≤1.07 >1.07, <2.19 ≥2.19	0.9% within 90 days 2.0% within 90 days 5.4% within 90 days
RIETE risk scheme Ruiz-Gimenez et al., 2008 (10) Developed in patients with acute venous thromboembolism	Recent major bleeding (<15 days before thrombotic event) (2 points) Creatinine >1.2 mg/dl (1.5 points) Anemia (1.5 points) Malignancy (1 point) Clinically overt pulmonary embolism* (1 point) Age >75 yrs (1 point)	Low Intermediate High	0 1–4 >4	0.1% at 3 months 2.8% at 3 months 6.2% at 3 months

*Data on ethanol abuse, drug abuse, aspirin, and genetic factors not available in the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) study database. †Hemorrhage rates when risk scheme applied to Gage et al. (8) atrial fibrillation cohort.

GI = gastrointestinal; Hct = hematocrit; HEMORR$_2$HAGES = Hepatic/renal disease, Ethanol abuse, Malignancy, Older age, Reduced platelet count, Rebleeding risk, Hypertension, Anemia, Genetic factors, Excessive fall risk, and Stroke; MI = myocardial infarction; PY = person-years; RIETE = Registro Informatizado de la Enfermedad TromboEmbólica.

Results

There were 9,186 subjects in the ATRIA study cohort, contributing 32,888 person-years of warfarin exposure (median warfarin duration 3.5 years [interquartile range: 1.2 to 6.0 years]). Because anticoagulated patients could discontinue warfarin and subsequently resume therapy, individual patients could contribute multiple periods on warfarin; 2,790 patients (30%) had >1 period on warfarin and 709 patients (8%) had >2 periods on warfarin.

Model development. We identified 461 validated incident warfarin-associated major hemorrhages, an annualized rate of 1.40% hemorrhages per year. The derivation cohort contained 307 major hemorrhages among 6,123 patients, and the validation cohort 154 major hemorrhages among 3,063 patients.

Table 2 compares the characteristics of subjects with and without major hemorrhage in the derivation cohort. Variables associated with major hemorrhage at a hazard ratio ≥1.5 on bivariate analysis were considered for the final model and tested in 1,000 bootstrap samples. Among the various definitions of renal disease and prior hemorrhage,

Table 2 Clinical Characteristics of 6,123 Subjects With Atrial Fibrillation in Derivation Cohort Followed-Up for 21,923 Person-Years on Warfarin, Comparing Subjects Who Sustained Major Hemorrhage and Subjects Without Major Hemorrhage

Clinical Characteristics	With Major Hemorrhage (n = 307)	Without Major Hemorrhage (n = 5,816)	Hazard Ratio (95% CI)	p Value
Age, yrs				
≥65	91.5	84.3	3.3 (2.1–5.0)	<0.001
≥70	79.7	72.1	2.7 (2.0–3.7)	<0.001
≥75	61.7	53.1	2.5 (2.0–3.2)	<0.001
Female	37.4	42.0	1.0 (0.8–1.2)	0.81
Nonwhite race	13.8	13.4	1.2 (0.9–1.6)	0.20
Any diagnosis of cancer	18.0	15.1	1.7 (1.3–2.2)	<0.001
Prior stroke	17.4	12.4	1.4 (1.1–1.9)	0.01
Diagnosed hypertension	64.7	61.9	1.5 (1.2–1.9)	<0.001
Diabetes mellitus	22.1	20.5	1.3 (1.0–1.7)	0.03
Recent myocardial infarction	0.5	0.4	0.2 (0.0–1.2)	0.08
Prior intracranial hemorrhage	0.9	0.5	0.9 (0.2–3.6)	0.89
Prior gastrointestinal hemorrhage	12.1	6.8	2.1 (1.5–2.9)	<0.001
Prior other hemorrhage	2.9	3.1	1.3 (0.7–2.3)	0.48
Prior hematuria	10.3	5.0	2.8 (1.9–3.9)	<0.001
Any prior hemorrhage diagnosis (all cause)	24.1	14.5	2.2 (1.7–2.8)	<0.001
Any prior hemorrhage diagnosis				
>90 days prior	21.9	13.4	3.4 (2.6–4.3)	<0.001
Within 90 days	2.2	1.0	0.3 (0.1–0.7)	0.008
Diagnosed peptic ulcer disease	5.7	4.6	1.4 (0.9–2.2)	0.11
Diagnosed cirrhosis	1.2	0.5	2.6 (1.1–6.1)	0.03
History of hepatitis	1.3	1.0	1.3 (0.4–4.1)	0.61
Prior hospital discharge diagnosis of mechanical fall	6.5	5.3	2.2 (1.5–3.2)	<0.001
Diagnosed neuropsychiatric disease	3.3	4.3	1.2 (0.7–2.0)	0.51
On clopidogrel or ticlopidine	0.9	1.0	0.5 (0.2–1.3)	0.14
Anemia	18.8	12.1	4.2 (3.4–5.3)	<0.001
Platelet count <90,000	0.6	0.5	0.5 (0.1–3.3)	0.45
Serum creatinine, mg/dl				
>2.0	4.0	2.0	4.8 (3.4–6.8)	<0.001
>1.5	9.5	5.1	3.0 (2.2–3.9)	<0.001
>1.2	18.0	10.5	1.8 (1.4–2.3)	<0.001
eGFR <30 ml/min	5.9	2.7	4.3 (3.2–5.8)	<0.001
On dialysis	0.6	0.4	2.4 (1.0–5.5)	0.05
Hemoglobin A1c >7.0	4.1	4.3	0.9 (0.5–1.6)	0.66

Values are % person-years unless otherwise indicated.
CI = confidence interval; eGFR = estimated glomerular filtration rate.

"severe renal disease" (defined as estimated glomerular filtration rate <30 ml/min or dialysis dependent) and "any prior hemorrhage diagnosis (all-cause)" were selected over alternative definitions based on bootstrap analysis. Five final variables emerged in >50% of bootstrap samples: anemia, severe renal disease, age ≥75 years, any prior hemorrhage diagnosis, and diagnosed hypertension. Based on the final model's regression coefficients, anemia and severe renal disease were assigned 3 points, age ≥75 years 2 points, and prior hemorrhage and diagnosed hypertension 1 point each, resulting in a risk scheme with a possible range of 0 to 10 points (Table 3).

Model validation and performance. When applied to the validation set, the model generated regression coefficients similar to those in the derivation dataset, with good discrimination (*c*-index 0.74 [0.70 to 0.78]) and acceptable calibration by the goodness-of-fit test (p = 0.29). Bleeding rates in the combined cohort ranged from 0.4% to 17.3% per year (Table 4). The continuous risk score was collapsed to a 3-category scheme, where "low-risk" (0 to 3 points) patients had hemorrhage rates of <1% per year, and "high-risk" (5 to 10 points) patients had rates >5% per year (Table 4). The high-risk category effectively concentrated hemorrhage events such that 42% of hemorrhage events occurred in only 10.2% of cohort person-years. The vast majority of remaining patients and person-years were low risk (Fig. 1).

Compared with other risk schemes, the ATRIA study risk score had the highest *c*-index point estimates for both the full range of scores and the 3-category scale and

Table 3 Final ATRIA Risk Score: Model Regression Coefficients and Hazard Ratios From Derivation, Validation, and Combined Cohorts

Variable	Points	Derivation Cohort		Validation Cohort		Combined Cohort	
		Regression Coefficient	Hazard Ratio	Regression Coefficient	Hazard Ratio	Regression Coefficient	Hazard Ratio
Anemia	3	1.19	3.28	1.17	3.22	1.18	3.27
Severe renal disease*	3	0.97	2.63	0.88	2.40	0.93	2.53
Age ≥75 yrs	2	0.71	2.03	0.65	1.92	0.69	1.99
Any prior hemorrhage diagnosis	1	0.52	1.68	0.28	1.32	0.44	1.56
Diagnosed hypertension	1	0.27	1.31	0.43	1.54	0.32	1.38

*Defined as estimated glomerular filtration rate <30 ml/min or dialysis-dependent.
ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation.

identified a comparatively large proportion of the cohort as either low or high risk (Table 5). In contrast, other risk schemes either led to much smaller fractions of the cohort categorized as high risk or observed relatively low event rates in their high-risk category. The ATRIA study scheme led to sizable net reclassification improvement when compared with all other risk schemes, ranging from 27.7% to 56.6% improvement (Table 5).

Discussion

Accurate prediction of hemorrhage risk on warfarin is vital to the anticoagulation therapy decision. Based on 5 easily available clinical variables, the ATRIA score reflects the experience of a large, diverse group of patients with atrial fibrillation assembled from community care and followed up for a longer period than prior studies. The model development used rigorous contemporary methods such as split-sample testing and bootstrap sampling approaches to underwrite internal validity.

When collapsed into a 3-category risk score, the ATRIA study risk scheme was able to identify sizable proportions of patients who fell into the most clinically meaningful categories, namely, low or high risk for hemorrhage. The low-risk category, accounting for 83% of follow-up, had an observed major hemorrhage rate of <1% per year. The high-risk category represented only 10.2% of patient follow-up yet accounted for 42% of the major bleeding events. The ATRIA study scheme led to improvements in accurate net reclassification when compared to alternative schemes. The c-index of 0.74, while not representing perfect discrimination, indicates good performance for a prediction model and compares favorably to other widely used risk stratification schemes such as the $CHADS_2$ (congestive heart failure, hypertension, age >75 years, diabetes mellitus, and stroke) stroke risk index, which has a c-index of ~0.6 (15). Certainly, identifying novel predictors of bleeding and improving current methods of risk stratification are important areas of further investigation.

Table 4 Observed Major Bleeding Rates by Risk Score and Risk Category From Each Cohort

	Derivation Cohort		Validation Cohort		Combined Cohort	
	Events/PY	Events/100 PY	Events/PY	Events/100 PY	Events/PY	Events/100 PY
Risk score, points*						
0	12/3,415	0.35	9/1,879	0.48	21/5,294	0.40
1	26/4,925	0.53	14/2,395	0.58	40/7,320	0.55
2	40/3,757	1.06	14/1,806	0.78	54/5,563	0.97
3	53/5,998	0.88	38/2,990	1.27	91/8,988	1.01
4	44/1,623	2.71	18/746	2.41	62/2,369	2.62
5	42/663	6.34	13/311	4.18	55/973	5.65
6	53/1,089	4.87	31/607	5.11	84/1,696	4.95
7	17/285	5.97	5/141	3.56	22/426	5.17
8	2/45	4.43	4/17	23.11	6/62	9.61
9	14/102	13.78	6/59	10.13	20/161	12.43
10	4/23	17.74	2/12	16.34	6/35	17.25
Risk category, points*						
Low (0–3)	131/18,094	0.72	75/9,071	0.83	206/27,166	0.76
Intermediate (4)	44/1,623	2.71	18/746	2.41	62/2,369	2.62
High (5–10)	132/2,206	5.99	61/1,147	5.32	193/3,353	5.76
Overall	307/21,923	1.40	154/10,965	1.40	461/32,888	1.40

*Three points for anemia, severe renal disease (estimated glomerular filtration rate <30 ml/min or on dialysis); 2 points for age ≥75 years; 1 point for prior bleeding, hypertension.
PY = person-years.

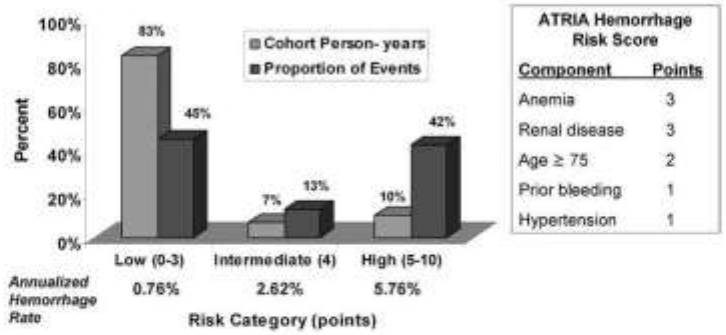

Figure 1 Distribution of Cohort Person-Years and Hemorrhage Events by Risk Categories

Blue bars show the proportion of cohort person-years in low, intermediate, and high bleeding risk categories. **Purple bars** show the proportion of the total hemorrhage events (n = 461) captured by each risk category. ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation.

The variables in our model have each been linked to increased hemorrhage risk in prior studies (5-10). Anemia was strongly associated with future bleeding risk. Although we were unable to determine the mechanism of association, anemia may reflect a predisposition to hemorrhage or recent subclinical hemorrhage. Severe renal disease was also a powerful predictor of hemorrhage risk. All-cause prior bleeding was associated with future bleeding, and presumably identifies patients with a potential bleeding lesion or diathesis. Finally, older age and hypertension were independently associated with hemorrhage risk. Similar to other hemorrhage risk schemes, this analysis focused on all-cause major hemorrhage, both intracranial and extracranial. Although intracranial hemorrhages are the most important outcomes, the rarity of such events makes their risk prediction challenging (16). High-quality models to predict intracranial hemorrhage are vitally needed.

Our risk model is clinically applicable when counseling patients about the relative benefits and harms of anticoagulation therapy. Particularly as newer, easier to administer anticoagulants become available, accurate estimates of hemorrhage risk will strongly influence the anticoagulation decision. Our risk score may not affect the anticoagulation therapy decision for most patients at high risk for stroke, because they derive a large benefit from anticoagulation. However, bleeding risk is significantly more influential in patients at moderate or lower stroke risk. Our bleeding risk estimates can be incorporated into formal decision-analysis models or can be used to counsel individual patients about their estimated risks of stroke and bleeding. For such patients, providing estimates of the risk of bleeding on anticoagulation can be a very informative addition to individualized patient decision making.

There are several limitations to our analysis. Our assessment of clinical risk factors was based on computerized databases that did not have information on several covariates such as measurements of blood pressure and genotype. We lacked information about nonprescription use of aspirin or nonsteroidal anti-inflammatory drugs. Although the hemorrhage rate in the ATRIA study was generally lower than that described by the other risk schemes, the rates are similar to some recent randomized trials (17). Finally, it

Table 5 Comparison of Risk Stratification Capacity (% Cohort PY), Annualized Major Hemorrhage Rate, c-Index, and Net Reclassification Improvement Across Hemorrhage Risk Schemes

Risk Scheme (Ref. #)/ First Author (Ref. #)	Low Risk		Intermediate Risk		High Risk		c-Index (95% CI) for 3 Category Scores*	c-Index (95% CI) for Continuous Scores†	Net Reclassification Improvement‡
	% PY	Rate	% PY	Rate	% PY	Rate			
ATRIA risk score	82.6	0.76	7.2	2.62	10.2	5.76	0.69 (0.66–0.71)	0.74 (0.72–0.76)	Referent
Outpatient Bleeding Index (5)	10.1	0.39	83.0	1.31	6.9	3.96	0.59 (0.56–0.61)	0.66 (0.65–0.70)	50.5%
Kuijer et al. (6)	7.2	0.42	77.7	1.40	15.1	1.89	0.56 (0.55–0.58)	0.57 (0.54–0.59)	56.6%
Kearon et al. (7)	58.2	0.61	38.7	2.27	3.1	5.53	0.67 (0.65–0.69)	0.69 (0.67–0.71)	27.7%
HEMORR$_2$HAGES (8)	65.9	0.72	29.0	2.49	5.1	3.96	0.67 (0.65–0.70)	0.71 (0.69–0.73)	26.9%
Shireman et al. (9)	78.6	0.87	20.3	3.18	1.0	6.72	0.64 (0.61–0.66)	0.70 (0.68–0.73)	33.4%
RIETE risk scheme (10)	37.6	0.56	62.0	1.88	0.4	10.20	0.63 (0.61–0.66)	0.68 (0.65–0.70)	44.8%

*The c-index calculated when risk schemes were separated into 3 categories (low, intermediate, high). †The c-index calculated when risk schemes were in a continuous format. ‡Net reclassification improvement calculated using the method of Pencina et al. (14).

Abbreviations as in Table 1.

will be important to test the ATRIA study risk scheme in a separate population. Although internal validation reduces the likelihood of chance playing a major role in development of our model, external validity needs to be tested empirically.

The risk of anticoagulant-associated hemorrhage is a major deterrent to more widespread use of anticoagulants. Risk stratification schemes can help clinicians estimate the magnitude of hemorrhage risk when prescribing or continuing anticoagulant therapy. Such schemes can also provide important information for comparing the hemorrhage risk of patients enrolled in clinical studies or when comparing the safety of different anticoagulation strategies (18).

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Key Words: anticoagulants ■ atrial fibrillation ■ hemorrhage ■ risk prediction ■ warfarin.

APPENDIX

For a list of ICD-9 codes for hemorrhage outcomes, please see the online version of this article.

Journal of the American College of Cardiology
© 2011 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 57, No. 2, 2011
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.09.024

Comparative Validation of a Novel Risk Score for Predicting Bleeding Risk in Anticoagulated Patients With Atrial Fibrillation

The HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) Score

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Objectives The purpose of this study was to investigate predictors of bleeding in a cohort of anticoagulated patients and to evaluate the predictive value of several bleeding risk stratification schemas.

Background The risk of bleeding during antithrombotic therapy in patients with atrial fibrillation (AF) is not homogeneous, and several clinical risk factors have been incorporated into clinical bleeding risk stratification schemas. Current risk stratification schemas for bleeding during anticoagulation therapy have been based on complex scoring systems that are difficult to apply in clinical practice, and few have been derived and validated in AF cohorts.

Methods We investigated predictors of bleeding in a cohort of 7,329 patients with AF participating in the SPORTIF (Stroke Prevention Using an ORal Thrombin Inhibitor in Atrial Fibrillation) III and V clinical trials and evaluated the predictive value of several risk stratification schemas by multivariate analysis. Patients were anticoagulated orally with either adjusted-dose warfarin (target international normalized ratio 2 to 3) or fixed-dose ximelagatran 36 mg twice daily. Major bleeding was centrally adjudicated, and concurrent aspirin therapy was allowed in patients with clinical atherosclerosis.

Results By multivariate analyses, significant predictors of bleeding were concurrent aspirin use (hazard ratio [HR]: 2.10; 95% confidence interval [CI]: 1.59 to 2.77; $p < 0.001$); renal impairment (HR: 1.98; 95% CI: 1.42 to 2.76; $p < 0.001$); age 75 years or older (HR: 1.63; 95% CI: 1.23 to 2.17; $p = 0.0008$); diabetes (HR: 1.47; 95% CI: 1.10 to 1.97; $p = 0.009$), and heart failure or left ventricular dysfunction (HR: 1.32; 95% CI: 1.01 to 1.73; $p = 0.041$). Of the tested schemas, the new HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score performed best, with a stepwise increase in rates of major bleeding with increasing HAS-BLED score ($p_{trend} < 0.0001$). The c statistic for bleeding varied between 0.50 and 0.67 in the overall entire cohort and 0.68 among patients naive to warfarin at baseline ($n = 769$).

Conclusions This analysis identifies diabetes and heart failure or left ventricular dysfunction as potential risk factors for bleeding in AF beyond those previously recognized. Of the contemporary bleeding risk stratification schemas, the new HAS-BLED scheme offers useful predictive capacity for bleeding over previously published schemas and may be simpler to apply. (J Am Coll Cardiol 2011;57:173–80) © 2011 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is associated with a substantial risk of stroke and systemic embolism. Thromboprophylaxis with oral anticoagulation (OAC) is most effective in reducing stroke compared with antiplatelet therapy (1,2). Compared with

From the *University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, England; †AstraZeneca R&D, Mölndal, Sweden; and ‡The Cardiovascular Institute, Mount Sinai Medical Center, New York, New York. The SPORTIF III and V studies were sponsored by AstraZeneca. Dr. Lip has received funding for research, educational symposia, consultancy, and lecturing from different manufacturers of drugs used for the treatment of atrial fibrillation and thrombosis, including AstraZeneca, Boehringer, Nayer, Pfizer/BMS, Biotronic, Astellas, Sanofi, Cardiome, and Merck; and is a clinical advisor to the UK NICE Guidelines on AF management, and a task force member of the 2010 ESC guidelines and ACCP9 writing committee. Dr. Frison is an employee of AstraZeneca. Dr. Halperin has received consulting fees from several pharmaceutical manufacturers involved in the development of novel oral anticoagulants for the prevention of thromboembolism in patients with atrial fibrillation, including AstraZeneca, the sponsor of the SPORTIF trials. Dr. Lane has received an investigator-initiated educational grant from Bayer Healthcare, and has received sponsorship to attend meetings from AstraZeneca.

Manuscript received May 11, 2010; revised manuscript received August 18, 2010, accepted September 6, 2010.

JACC Vol. 57, No. 2, 2011
January 11, 2011:173–80

Abbreviations and Acronyms

AF = atrial fibrillation
CI = confidence interval
HR = hazard ratio
INR = international normalized ratio
LV = left ventricular
OAC = oral anticoagulation

OAC, antiplatelet therapy confers a smaller benefit for stroke prevention (1,2) and is associated with similar rates of major bleeding, particularly among elderly patients with AF (3).

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Given that increasing numbers of patients with AF will be treated with OAC, attention has been directed toward estimation of both stroke and bleeding risk to guide the selection of the most appropriate prophylactic measures. Accurate estimation of stroke and bleeding risks is difficult (4), leading to the development of various stroke risk stratification schemas to help identify subjects who may benefit most from OAC therapy because of their higher intrinsic risk of stroke (5). Like the thromboembolic risk of patients with AF, the risk of bleeding during anticoagulation is not homogeneous, and various clinical risk factors have been identified that are associated with incremental bleeding risk. Current schemes for bleeding risk stratification by Shireman et al. (6), Gage et al. (7) (with the acronym $HEMORR_2HAGES$), Beyth et al. (8), and Kuijer et al. (9) have been difficult to apply in clinical practice. Some use complex scoring systems (6,9), and only a few have been derived (and validated) in patients with AF (7,10), with others derived from general anticoagulated populations that may have different clinical profiles from those of AF patients (who are often older with more comorbidities and polypharmacy) (8).

Thus, contemporary guidelines simply list risk factors for bleeding and given the lack of a simple, pragmatic, widely accepted method for bleeding risk assessment applicable to patients with AF, no specific schema is currently recommended for routine clinical use (11). It is recognized that several risk factors predisposing to bleeding are also risk factors for stroke (12), and although some schemas (e.g., $CHADS_2$ [congestive heart failure, hypertension, age >75 years, diabetes mellitus and previous stroke or transient ischemic attack (doubled)] [13]) have modest value for predicting stroke, they are very good at predicting a patient's risk of bleeding (14,15).

We recently derived and validated the HAS-BLED bleeding risk schema for AF (also called the Birmingham AF bleeding schema: Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) in a European cohort (16). The predictive accuracy of this schema was good in the overall population, especially when patients were treated with antiplatelet agents alone or with no antithrombotic therapy, but further validation and comparison with other published bleeding risk schemas are necessary.

The objective of this analysis was to determine risk factors for bleeding and compare the performance of bleeding risk stratification schemas in a large cohort of anticoagulated AF patients in a contemporary clinical trial. To achieve this, we used the combined dataset of the SPORTIF (Stroke Prevention Using an ORal Thrombin Inhibitor in Atrial Fibrillation) III and V trials, which compared warfarin with the oral direct thrombin inhibitor ximelagatran for the prevention of stroke and systemic embolism in patients with AF at moderate to high risk of stroke (17,18). Although ximelagatran was not inferior to well-controlled warfarin in reducing the risk of stroke and systemic embolism in these trials (17,18), concerns about liver safety led to the withdrawal of ximelagatran from further clinical development.

Patients and Methods

The SPORTIF III and V clinical trials were designed as noninferiority phase III trials comparing ximelagatran with warfarin in patients with nonvalvular AF at moderate to high risk of thromboembolism, and a pooled analysis of the results of both trials was pre-specified. SPORTIF III was an open-label trial in 23 countries (17), whereas SPORTIF V was a double-blind trial conducted in North America (18). Inclusion criteria for both trials were similar and included age 18 years and older, persistent or paroxysmal AF, and at least 1 of the following stroke risk factors: hypertension (defined as high blood pressure requiring antihypertensive medication, but below 180/100 mm Hg at randomization), age 75 years and older, previous stroke, transient ischemic attack or systemic embolic event; left ventricular (LV) dysfunction (ejection fraction <40% or symptomatic heart failure), age 65 years and older with coronary artery disease, and age 65 years and older with diabetes mellitus. End points were evaluated in a blinded manner by a central events adjudication committee.

We initially investigated predictors of bleeding risk in the combined SPORTIF III and V trial cohort of 7,329 subjects. Major bleeding was defined as fatal or clinically overt bleeding associated with either transfusion of ≥2 U of blood or ≥20 g/l decrease in hemoglobin or bleeding involving a critical anatomic site other than the brain parenchyma. Intracerebral bleeding counted as primary efficacy events. Clinically overt bleeding not satisfying criteria for major bleeding was classified as minor bleeding.

We then tested the predictive value of several bleeding risk schemas in this cohort: Shireman et al. (6), $HEMORR_2HAGES$ (7), Beyth et al. (8), Kuijer et al. (9), and HAS-BLED (16) (Table 1). For each risk stratification schema, we calculated the c statistic as a measure of predictive accuracy. In the $HEMORR_2HAGES$ scheme, we considered blood pressure >160 mm Hg systolic as uncontrolled hypertension, a history of malignancy as similar to current malignancy, alcohol consumption of 20 U weekly as ethanol abuse creatinine clearance <50 ml/min as renal disease, a low platelet count as less than the lower limit

Table 1 Contemporary Bleeding Risk Stratification Schemas

	Low	Moderate	High	Calculation of Bleeding Risk Score
Kuijer et al., 1999 (9)	0	1–3	>3	(1.6 × age) + (1.3 × sex) + (2.2 × cancer) with 1 point for age ≥60 yrs, female or malignancy, and 0 if none
Beyth et al., 1998 (8)	0	1–2	≥3	Age ≥65 yrs, GI bleed in past 2 weeks, previous stroke, comorbidities (recent MI, Hct <30%, diabetes, creatinine >1.5 ml/l) with 1 point for presence of each condition and 0 if absent
Gage et al., 2006 (7)	0–1	2–3	≥4	HEMORR$_2$HAGES score: liver/renal disease, ETOH abuse, malignancy, age >75 yrs, low platelet count or function, rebleeding risk, uncontrolled hypertension, anemia, genetic factors (CYP2C9), risk of fall or stroke, with 1 point for each risk factor present with 2 points for previous bleed
Shireman et al., 2006 (6)	≤1.07	>1.07–<2.19	>2.19	(0.49 × age >70 yrs) + (0.32 × female) + (0.58 × remote bleed) + (0.62 × recent bleed) + (0.71 × alcohol/drug abuse) + (0.27 × diabetes) + (0.86 × anemia) + (0.32 × antiplatelet drug use) with 1 point for presence of each, and 0 if absent
Pisters et al., 2010 (16)	0	1–2	≥3	HAS-BLED score: Hypertension, Abnormal Renal/Liver Function (1 point each), Stroke, Bleeding History or Predisposition, Labile INR, Elderly Drugs/Alcohol concomitantly (1 point each); maximum 9 points

ETOH = ethyl alcohol; GI = gastrointestinal; Hct = hematocrit; INR = international normalized ratio; MI = myocardial infarction.

of normal, and hemoglobin content less than the lower limit of normal as anemia. Relevant genetic and laboratory data (required for calculation of some schemes), apart from serum creatinine and hematocrit, were not available for the SPORTIF AF cohort. For HAS-BLED, labile INR was defined as <60% time in the therapeutic range (INR 2 to 3 inclusive), concomitant platelet inhibitor agents as aspirin or nonsteroidal anti-inflammatory drugs (clopidogrel was not allowed in the trial), elderly older than 75 years of age, given that the majority of patients (76%) in the cohort were older than 65 years of age. In addition, we report the c statistics in subgroups of individuals who were warfarin naive at baseline as well as those taking warfarin plus aspirin concurrently.

Statistical analysis. Categorical data were evaluated with the Fisher exact test or the chi-square test for >2 categories and continuous data using Student *t* test. All tests were performed 2-tailed, with p values ≤0.05 considered statistically significant. No adjustment was made for multiple testing because all reported results are explorative. Annualized event rates assume constant rates over time. Unless otherwise stated, all analyses were performed on pooled data from the SPORTIF III and V trial cohorts. All randomized patients were included in the intention-to-treat population. An on-treatment analysis accounted for time until therapy was interrupted for up to 30 consecutive days (or up to 60 days for cardioversion) or 60 days cumulatively. Assessment of major bleeding used the on-treatment approach. Given the wide range of time in the studies for individual patients (common study closure, intended duration of study treatment ranging between 12 and 26 months), statistical analyses had to take time at risk into account; this was done either through Cox regression analyses or by using patient-years as analyses unit. All analyses on major bleeding in this paper are based on on-treatment analyses (17,18). Patients are contributing with time at risk as long as they are receiving study treatment (according to the on-treatment definition) or until they experienced major bleeding. Patients were not censored for reasons other than major bleeding or study drug discontinuation.

Univariate Cox regression modeling was used to estimate the hazard ratios (HRs) and 95% confidence intervals for individual risk factors with major bleeding as the dependent variable. All potential risk factors investigated in the univariate analyses were included in the multivariate Cox regression analyses; only those variables with p values that remained significant at the 5% level in the presence of other selected variables were retained in the final model. *c*-statistics were estimated to quantify the predictive accuracy of the risk schemes, with 95% confidence intervals obtained by bootstrapping analyses. The Hosmer-Lemeshow test for calibration was also performed whenever a *c*-statistic was calculated. All analyses were performed using SAS statistical software (version 8.2, SAS Institute, Inc., Cary, North Carolina). More detailed descriptions of the analytical methods used for the SPORTIF III and V trials are published elsewhere (17,18).

Results

Baseline characteristics of AF patients with known status regarding major bleeding during follow-up are summarized in Table 2. Patients in the whole cohort experiencing major bleeding events (n = 217) were more often elderly ($p < 0.0001$), nonsmokers ($p = 0.016$) with diabetes ($p = 0.018$), LV dysfunction ($p = 0.018$), previous stroke or transient ischemic attack ($p < 0.0001$), and impaired renal function ($p < 0.0001$). As expected, those with bleeding events had a higher mean $CHADS_2$ score than those without bleeding events ($p < 0.0001$).

Among the 7,329 patients, 79% were previously receiving vitamin K antagonist treatment, whereas 21% were vitamin K antagonist naive. Among those previously receiving vitamin K antagonist treatment, 46% had their AF diagnosed >5 years ago, 16% between 1 and 5 years, and the remaining 38% within the preceding year. The overall mean (SD) for the number of days in the on-treatment analysis

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Table 2 Baseline Characteristics of Atrial Fibrillation Patients With Known Follow-up Status Regarding Major Bleeding

Characteristic	Bleeding Event (n = 234)	No Bleed (n = 7,095)	p Value
Age, yrs, mean (SD)	73.9 (8.6)	70.9 (8.9)	<0.0001
>65	196 (84)	5,349 (75)	0.0031
≥75	125 (53)	2,679 (38)	<0.0001
Female sex	73 (31)	2,184 (31)	0.89
Body mass index, kg/m^2	28.7 (6.6)	29.0 (5.8)	0.50
AF type			
Duration since first diagnosed (yrs)	6.4 (5.9)	6.3 (7.1)	0.91
Paroxysmal	26 (11)	810 (12)	1.00
Persistent/permanent	208 (89)	6,282 (88)	1.00
Medical history			
Hypertension	180 (77)	5445 (77)	1.00
Diabetes mellitus	67 (29)	1658 (23)	0.071
Coronary artery disease	117 (50)	3162 (45)	0.11
LV dysfunction	102 (44)	2579 (36)	0.027
Stroke/TIA	61 (26)	1478 (21)	0.060
SEEs	8 (3)	320 (5)	0.52
$CHADS_2$ score, mean (SD)	2.6 (1.2)	2.2 (1.2)	<0.0001
Bleeding risk factors			
Previous clinically significant bleed	19 (8)	441 (6)	0.22
SBP at entry, mean (SD)	136 (19)	135 (18)	0.48
CrCl <50 ml/min	57 (24)	885 (13)	<0.0001
Alcohol use	97 (41)	3,230 (46)	0.23
Smoking	11 (5)	667 (9)	0.011

Values shown are n (%) unless otherwise indicated.
AF = atrial fibrillation; $CHADS_2$ = congestive heart failure, hypertension, age >75 years, diabetes mellitus and previous stroke or transient ischemic attack (doubled); CrCl = creatinine clearance; LV = left ventricular; SEEs = systemic embolic events; SBP = systolic blood pressure; TIA = transient ischemic attack.

was 499 (196) days; the corresponding results for patients without and with major bleeding were 503 (194) days and 380 (217) days, respectively.

Univariate and multivariate analyses of risk factors predictive of major bleeding are shown in Table 3. By univariate analysis, significant predictors of bleeding were concurrent aspirin use, reduced creatinine clearance (<50 ml/min), advanced age (75 years and older), diabetes mellitus, LV dysfunction, smoking, and previous stroke or transient ischemic attack. By multivariate analysis, significant predictors of bleeding were aspirin use ($p < 0.001$), renal impairment ($p < 0.001$), age 75 years and older ($p = 0.0008$), diabetes ($p = 0.0089$), and LV dysfunction ($p = 0.041$).

In Table 4, rates of major bleeding by HAS-BLED score are presented for the entire cohort and for patients assigned to warfarin therapy. *c*-statistics for prediction of major bleeding were similar (0.66 and 0.67; $p_{trend} < 0.0001$ for both). The relationship between the individual components of the HAS-BLED scheme and clinical bleeding events is shown in Tables 5 and 6. Labile INR, advanced age, concomitant aspirin or nonsteroidal anti-inflammatory drug use were consistently predictive of major bleeding in this cohort.

Comparison of contemporary bleeding risk stratification schemas revealed variable classification of AF patients into various bleeding risk strata (Table 7). In this analysis, there was no significant difference in c statistics between patients in the warfarin arms compared with those in the ximelagatran arms of the SPORTIF trials. Among those treated with warfarin, the HAS-BLED scheme exhibited a marginally better *c*-statistic value (0.67) than the other 4 schemas evaluated, with the lowest *c*-statistic (0.50) associated with the scheme of Kuijer et al. (9). The HAS-BLED scheme classified 20.4% of the cohort into the low-risk category, with a bleeding rate of <1% per year, whereas subjects classified as low risk by the other schemes had higher bleeding rates (>1.9% per year). Among patients who were warfarin naive at entry (n = 769) and in those treated with

Table 3 Risk Factors for Major Bleeding by Univariate and Multivariate Analyses

	Event Rate (%/Patient-Year)					
	Risk Factor Present		Univariate Analyses		Multivariate Analyses*	
Risk Factor	Yes	No	HR (95% CI)†	p Value	HR (95% CI)†	p Value
Aspirin use	3.94	1.94	2.02 (1.54–2.65)	<0.0001	1.92 (1.40–2.51)	<0.0001
CrCl <50 ml/min	4.91	2.01	2.48 (1.84–3.35)	<0.0001	1.90 (1.38–2.62)	<0.0001
Age ≥75 yrs	3.42	1.73	1.97 (1.53–2.55)	<0.0001	1.71 (1.30–2.25)	0.0001
Diabetes mellitus	2.96	2.17	1.36 (1.02–1.80)	0.035	1.36 (1.03–1.81)	0.033
LV dysfunction	2.85	2.07	1.37 (1.06–1.77)	0.017	1.31 (1.01–1.70)	0.043
Smoking	1.20	2.47	0.49 (0.26–0.89)	0.019		
Previous stroke or TIA	3.05	2.18	1.40 (1.04–1.87)	0.024		
Coronary artery disease	2.65	2.11	1.25 (0.97–1.62)	0.083		
Clinically significant bleeding	3.15	2.30	1.36 (0.85–2.18)	0.19		
Alcohol abuse	2.14	2.53	0.84 (0.65–1.09)	0.20		
Statin use	2.08	2.48	0.84 (0.63–1.11)	0.22		
Female	2.41	2.32	1.04 (0.79–1.37)	0.79		
Hypertension	2.36	2.33	1.01 (0.75–1.37)	0.94		

*Only factors associated with $p < 0.05$ in the presence of other selected variables were retained in the final model. †HR (95% CI) derived by Cox regression modeling.
CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 2.

Table 4 Major Bleeding Rates by HAS-BLED Score in the Overall SPORTIF Cohort (n = 7,329) and Those Taking Warfarin Only (n = 3,665)

HAS-BLED Score	Patients With Particular Score in the Whole Cohort*	Major Bleeding Events†	Patients With Particular Score Among Those Taking Warfarin Only*	Major Bleeding Events†
0	1,757 (24.0)	21 (1.2)	746 (20.4)	7 (0.9)
1	2,717 (37.1)	75 (2.8)	1,283 (35.0)	44 (3.4)
2	1,752 (23.9)	63 (3.6)	950 (25.9)	39 (4.1)
3	834 (11.4)	50 (6.0)	483 (13.2)	28 (5.8)
4	241 (3.3)	22 (9.5)	180 (4.9)	16 (8.9)
5	27 (0.4)	2 (7.4)	22 (0.6)	2 (9.1)
6	1 (0.0)	0	1 (0.0)	0
	c-statistic = 0.654; p value for trend <0.0001		c-statistic = 0.659; p value for trend <0.0001	

Values are n (%). *Percentage of column total. †Percentage of row total.
HAS-BLED = Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly; SPORTIF = Stroke Prevention Using an ORal Thrombin Inhibitor in Atrial Fibrillation.

warfarin plus aspirin concurrently (n = 772), the HAS-BLED schema displayed the highest *c*-statistic values (0.68 and 0.60, respectively) of the 5 risk schemas evaluated.

We also tested, with multivariate Cox regression models, whether the new score adds significantly to models already incorporating the 4 older scores 1 at a time. In all 4 instances, HAS-BLED was associated with $p < 0.0001$ when inserted into models already incorporating the older scores. In contrast, none of the other 4 older scores added significantly when inserted 1 at a time into a model already including HAS-BLED (full data not shown). The Hosmer-Lemeshow test for calibration was also performed in conjunction with all c statistics reported in Tables 7 and 8. None of the p values were <0.05 for any of the risk scores (i.e., lack of goodness of fit was not indicated). For HAS-BLED, for example, the p values were 0.24 for all patients and 0.13 for the warfarin patient cohort. For the schema by Shireman et al. (6) (the only one with a p value <0.1), the p value was 0.075 for the warfarin patients (and 0.29 for all patients) (complete data not shown).

There was a progressive increase in the HR for bleeding from the low-risk to moderate-risk stratum and from the moderate-risk to the high-risk stratum according to the HAS-BLED scheme (Table 8) that was less apparent with the other bleeding risk schemas.

Discussion

This analysis of the performance of various bleeding risk stratification schemas over >11,000 patient-years of anticoagulation exposure confirms the predictive value of previously identified risk factors, including advanced patient age, concomitant use of aspirin or nonsteroidal anti-inflammatory drugs during anticoagulation use, and renal impairment. In addition, the data identify associations of diabetes mellitus and clinical heart failure or LV systolic dysfunction with an increased risk of bleeding during therapeutic anticoagulation in this particular cohort of patients with AF. Of the various risk stratification schemas evaluated, the HAS-BLED schema more accurately discriminated patients on the basis of bleeding risk, based on the magnitude of the c statistic.

Risk factors for bleeding with OAC have largely been derived from cohort studies or secondary analyses of clinical

Table 5 Risk Factors for Major Bleeding According to the HAS-BLED Score: Whole Cohort (n = 7,329)

Risk Factor	SPORTIF III/V Cohort Definition	Risk Factors Present, n (%)	Major Bleeding: With Risk Factors, n (%)	Major Bleeding: Without Risk Factors, n (%)	Univariate Analyses: HR (95% CI)	Univariate Analyses: p Value	Multivariate Analyses: HR (95% CI)	Multivariate Analyses: p Value
Hypertension	SBP >160 mm Hg at entry	533 (7.3)	19 (3.6)	215 (3.2)	1.14 (0.71–1.82)	0.59	1.10 (0.69–1.76)	0.70
Abnormal renal function*	CrCl <50 ml/min	942 (12.9)	57 (6.0)	177 (2.8)	2.48 (1.84–3.35)	<0.0001	1.77 (1.28–2.44)	0.0005
Stroke before entry	Yes/no	918 (12.5)	35 (3.8)	199 (3.1)	1.32 (0.92–1.89)	0.13	1.24 (0.87–1.78)	0.23
Bleeding history	History of clinically significant bleeding	460 (6.3)	19 (4.1)	215 (3.1)	1.36 (0.86–2.18)	0.19	1.31 (0.82–2.09)	0.26
Labile INR	TTR <60%	1,235 (33.7)	65 (5.3)	71 (2.9)	2.14 (1.53–2.99)	<0.0001	2.05 (1.54–2.74)	<0.0001
Elderly	Age >75 yrs at entry	2,441 (33.3)	116 (4.8)	118 (2.4)	2.10 (1.63–2.72)	<0.0001	1.76 (1.34–2.33)	<0.0001
	Age >65 yrs at entry	5,545 (75.7)	196 (3.5)	38 (2.1)	1.74 (1.23–2.47)	0.0017		
Drugs†	Aspirin or NSAID	3,051 (41.6)	136 (4.5)	98 (2.3)	1.92 (1.48–2.49)	<0.0001	1.85 (1.43–2.40)	<0.0001
Alcohol	Alcohol >20 U/week	204 (2.8)	6 (2.9)	228 (3.2)	1.00 (0.44–2.25)	1.00	1.11 (0.49–2.51)	0.80
Aspirin use	Aspirin at any time	1,578 (21.5)	80 (5.1)	154 (2.7)	2.02 (1.54–2.65)	<0.0001		
NSAID	NSAID at any time	1,956 (26.7)	89 (4.6)	145 (2.7)	1.58 (1.21–2.06)	0.0007		

*Abnormal liver function was an exclusion criterion for these studies. †Concomitant use of clopidogrel was not allowed.
NSAID = nonsteroidal anti-inflammatory drug; other abbreviations as in Tables 1, 2, 3, and 4.

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Table 6 Risk Factors for Major Bleeding According to the HAS-BLED Score: Warfarin Patients Only (n = 3,665)

Risk Factor	SPORTIF III/V Cohort Definition	Risk Factors Present, n (%)	Major Bleeding		Univariate Analyses		Multivariate Analyses	
			With Risk Factors, n (%)	Without Risk Factors, n (%)	HR (95% CI)	p Value	HR (95% CI)	p Value
Hypertension	SBP >160 mm Hg at entry	260 (7.1)	7 (2.7)	129 (3.8)	0.69 (0.32–1.47)	0.34	0.65 (0.30–1.39)	0.27
Abnormal renal function*	CrCl <50 ml/min	488 (13.4)	31 (6.4)	105 (3.3)	2.15 (1.44–3.21)	0.0002	1.46 (0.95–2.26)	0.085
Stroke before entry	Yes/no	450 (12.3)	18 (4.0)	118 (3.7)	1.17 (0.71–1.92)	0.53	1.12 (0.68–1.84)	0.66
Bleeding history	History of clinically significant bleeding	208 (5.7)	10 (4.8)	126 (3.6)	1.32 (0.69–2.51)	0.40	1.31 (0.68–2.49)	0.42
Labile INR	TTR <60%	1,235 (33.7)	65 (5.3)	71 (2.9)	2.14 (1.53–2.99)	<0.0001	2.06 (1.47–.89)	<0.0001
Elderly	Age >75 yrs at entry	1,222 (33.3)	67 (5.5)	69 (2.8)	2.07 (1.48–2.89)	<0.0001	1.82 (1.27–2.62)	0.0012
	Age >65 yrs at entry	2,762 (75.4)	112 (4.1)	24 (2.7)	1.57 (1.01–.44)	0.044		
Drugs†	Aspirin or NSAID	1,487 (40.6)	79 (5.3)	57 (2.6)	2.06 (1.47–2.90)	<0.0001	1.96 (1.39–2.76)	0.0001
Alcohol	Alcohol >20 U/week	99 (2.7)	3 (3.0)	133 (3.7)	0.89 (0.28–2.78)	0.84	1.00 (0.32–3.17)	0.99
Aspirin use	Aspirin at any time	772 (21.1)	50 (6.5)	86 (3.0)	2.39 (1.69–3.39)	<0.0001		
NSAID	NSAID at any time	954 (26.0)	50 (5.2)	86 (3.2)	1.59 (1.12–2.25)	0.0093		

*Abnormal liver function was an exclusion criterion for these studies. †Concomitant use of clopidogrel was not allowed.
Abbreviations as in Tables 1, 2, 3, 4, and 5.

trial data. A systematic review of the literature confined to AF populations identified advanced age, uncontrolled hypertension, ischemic heart disease, cerebrovascular disease, anemia, concomitant antiplatelet therapy, and previous bleeding as predictors of major bleeding events during anticoagulation (19), and labile INR control, advanced patient age, and concomitant aspirin or nonsteroidal anti-inflammatory drug use have been consistently identified as predictors in other analyses (10). Diabetes mellitus, controlled hypertension, and sex were not significant risk factors for bleeding in the systematic review forming the basis for the UK-NICE clinical practice guidelines (19). Other factors specifically associated with an incremental risk of intracerebral hemorrhage during OAC include associated cerebrovascular disease and concomitant antiplatelet therapy; tobacco use or alcohol consumption; ethnicity; genotype; certain vascular abnormalities, such as amyloid angiopathy, leukoaraiosis, and microbleeds detected by brain imaging; and possibly genetic variations (20). Thus, the bleeding risk associated with diabetes mellitus and clinical heart failure or LV systolic dysfunction in anticoagulated AF populations requires further study.

Of note, many of the risk factors for anticoagulation-related bleeding are also indications for the use of anticoagulants in AF patients (10,14,15,19). Patients in whom major bleeding complications developed during anticoagulation therapy had a higher mean $CHADS_2$ score than those without bleeding, consistent with previous observa-

Table 7 Predictive Value of Contemporary Bleeding Risk Schemas in Patients Taking Warfarin Compared With the Whole Study Cohort and Subgroups of Warfarin-Naive Patients and Those Taking Warfarin Plus Aspirin

Bleeding Risk Score (Ref. #)	Warfarin Patients (n = 3,665)				c-Statistic* (95% CI)		
	Low	Moderate	High	c-Statistic* (95% CI)	All Patients (n = 7,329)	Warfarin-Naive Patients at Baseline (n = 769)	Patients Taking Warfarin + Aspirin (n = 772)
HAS-BLED (16)							
% in risk category	20.4	60.9	18.7	0.66	0.65 (0.61–0.68)	0.66 (0.55–0.74)	0.60 (0.53–0.68)
Bleeding events, n (%)†	7 (0.9)	83 (3.7)	46 (6.7)	(0.61–0.70)			
Shireman et al. (6)							
% in risk category	82.2	17.7	0.1	0.63	0.64 (0.61–0.68)	0.61 (0.52–0.71)	0.58 (0.51–0.66)
Bleeding events, n (%)	99 (3.3)	37 (5.7)	0 (0.0)	(0.58–0.67)			
$HEMORR_2HAGES$ (7)							
% in risk category	73.5	23.8	2.7	0.61	0.62 (0.58–0.65)	0.62 (0.52–0.72)	0.58 (0.51–0.66)
Bleeding events, n (%)	81 (3.0)	53 (6.1)	2 (2.0)	(0.56–0.65)			
Beyth et al. (5)							
% in risk category	10.2	79.6	10.2	0.56	0.57 (0.53–0.60)	0.50 (0.44–0.57)	0.52 (0.46–0.57)
Bleeding events, n (%)	8 (2.1)	113 (3.9)	15 (4.0)	(0.51–0.60)			
Kuijer et al. (9)							
% in risk category	9.0	85.7	5.3	0.52	0.49 (0.46–0.52)	0.44 (0.38–0.51)	0.49 (0.45–0.55)
Bleeding events, n (%)	11 (3.0)	120 (3.8)	5 (2.6)	(0.48–0.56)			

*All c-statistics have been calculated based on the entire range for each risk score. †Bleeding rates are per patient.
Abbreviations as in Tables 1, 3, and 4.

Table 8 Hazard Ratios (95% Confidence Interval) of Risk Categories for the 5 Bleeding Risk Stratification Schemas Among Warfarin Patients (n = 3,665)

Schema (Ref. #)	Moderate vs. Low	High vs. Moderate	High vs. Low
HAS-BLED (16)			
HR (95% CI)	4.31 (1.99–9.33)	2.02 (1.41–2.90)	8.56 (3.86–18.98)
p value	0.0002	0.0001	<0.0001
Shireman et al. (6)			
HR (95% CI)	1.87 (1.28–2.72)	—	—
p value	0.0012		
HEMORR$_2$HAGES (7)			
HR (95% CI)	2.19 (1.55–3.10)	0.34 (0.08–1.38)	0.75 (0.18–3.06)
p value	<0.0001	0.13	0.69
Beyth et al. (5)			
HR (95% CI)	1.87 (0.91–3.82)	1.10 (0.64–1.89)	2.07 (0.88–4.90)
p value	0.09	0.73	0.096
Kuijer et al. (9)			
HR (95% CI)	1.17 (0.63–2.16)	0.67 (0.27–1.64)	0.78 (0.27–2.24)
p value	0.63	0.38	0.64

Abbreviations as in Tables 3, 4, and 7.

tions (14,15). It has been suggested that the CHADS$_2$ stroke risk stratification and the HEMORR$_2$HAGES bleeding risk scores are so closely correlated that they classify two-thirds of patients into similar risk strata for hemorrhagic and ischemic events, casting doubt on the clinical utility of combining the 2 schemas (21).

The available bleeding risk stratification schemas classify variable proportions of AF patients into low-, moderate-, and high-risk categories. In this respect, the HAS-BLED schema displayed better predictive power than the 4 other tested bleeding risk stratification methods for bleeding events among patients in the combined SPORTIF III and V cohort, as well as for those randomized to the adjusted-dose arms, the subgroup who were warfarin naive at entry and those taking aspirin concurrently with warfarin, based on comparative *c* statistics.

Optimum selection of patients with AF for anticoagulant therapy depends not only on assessment of their intrinsic risk of thromboembolism but also on identification of those at increased risk of the development of bleeding complications. Even in patients at moderate or intermediate risk of stroke, accurate identification of those at low risk of bleeding may guide a preference for anticoagulation over aspirin, given additional data showing that anticoagulation may be the better option for stroke prevention (22), with a net clinical benefit (even when considering potential bleeding risk) in favor of anticoagulation rather than antiplatelet therapy. Of patients enrolled in the SPORTIF trials by virtue of at least 1 stroke risk factor other than AF, approximately 1 in 5 were in the low-risk category for bleeding based on the HAS-BLED criteria, and major bleeding occurred at a rate of <1% per year in these cases during treatment. In contrast, patients classified as low risk by the other 4 schemas experienced higher rates of bleeding (>1.9% per year) during the same period. There was a progressive increment in HR for bleeding from the lowest to highest risk strata delineated by the HAS-BLED schema, but this gradient was not verified for the other scales tested.

These findings in a large clinical trial cohort are broadly comparable to those in the initial validation of HAS-BLED in >3,000 patients with AF in the Euro Heart survey followed for 1 year (16). In that analysis, the HAS-BLED schema also displayed predictive accuracy (*c*-statistic = 0.72), outperforming other bleeding risk schemas in AF patients treated with platelet inhibitor drugs or without antithrombotic therapy (*c*-statistic = 0.91 and 0.85, respectively), indicating that bleeding risk estimated by this method is not confined to anticoagulated patients. Whether bleeding risk estimated by this method will also apply to patients treated with newer anticoagulant drugs, such as dabigatran, rivaroxaban, apixaban, and edoxaban currently under development for stroke prevention in patients with AF, has not been evaluated. Estimation of bleeding risk will likely be important with these new agents even if they show efficacy superior or noninferior to that of warfarin and similar or lower rates of major bleeding because prophylactic therapy could potentially be applied more broadly across the patient population at risk (22).

With particular reference to dabigatran, 2 doses of which were compared with warfarin in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial (23), the availability of an accurate bleeding risk assessment tool could potentially prove valuable in dose selection for individual patients if combined with stroke risk assessment. Although it is appealing to think that the HAS-BLED schema could be effectively applied in this context, further validation of its predictive value for bleeding in relation to dabigatran dose would be necessary if the compound were approved and brought to market for routine clinical use.

Study limitations. Assessment of bleeding risk is complicated by variation in the criteria used to define major, clinically relevant nonmajor and minor bleeding events, although these have been more uniform in recent trials than in earlier studies (24). Furthermore, bleeding rates and risk factors derived from clinical trial populations in which patients are carefully selected according to specific research protocols, anticoagulated using standard drug supply sources and monitored with stable thromboplastin reagents by dedicated personnel according to rigid criteria, may differ from those in clinical practice. Also, many of the patients were not warfarin naive and bleeding risk prediction might be much better if it took into account the time-specific context of treatment, including when warfarin was started and recent experience (e.g., in the past month) with antiplatelet drugs and INR control, and whether it predicted risk of bleeding in the next month (rather than on average over the course of therapy); however, the addition of these variables would introduce such complexity and reduce practical utility for everyday clinical use.

Advancing age is a continuous variable linearly related to the risks of stroke and bleeding (19). In the clinical trial

cohort that formed the basis for this report, >75% of participants were older than 65 years of age and the elderly criterion for the HAS-BLED schema was taken as age 75 years and older at study entry. Setting this threshold at age 65 years would have a small effect on the results (shifting the *c* statistic from 0.67 to 0.65 for the 3,665 patients assigned to warfarin). Bleeding in elderly patients with AF is more related to biological age rather than chronological age and is often multifactorial, being affected by comorbidity, anticoagulation intensity and lability, and frequent changes in concomitant pharmacology (10,19,21). Also, in comparing the different prediction schemas, it is important to recognize that some include only risk factors that could be known at the time of starting warfarin, whereas 2 schemas (HAS-BLED and that of Shireman et al. [6]) include time-dependent risk factors. The HAS-BLED score already accounts for some of these variables, enhancing its predictive value as a cumulative assessment of bleeding risk.

Conclusions

This analysis identifies diabetes and LV dysfunction as potential clinical correlates of bleeding in an anticoagulated clinical trial cohort of patients with nonvalvular AF. The HAS-BLED score may be a useful assessment of bleeding risk in AF patients in everyday clinical practice.

Acknowledgments

Investigators in the SPORTIF III and V are listed in references 17 and 18, respectively.

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Key Words: anticoagulation ▪ atrial fibrillation ▪ bleeding risk stratification ▪ risk factors.

Electrophysiology

Clinical classification schemes for predicting hemorrhage: Results from the National Registry of Atrial Fibrillation (NRAF)

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Background Although warfarin and other anticoagulants can prevent ischemic events, they can cause hemorrhage. Quantifying the rate of hemorrhage is crucial for determining the risks and net benefits of prescribing antithrombotic therapy. Our objective was to find a bleeding classification scheme that could quantify the risk of hemorrhage in elderly patients with atrial fibrillation.

Methods We combined bleeding risk factors from existing classification schemes into a new scheme, $HEMORR_2HAGES$, and validated all bleeding classification schemes. We scored $HEMORR_2HAGES$ by adding 2 points for a prior bleed and 1 point for each of the other risk factors: **h**epatic or renal disease, **e**thanol abuse, **m**alignancy, **o**lder (age > 75 years), **r**educed platelet count or function, **h**ypertension (uncontrolled), **a**nemia, **g**enetic factors, **e**xcessive fall risk, and **s**troke. We used data from quality improvement organizations representing 7 states to assemble a registry of 3791 Medicare beneficiaries with atrial fibrillation.

Results There were 162 hospital admissions with an *International Classification of Diseases, Ninth Revision, Clinical Modification* code for hemorrhage. With each additional point, the rate of bleeding per 100 patient-years of warfarin increased: 1.9 for 0, 2.5 for 1, 5.3 for 2, 8.4 for 3, 10.4 for 4, and 12.3 for ≥5 points. In patients prescribed warfarin, $HEMORR_2HAGES$ had greater predictive accuracy (*c* statistic 0.67) than other bleed prediction schemes ($P < .001$).

Conclusions Adaptations of existing classification schemes, especially a new bleeding risk scheme, $HEMORR_2HAGES$, can quantify the risk of hemorrhage and aid in the management of antithrombotic therapy. (Am Heart J 2006;151:713-9.)

Although warfarin and other anticoagulants can prevent stroke,[1-3] myocardial infarction,[4,5] and venous thromboembolism,[6,7] they often cause bleeding.[8-11] Anticoagulants, primarily warfarin, cause 10% of drug-related adverse events in Medicare outpatients.[12,13] Not only do these hemorrhages decrease the net benefit of anticoagulant therapy, but the fear of iatrogenic hemorrhage causes physicians to avoid anticoagulants in some patients with atrial fibrillation who are likely to benefit from them.[14-17]

Quantifying the risk of hemorrhage could improve the use of antithrombotic therapy in several ways. First, it would aid in patient selection by allowing clinicians to identify patients for whom the benefits of anticoagulants outweigh the risks. For example, clinical prediction rules for stroke[18-21] could be combined with bleeding risk schemes to identify patients with atrial fibrillation who are likely to benefit, rather than be harmed, from anticoagulant therapy.[22] Second, a valid bleeding risk scheme would allow clinicians to monitor antithrombotic therapy more carefully in patients at high risk of bleeding, thereby decreasing their risk of hemorrhage.[23] Finally, a prediction rule could help identify which asymptomatic patients with a supratherapeutic international normalized ratio (INR) should receive vitamin K. To date, no bleeding risk scheme has been developed or tested in elderly atrial fibrillation population, a growing population in whom clinicians are reluctant to prescribe anticoagulants because of fear of hemorrhage.[14-16,24,25]

Here, we adapt 3 previously published bleeding risk schemes[9-11] to Medicare beneficiaries with atrial

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This project was supported by the Agency for Healthcare Research and Quality (R01 HS10133) and by the American Heart Association.

The conclusions presented are solely those of the authors and do not represent those of the 5 peer review organizations, Agency for Healthcare Research and Quality, or Centers for Medicare and Medicaid Services. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services or does mention of commercial products imply endorsement of them by the US Government. The authors assume full responsibility for the accuracy and completeness of the ideas presented.

Submitted October 2, 2004; accepted April 28, 2005.

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0002-8703/$ - see front matter

doi:10.1016/j.ahj.2005.04.017

fibrillation and form a new scheme. Then we compare the accuracy of all 4 schemes in predicting hemorrhage.

Methods

Existing classification schemes for predicting hemorrhage

To find the existing clinical prediction rules for hemorrhage, we searched PubMed with keywords (anticoagulant OR coumarin) AND (Bleed# OR hemorrhage) AND (scheme OR risk assessment OR prediction rule OR decision support techniques OR statistical model#). This search identified 195 references. We obtained the full text of English-language articles that appeared to be relevant based on their title and abstract. We reviewed the bibliographies of relevant articles for pertinent references and searched an electronic database of >1000 articles about antithrombotic therapy that we update weekly.

We excluded 3 schemes that correlated risk of bleeding to maximum achieved INR because maximum INR is not known at the start of anticoagulant therapy.[26–28] We excluded one scheme because it performed no better than chance[29] and another that was tailored for patients receiving heparin.[30]

Ultimately, we were left with 3 schemes that quantified the association between comorbid conditions and bleeding: the Outpatient Bleeding Risk Index of Landefeld and Goldman[8] and Beyth et al,[9] the scheme of Kuijer et al,[10] and the scheme of Kearon et al.[11] None of these schemes had been developed in or evaluated in an elderly atrial fibrillation population.

Landefeld and Goldman[8] derived their original scheme in a cohort of 562 patients prescribed warfarin, primarily for placement of a prosthetic heart valve. It included 4 risk factors for major bleeding, each scored as 1 point: (1) age ≥65 years, (2) history of gastrointestinal bleeding, (3) history of stroke, and (4) any of 4 specific comorbid conditions (recent myocardial infarction, anemia, renal insufficiency, or atrial fibrillation). Nieuwenhuis et al[30] found that the original Landefeld scheme was not a valid predictor of short-term hemorrhage in 194 patients with acute venous thromboemboli. Subsequently, Beyth et al[9] modified the scheme by replacing atrial fibrillation with diabetes mellitus and found that this Landefeld-Beyth scheme performed well in an inception cohort of 264 participants.

Kuijer et al[10] developed 2 versions of a bleeding risk classification scheme in 241 patients with venous thromboembolism. They advocated use of the version that included 3 risk factors for major bleeding: age >60 years (1.6 points), female sex (1.3 points), and presence of malignancy (2.2 points).

In a study of 738 patients with prior venous thromboemboli, Kearon et al[11] evaluated the following risk factors for bleeding: age ≥65 years, previous stroke, previous peptic ulcer disease, previous gastrointestinal bleeding, renal impairment, anemia, thrombocytopenia, liver disease, diabetes mellitus, and the use of antiplatelet therapy. The rate of major bleeds per 100 patient-years of warfarin therapy was greater in patients who had ≥1 of these risk factors than in patients who had none.

To adapt these 3 schemes to this elderly population and to allow for a fair comparison, we used the same definition of increased age (≥75 years) for all schemes rather than the younger ages originally proposed. We chose 75 years as the threshold because of an increased risk of hemorrhage after this age,[31–33] and because 75 is the median age of the atrial fibrillation population.[34]

Development of the new classification scheme HEMORR$_2$HAGES

To form a new scheme, we included bleeding risk factors from the following sources: the 3 prior clinical prediction rules, a recent systematic review,[35] and our PubMed search. When combined, the predictors of major bleeding spelled "HEMORRHAGES": **h**epatic or renal disease, ethanol abuse, **m**alignancy, **o**lder (age > 75 years), **r**educed platelet count or function,[11,30] **r**ebleeding risk, **h**ypertension (uncontrolled), **a**nemia,[9,11,36] **g**enetic factors (CYP 2C9 single-nucleotide polymorphisms),[37–42] **e**xcessive fall risk (including neuropsychiatric disease),[42] and **s**troke. The relative risks (RRs) for each bleeding risk factor varied widely among studies, but the median RRs for most factors ranged from approximately 1.4 to 2.4.[35] Based on this observation and the merits of simplicity, we elected to weigh each bleeding risk factor 1 point, except that we awarded 2 points for a prior bleed (R in the mnemonic) because of its greater RR and named the new scheme "HEMORR$_2$HAGES." In a post hoc analysis, we awarded 1 point for prior bleed, but the results were similar to using 2 points and, therefore, are not shown. We identified these factors from structured medical record abstraction supplemented with *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes (Appendix A). Because we did not have access to DNA, we were not able to capture genetic risk factors for bleeding.

Formation of the National Registry of Atrial Fibrillation data set

As previously detailed,[18] the National Registry of Atrial Fibrillation (NRAF) contains de-identified patient records gathered by 5 quality improvement organizations (QIO). The participating QIOs serve 7 states (California, Connecticut, Louisiana, Maine, Missouri, New Hampshire, and Vermont). These QIOs had assembled state-specific cohorts of patients with atrial fibrillation for quality improvement projects under the Health Care Quality Improvement Initiative of the Centers for Medicare and Medicaid Services (CMS)[43]; no additional charts were abstracted to create the NRAF data set. Using Medicare Provider Analysis and Review (MEDPAR) Part A records, QIO reviewers used the appropriate *ICD-9-CM* code (427.31) in either a principal or secondary diagnosis to identify Medicare beneficiaries who had atrial fibrillation. Through structure medical record review, QIO reviewers confirmed the presence of chronic or recurrent atrial fibrillation during the index hospitalization. They also documented comorbid conditions and the antithrombotic therapy prescribed at hospital discharge.

To obtain outcomes, reviewers linked abstractions of index hospitalizations to MEDPAR records and the denominator file of living Medicare beneficiaries. After linking follow-up data and removing identifiers, the QIOs sent the de-identified records to Washington University for inclusion into the NRAF data set. The study was approved by the human subjects' committee at the Washington University Medical Center, the participating QIOs, and CMS.

We used the QIO records to develop the NRAF data set of Medicare beneficiaries who had chronic or recurrent atrial fibrillation. We obtained 7 bleeding risk factors from the

Table I. NRAF participants

Bleeding risk factor	Warfarin (n = 1604)	Aspirin (n = 660)	Neither (n = 1527)
Hepatic or renal disease (%)	7.9	12	12
Ethanol abuse (%)	0.7	0.5	0.9
Malignancy (%)	4.8	3.2	9
Older (age >75 y) (%)	69.2	78.4	76.6
Reduced platelet count or function* (%)	9.6	100	5.2
Rebleeding risk (%)	15.9	21.4	22.1
Hypertension (uncontrolled) (%)	0.4	0.5	0.6
Anemia (%)	8.5	10.5	14.8
Genetic factors (%)	NA	NA	NA
Excessive fall risk or neuropsychiatric disease (%)	18.8	27.7	24.1
Stroke (%)	37.2	30	23.6
Mean HEMORR$_2$HAGES score	1.9	3.1	2.1

NA, Not available.
*When aspirin use is excluded, the percentages are 2.6, 1.7, and 5.2.

medical record reviews and 4 from the appropriate *ICD-9-CM* codes from the index hospitalization (Appendix A).

Outcomes assessment

The study outcome was time to hospitalization for hemorrhage, as determined by Medicare claims. To identify major bleeds from the MEDPAR data, we used *ICD-9-CM* codes validated by White et al,[44] except that we excluded 3 *ICD-9-CM* codes that were unrelated to antithrombotic therapy and added *ICD-9-CM* codes that had appropriate definitions or high positive predictive value.[45] To improve sensitivity in identifying major bleeds and based on recent findings, we included *ICD-9-CM* codes for hemorrhage in any position, rather than only the primary one. To improve specificity, we used the fifth digit to include only active hemorrhage.

We censored beneficiaries at the time of the first post–baseline hospitalization or at a maximum of 1000 days after the baseline hospitalization. We excluded patients who died outside of hospital and had no post–baseline hospitalizations because the presence of hemorrhage at the time of death could not be determined.

Statistical analyses

We used the κ statistic[46] to quantify the agreement (corrected for chance) between the schemes in classifying patients into low-, medium-, or high-risk for hemorrhage. We quantified the discriminant ability of the classification schemes with the c statistic.[47] In this setting, c reflects concordance of predicted and observed hemorrhage-free time, with $c = 0.5$ for no discriminative ability and $c = 1.0$ for perfect discriminative ability. We compared c values of the schemes in 500 bootstrapped samples[48] and derived 95% CIs for the differences between schemes, using the percentile method. We also compared how well schemes improved the prediction of hemorrhage using a Cox proportional hazard model and Graf-modified Brier scores.[49] Because these 2 statistics agreed with the c statistics, we report only the latter. We performed statistical analyses in SAS (SAS Institute Inc, Cary, NC). All comparisons were 2-tailed, and P values < .05 were considered statistically significant.

Table II. Risk of major bleeding in NRAF participants prescribed warfarin, stratified by HEMORR$_2$HAGES score

HEMORR$_2$HAGES score*	n	No. of bleeds	Bleeds per 100 point-years warfarin (95% CI)
0	209	4	1.9 (0.6-4.4)
1	508	11	2.5 (1.3-4.3)
2	454	20	5.3 (3.4-8.1)
3	240	15	8.4 (4.9-13.6)
4	106	9	10.4 (5.1-18.9)
≥5	87	8	12.3 (5.8-23.1)
Any score	1604	67	4.9 (3.9-6.3)

*HEMORR$_2$HAGES is scored by adding 1 point for each bleeding risk factor: hepatic or renal disease, ethanol abuse, malignancy older (age > 75 years), reduced platelet count or function, rebleeding risk (2 points), hypertension (uncontrolled), anemia, genetic factors (not available in this study), excessive fall risk, and stroke.

Results

The NRAF data set included 3932 Medicare beneficiaries with chart-confirmed atrial fibrillation. After excluding records with missing information (n = 141), we analyzed the remaining 3791 patients. Mean age was 80.2 years, and 57% of the cohort was women. During 3138 patient-years of follow-up, there were 162 admissions with a bleed (5.2 bleeds per 100 patient-years). Two thirds (67.3%) of these bleeds were gastrointestinal hemorrhages, 15.4% were intracranial, and 17.3% were in other locations. The 30-day mortality of patients admitted with a bleed (in any location) was 21.6%.

One thousand six hundred four (1604) patients were discharged on warfarin (113 of whom also received aspirin), 660 patients were discharged on aspirin (or a thienopyridine) alone, and 1527 were prescribed no antithrombotic therapy on discharge. Compared with patients discharged on warfarin (mean age 79 years), patients discharged on aspirin or no antithrombotic therapy were older (mean age 81 years) and had more risk factors for bleeding (Table I): the mean HEMORR$_2$HAGES score was 1.9 in patients prescribed warfarin, 3.1 in patients prescribed aspirin (2.1 if aspirin use did not count toward reduced platelet count/function), and 2.1 in patients not prescribed with antithrombotic therapy ($P < .001$). Unadjusted bleeding rates were slightly greater in the aspirin cohort: 4.9 bleeds per 100 point-years warfarin, 5.9 bleeds per 100 patient-years aspirin, and 5.1 bleeds per 100 patient-years without antithrombotic therapy.

Agreement between the bleeding risk schemes

To assess agreement, we classified patients with a score of 0 or 1 on HEMORR$_2$HAGES or the scheme of Kearon as low-risk, 2 or 3 as intermediate-risk, and ≥4 as high-risk. Then we compared low-, medium-, and high-risk cohorts from all 4 schemes. Weighted κ statistics indicated poor agreement between schemes, ranging from a low of 0.14

Table III. Risk of major bleeding in NRAF participants prescribed warfarin, stratified by prior risk-classification schemes

Scheme	Risk score	n	Bleeds per 100 patient-years warfarin (95% CI)	Originally reported bleeds per 100 point-years warfarin* (95% CI or range)
Landefeld and Goldman,[8]	0	169	1.1 (0.3-4.3)	0-3
Beyth et al,[9] and Wells et al[54]	1-2	1174	4.9 (3.6-6.5)	4.3-12
	3-4	261	8.8 (5.6-14.0)	30-48
Kuijer et al[10]	0	225	2.9 (1.3-6.5)	0-4
	>0 and <3	1312	5.2 (4.0-6.7)	1-8
	≥3	67	7.5 (2.8-19.9)	24-43
Kearon et al[11]	0	181	2.5 (1.1-6.1)	0.2-0.4
	1	603	2.5 (1.4-4.3)	1.8-2.0
	2	537	6.5 (4.5-9.4)	1.0-2.3
	3	229	9.3 (5.7-15.3)	NA
	≥4	54	15.3 (6.4-36.8)	NA

*Bleeding rates from Kuijer et al[10] are cumulative percentages for 3 months rather than 1 year.

Table IV. *c* Indices quantifying ability of schemes to predict major hemorrhage, stratified by therapy

	c Indices (SD), stratified by cohort		
Scheme	Warfarin (n = 1604)	Aspirin (n = 660)	Neither (n = 1527)
Landefeld and Goldman[8] and Beyth et al[9]	0.65 (0.03)	0.69 (0.05)	0.65 (0.03)
Kuijer et al[10]	0.58 (0.03)	0.58 (0.05)	0.47 (0.03)
Kearon et al[11]	0.66 (0.03)	0.64 (0.05)	0.66 (0.04)
HEMORR$_2$HAGES	0.67* (0.04)	0.72* (0.05)	0.66 (0.04)

*$P < .001$ compared with the other 3 schemes (analysis of variance test).

(for Kuijer vs Kearon) to a high of 0.52 (for HEMORR$_2$HAGES vs Kearon). Thus, the 4 bleeding schemes classified patients very differently.

Bleeding rates were lower in low-risk patients and greater in high-risk patients, validating all schemes (Tables II and III). The highest bleeding rate was 15.3 per 100 patient-years of warfarin in patients with a Kearon score of ≥4.

Validation of the schemes in patients prescribed warfarin (n = 1604)

Among Medicare beneficiaries prescribed warfarin, HEMORR$_2$HAGES had the best discriminant ability (Table IV). In 500 bootstrapped samples, the *c* index for HEMORR$_2$HAGES was 0.67, significantly greater than the *c* index for the other schemes ($P < .001$).

The 660 patients prescribed aspirin on discharge were admitted with 30 bleeds. HEMORR$_2$HAGES also had a better discriminant ability than the other schemes in this cohort: the *c* statistic for HEMORR$_2$HAGES was 0.72, significantly ($P < .001$) greater than *c* for the other schemes (Table IV). Comparison of the likelihood ratio χ^2 values from Cox models corroborated our finding that HEMORR$_2$HAGES was the most accurate predictor of bleeding in the warfarin and aspirin cohorts.

The 1527 patients prescribed no antithrombotic therapy at hospital discharge were admitted with 65 bleeds. In this cohort, HEMORR$_2$HAGES and Kearon et al[11] both had the greater *c* index (0.66).

Discussion

HEMORR$_2$HAGES and adaptations of 3 previously existing bleeding risk classification schemes successfully quantified the rate of hemorrhage in 3791 Medicare beneficiaries with atrial fibrillation. Our finding that the schemes, especially HEMORR$_2$HAGES, accurately predicted bleeding is important because although prior studies have quantified the rate of stroke in atrial fibrillation,[18,21,50] only 2 smaller studies have quantified the rate of bleeding in this growing population.[51,51] Quantifying the rate of bleeding is important because fear of hemorrhage is a major reason why antithrombotic therapy has been underused in patients with atrial fibrillation.[14,16]

The average rate of hospitalization for bleeding in patients prescribed warfarin was 4.9 per 100 patient-years, but the rate depended on the number of comorbid conditions. High-risk patients identified by any of the schemes had a hemorrhage rate (7.5-15.3) much greater than the rate in low-risk patients (1.1-2.9), validating the ability of the schemes to risk-stratify elderly patients with atrial fibrillation. For comparison, the rate of major bleeding in atrial fibrillation trials averaged 2.4 major bleeds per 100 patient-years of warfarin therapy.[2,3,52] Trial participants were elderly (mean age 72 years) but, otherwise, had few risk factors for bleeding.

Studies that exclusively enrolled patients new to warfarin reported greater rates of bleeding.[8-10,53,54] In particular, bleeding in the inception cohorts studied by Landefeld and Goldman,[8] Beyth et al,[9] and Kuijer et al[10]

had higher rates of bleeding, at least in high-risk cohorts (Table III). In contrast, participants enrolled by Kearon et al[11] (Table III) had successfully taken warfarin therapy for at least 3 months before enrolling in that trial, which contributed to their low bleeding rates. Half of the participants of Kearon were randomized to low-dose warfarin (target INR 1.5-1.9), which also may have prevented bleeds.

Adaptations of the 3 original schemes to the Medicare beneficiaries had lower discriminant ability than reported from the original studies. In 264 outpatients beginning warfarin, Beyth et al [9] found a *c* statistic of 0.78, whereas we found a value of 0.65 for their scheme in the Medicare beneficiaries with atrial fibrillation who were prescribed warfarin. Likewise, Kuijer et al[10] found an area under the curve of 0.82 in their derivation cohort of 241 patients beginning a coumarin for an acute venous thromboembolism, whereas we calculated a *c* index of 0.58 for their scheme. The lower discriminant accuracy in our study, compared with the original smaller studies, highlights the need to study clinical prediction rules in different populations.

Our study had limitations inherent to use of inpatient administrative data. First, we imputed several bleeding risk factors from *ICD-9-CM* codes and used validated *ICD-9-CM* codes to identify incident hemorrhages. Thus, we could only capture bleeds that resulted in an in-state hospitalization. Second, we knew the antithrombotic therapy prescribed at hospital discharge but could not identify changes in or compliance with that therapy. The net effect of these 2 limitations is that all schemes might perform better in clinical practice than reported here. A minor limitation is that we could not determine whether supratherapeutic INR values or other factors (eg, use of heparin or invasive procedures) contributed to bleeding.

These limitations are offset by important strengths. First, the bleeding risk schemes were validated in a cohort of Medicare beneficiaries from 7 states representing diverse geographic regions of the United States. Second, we had more patients and more major bleeds in our study than prior studies of bleeding schemes combined.[8-11,54] Third, because HEMORR$_2$HAGES was derived from the literature rather than being data-driven, our study validates HEMORR$_2$HAGES in Medicare beneficiaries with atrial fibrillation. Fourth, our study population had many bleeding risk factors, allowing us to quantify the risk of hemorrhage for a wide range of comorbid conditions with precision. Finally, we used structured medical record review, rather than *ICD-9-CM* claims, to document the presence of atrial fibrillation, prescription of antithrombotic therapy, and most of the bleeding risk factors.

Although the present study validates HEMORR$_2$HAGES in Medicare beneficiaries with atrial fibrillation, the scheme was developed without reference to a specific patient population and therefore should be generalizable to other populations. For example, clinicians could use HEMORR$_2$HAGES to help select patients with a recent myocardial infarction who could be treated with aggressive antithrombotic therapy rather than aspirin alone,[4,55-57] patients with venous thromboemboli who can safely be treated long-term with an anticoagulant,[6,11] and patients with mechanical valves who could add aspirin to their anticoagulant.[58,59] For all 3 of these disease states, the more aggressive antithrombotic regimens are more effective at preventing ischemic events but can only be justified when they are unlikely to cause bleeding. Because HEMORR$_2$HAGES was a valid predictor of hemorrhage in patients who were prescribed warfarin or aspirin, it may be a valid predictor of hemorrhage in patients prescribed newer anticoagulants.[3,52]

In summary, the decision to take antithrombotic therapy should be based on individual risks and benefits. For example, by combining HEMORR$_2$HAGES with a clinical prediction rule for stroke,[18,21,50] clinicians can trade off the risks and benefits of prescribing anticoagulant versus antiplatelet therapy in elderly patients with atrial fibrillation.[22] Patients with a high risk of bleeding could avoid anticoagulants unless their risks of stroke were high enough to justify the risks, in which case they could take anticoagulants with vigilant monitoring.

We thank the CMS and the 5 QIOs who provided the de-identified data that made this research possible. The chart abstractions were performed as part of the Health Care Quality Improvement Initiative that was initiated and sponsored by CMS: under CMS contract number 500-99-CA02, Utilization and Quality Control PRO for the State of California, the California Medical Review, Inc, provided data on 549 Medicare beneficiaries from 1993 to 1998; under CMS contract number 500-96-P549, Utilization and Quality Control PRO for the State of Connecticut, Qualidigm provided data on 1598 Medicare beneficiaries from 1994 to 1997; under CMS contract number 500-99-LA02, Utilization and Quality Control PRO for the State of Louisiana, the Louisiana Health Care Review, Inc, provided data on 531 Medicare beneficiaries from 1996 to 1998; under CMS contract number 500-96-P612, Utilization and Quality Control PRO for the State of Missouri, the Missouri Patient Care Review Foundation provided data on 597 Medicare beneficiaries from 1993 to 1996; and under CMS contracts number 500-99-ME01, number 500-99-NH01, and number 500-99-VT01, Utilization and Quality Control PRO for the States of Maine, New Hampshire, and Vermont, the Northeast Health Care Quality Foundation provided data on 657 Medicare beneficiaries from 1996 to 1998.

We also thank Susan Gatchel and Elena Birman-Deych for their help.

Author contributions. Study concept and design: Drs Gage, Rich, and Radford; acquisition of data: Drs Gage, Waterman, and Radford; analysis and

interpretation of data: Drs Gage, Yan, Rich, and Radford; drafting of the manuscript: Drs Gage, Yan, and Milligan; critical revision of the manuscript for important intellectual content: Drs Gage, Yan, Milligan, Waterman, Culverhouse, Rich, and Radford; statistical expertise: Drs Yan and Culverhouse; obtained funding: Drs Gage, Waterman, and Radford; study supervision: Dr Gage.

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Appendix A

Data source for bleeding risk factors

Bleeding risk factor	Data source
Hepatic or renal disease	Chart review: some QIOs included only end-stage renal disease; others included patients with a creatinine >2.5 mg/dL and patients with end-stage liver disease or cirrhosis
Ethanol abuse	ICD-9-CM codes: 291.0-2, 303.x, 305.0x, 571.0-3, 535.3
Malignancy	ICD-9-CM codes: 141-172, 174-208
Older age	Chart review for age >75 years
Reduced platelet count or function	Chart review for aspirin use or thrombocytopenia; QIO review captured blood dyscrasias (eg, hemophilia) in some states
Rebleeding risk	Chart review for prior bleeding
Hypertension (uncontrolled)	ICD-9-CM codes: 401.0, 402.0x, 403.0x, 404.0x, 405.0x
Anemia	ICD-9-CM codes: 280.x, 281.x, 282.0-4, 282.60, 282.69, 283.x, 284.x, 285.x
Genetic factors	Not available in this study
Excessive fall risk	Chart review for: high risk of falling, dementia, Parkinson disease, or psychiatric disease
Stroke	Chart review or ICD-9-CM codes 434-436 in the primary position

ICD-9-CM codes are from the baseline hospitalization.

PROMOTING ADOPTION & USE

This roundtable has been convened because the Task Force and many prominent experts believe that the current state of practice surrounding the use of anticoagulants to treat atrial fibrillation is inadequate for many providers and patients. At the end of this roundtable, the forged consensus on the best tool(s) to assess whether or not a patient should start anticoagulation therapy will inform a number of advocacy activities led by the Alliance for Aging Research and the AFib Optimal Treatment Task Force. These activities will facilitate the medical community's adoption of the consensus and influence provider behavior and may include:

- Working with the Centers for Medicare and Medicaid Services (CMS) and private insurers to include anticoagulants and atrial fibrillation in their medication therapy management (MTM) programs.
- Engaging with various quality organizations to establish quality measures surrounding the use of the treatment tools in order to increase adoption and compliance. A quality measure linked to payment could drastically increase adoption.
- Raising awareness of and disseminating the consensus to key stakeholder (e.g. providers, patient organizations, and payers) through various communication networks and channels—thereby increasing the velocity of adoption in the health care community.

Medication Therapy Management

The Medicare Modernization Act of 2003 (MMA) established requirements that Part D sponsors must meet with regard to cost control and quality improvement including requirements for Medication Therapy Management (MTM) programs. Targeted beneficiaries for the MTM program are enrollees in Part D plans who have multiple chronic diseases, are taking multiple Part D drugs, and are likely to incur annual costs for covered Part D drugs that will place them in the coverage gap. Part D sponsors must offer a minimum level of medication therapy management services for each beneficiary enrolled in the MTM program that includes interventions for both beneficiaries and prescribers. They must also offer a comprehensive medication review (CMR) by a pharmacist or other qualified provider at least annually and perform quarterly medication reviews with follow-up interventions when necessary. The purpose of an MTM program is to ensure optimum therapeutic outcomes for targeted beneficiaries through improved medication use and reduce the risk of adverse events.

There are currently no MTM programs specifically for AFib.[5] However, the assessments on which a consensus is reached may be used as part of an MTM program for atrial fibrillation in the future. An MTM program for patients with atrial fibrillation is optimal because this population has a high prevalence of chronic health conditions and is likely to be treated with multiple drugs. Additionally, those living with atrial fibrillation often require careful monitoring of their use of over the counter drugs, including antihistamines, sleep aids and dietary supplements, which can interfere with rate control and anti-arrhythmic medications.

The following is a broad example of how an MTM program could incorporate this roundtable's consensus and change provider and patient behavior:

- The MTM program could support physician adoption and use of consensus risk assessments on patients with a diagnosis of atrial fibrillation.
- For certain scores on the risk assessments, the MTM program could suggest a recommended anticoagulant regime.

[5] 2010 Medicare Part D Medication Therapy Management (MTM) Programs. Centers for Medicare & Medicaid Services. June 8, 2010. https://www.cms.gov/prescriptiondrugcovcontra/downloads/MTMFactSheet.pdf.

- The MTM program could also cue pharmacists to provide certain counseling or educational material to the patient starting anticoagulant therapy.
- The MTM program could include patient supports to monitor and encourage therapy compliance.

The roundtable's consensus will be used to inform which of these parameters is best and formulate a recommendation on an atrial fibrillation MTM program to propose to Medicare. Formulation of a recommendation and strategic actions towards implementation may include:

- Surveying current MTM programs associated with heart failure to extract elements that may be useful for an atrial fibrillation MTM program.
- Convening key stakeholders from professional societies, advocacy organizations, academia and industry to design and form support around an atrial fibrillation MTM program.
- Meeting with CMS and payer groups to determine any barriers to adoption of an atrial fibrillation MTM program.
- Working with specialty societies (e.g. American College of Cardiology) to get endorsement of an atrial fibrillation MTM program.

All of this work paves the way for the federal rulemaking process in which CMS establishes which disease states it includes in its core MTM programs. Comments on the proposed rules for calendar year 2014 will be due in the fall of 2012. Over the next year comments could be submitted that detail a vetted atrial fibrillation MTM program.

Quality Measures

Establishing quality measures surrounding the use of anticoagulants in atrial fibrillation could increase consensus adoption and compliance by one or any combination of the following measure usages:

- Develop and disseminate measures for use by providers for internal quality improvement, recording, processes and health outcome measurement for anticoagulant use with atrial fibrillation patients.
- Incorporate metric based on the roundtable consensus into Medicare's existing quality improvement initiatives, such as the Hospital Inpatient Quality Reporting Program (described below), the Value Based Purchasing Program, readmissions, and the Physician Quality Reporting System to report on use of assessment tools when utilizing anti-coagulants
- Enabling providers to compare their performance against those of their peers, and patients to choose providers based on health outcomes.

In these ways, establishing measures around the risk assessment tools for anticoagulant use can spread awareness of the assessment consensus and deliver the optimal care, at the right time, in the appropriate setting.

National Quality Forum

The National Quality Forum (NQF) is a nonprofit organization that operates under a three-part mission to improve the quality of American healthcare by 1) building consensus on national priorities and goals for performance improvement and working in partnership to achieve them; 2) endorsing national consensus standards for measuring and publicly reporting on performance; and 3) promoting the attainment of national goals through education and outreach programs.[6] The NQF is one of the main endorsement bodies that providers and Medicare look to when establishing quality measures internally or across the Medicare system.

[6] About NQF. National Quality Forum. http://www.qualityforum.org/About_NQF/About_NQF.aspx.

National Committee on Quality Assurance

The National Committee for Quality Assurance (NCQA) is a not-for-profit organization dedicated to improving health care quality. NCQA has helped to build consensus around important health care quality issues by working with large employers, policymakers, doctors, patients and health plans to decide what is important, how to measure it, and how to promote improvement.[7]

As with NQF, the NCQA is a main body that providers and Medicare look to when deciding upon measures to include for internal tracking or across the Medicare system to improve health outcomes for beneficiaries.

Quality Measurement Submission Process

One of the main determinants as to whether a measure is adopted is the scientific acceptability of the measure's properties. Therefore, this roundtable is vitally important in ensuring the adoption of any anticoagulant risk assessment measures. The formal measurement submission and approval process takes a minimum of six months. However, the entire process can be a multi-year project. For example:

- Measures may be submitted to the NQF at any time to indicate "readiness" of a measure. The "readiness" process for our efforts begins with this roundtable and its consensus.
- After the consensus is established, AAR and its partners will begin the process of securing endorsement from professional societies and key opinion leaders.
- The NQF will then work with the steward of the measure (e.g. the American College of Cardiology) to identify any projects for which the measure may be appropriate and discuss next steps to enable submission of the measure
- During this process and depending on what measures are appropriate from the consensus, AAR and its partners will strategize on which of the above implementation means of the measures are optimal.
- AAR and its partners will meet with CMS officials to determine any barriers to the adoption and implementation of anticoagulation risk assessment measures.

An NQF or NCQA endorsed measure usually has to go through the federal rulemaking process to be part of any of Medicare's quality measurement programs. An example of such a program is the Hospital Inpatient Quality Reporting Program, detailed below.

Centers for Medicare & Medicaid Services and the Hospital Inpatient Quality Reporting Program

The Hospital Inpatient Quality Reporting (IQR) program is an example of how measures are tied to Medicare reimbursement. The IQR requires all hospitals (excluding psychiatric hospitals, rehabilitation hospitals, children's hospitals, long term care facilities, and cancer specialty hospitals) to submit data for specific quality measures for health conditions common among people with Medicare, and which typically result in hospitalization. Eligible hospitals that do not participate in the Hospital IQR program receive a 2.0 percent reduction in their annual market basket update.[8]

The following three measures have recently been added to the Hospital IQR program and are distinctly related to AFib:

- Stroke (STK)-2: Discharged on Antithrombotic Therapy: Percent of patients with an ischemic stroke prescribed antithrombotic therapy at discharge (NQF #0435).

[7] About NCQA. National Committee for Quality Assurance. http://www.ncqa.org/tabid/675/Default.aspx.

[8] Hospital Inpatient Quality Reporting (IQR) Program Overview. QualityNet. Accessed August 30, 2011. http://qualitynet.org/dcs/ContentServer?c=Page&pagename=QnetPublic%2FPage%2FQnetTier2&cid=1138115987129.

- Stroke (STK)-3: Anticoagulation Therapy for Atrial Fibrillation/Flutter: Percent of patients with an ischemic stroke with atrial fibrillation discharged on anticoagulation therapy (NQF #0436).
- Stroke (STK)-5: Antithrombotic Therapy By End of Hospital Day 2: Percent of patients with ischemic stroke who receive antithrombotic therapy by the end of hospital day two (NQF #0438).[9]

Health Reform Implementation

There are several major provisions of the Patient Protection and Affordable Care Act (PPACA) that will shift the healthcare landscape in the coming years. Some of these provisions potentially offer opportunities to promote the adoption of assessments for appropriate use of anticoagulants with atrial fibrillation patients.

The changes to the Medicaid program under the PPACA significantly expand Medicaid. When the law's provisions go into effect in 2014, the Congressional Budget Office (CBO) predicts that there will be a 25 percent increase in people who get their insurance through Medicaid (with 45 million Medicaid-insured lives instead of 36 million without health reform). The number of Medicaid enrollees grows from nine million in 2014 to 17 million in 2021 under current estimates. Engaging with state Medicaid Directors now, has the potential to have an impact on the growing rolls of Medicaid recipients in 2014.

Likewise, the implementation of health insurance exchanges will create an entirely new market. The exchanges are expected to enroll nine million people in 2014, increasing to 24 million in 2021. The idea is that each state will create a marketplace where consumers can compare and enroll for health insurance partially subsidized by the federal government. The federal government initially expected states to run the exchanges, and planned to offer a federal exchange as a back-up plan for states that could not or would not implement their own exchanges. Health insurance policies offered through the exchanges will have to meet certain requirements, including quality reporting, effective case management, care coordination, chronic disease management, and medication and care compliance initiatives. Engaging with private payers on some of these initiatives is another possible avenue for promotion and adoption of this roundtable's consensus.

Additionally, the 50 million people who get their insurance through Medicare are an increasingly important and growing population as "baby-boomers" enter retirement. The Centers for Medicare and Medicaid (CMS) has a number of initiatives underway to encourage increased access to primary care, care management, support for greater coordination among health care providers, electronic prescribing, programs to reduce obesity, and others. Some of these initiatives, like care management and coordination, may provide additional opportunities for promotion and adoption of the consensus.

Lastly, accountable care organizations (ACOs) are intended to incentivize higher quality care and more positive outcomes through shared savings and investment. ACO models are still being designed and transitioning from concepts to reality. However, there is a possibility these models will offer an opportunity for assessments like the consensus to be utilized to coordinate and ensure accountability for care within an ACO.

Dissemination

Lastly, AAR and its partners would employ many dissemination strategies including updates to providers and payers through Medicare Learning Network (MLN) Matters® Articles, publication of the consensus statement in peer-reviewed journals and professional publications, production of health care professional

[9] 76 *Fed. Reg.* at 51634.

education materials, and development of mobile applications. The purpose of this dissemination is to raise awareness and drive adoption during parallel efforts to gain an MTM program or establish quality measures. All of these actions are aimed at improving care and health outcomes for patients.

Medicare Learning Matters

A consensus document, as it applies to Medicare, could be disseminated via Medicare Learning Matters (MLN). MLN Matters® are national articles designed to inform Medicare FFS providers about the latest changes to the Medicare Program (commonly referred to as Change Requests). Articles are prepared in consultation with clinicians, billing experts, and CMS subject matter experts. They are tailored, by content and language, to specific provider type(s) who are affected by complex Medicare changes. MLN Matters® articles help explain critical provider information in an effort to reduce the amount of time providers need to incorporate these changes into their Medicare-related business functions.

Continuing Medical Education

The consensus document content could be disseminated via specialty targeted continuing medical education (CME) programs. CME credits can be obtained in live events, via the internet or via journals.

Peer Reviewed Journal Articles

The content from the consensus document could be published in peer reviewed general medical journals (e.g. Journal of the American Medical Association (JAMA), The New England Journal of Medicine) or specialty targeted medical journals (e.g. Stroke, Heart, Circulation.)

Mobile and Software Applications

Dissemination of the consensus document content could be distributed via mobile and software applications. For example the American Medical Association (AMA) is using a widely used mobile program to conduct a CME program "Factors That May Influence the Safety and Efficacy of Antiplatelet Therapy: A Key To Their Hearts Educational Activity."[10]

SmartPhone and Device applications (apps) could also be developed to assist use of the tools recommended by the consensus.

[10] ePocrates CME. ePocrates. https://www.epocrates.com/cmeLanding.do.

ABOUT US

About the Alliance for Aging Research

The private, not-for-profit Alliance for Aging Research is a national citizen advocacy organization working to improve the lives of Americans as they grow older by advancing biomedical and behavioral research in aging and health. The Alliance was founded in 1986 to promote and accelerate medical and scientific research into aging. As America's Baby Boom is transformed to an unprecedented Senior Boom, the Alliance is a valued and respected voice in the nation's capital: developing, implementing and advocating programs in research, health education and public policy.

The Alliance believes that science can help people live longer, more productive lives. Greater access to the latest scientific information will empower people to take control of their own health, while educating them on the importance and need for further medical advances. From policy issues to consumer health programs, the Alliance works to generate knowledge and action on age-related issues.

Simply speaking, we strive to *advance science* and *enhance lives* through a variety of activities and initiatives. The Alliance has made aging research a fast growing priority for medical research today. Since 1986 federal support for aging research has more than tripled, private research and development in aging-related health has reached an all time high, and new discoveries are making a lasting difference to the lives of millions of Americans.

About Applied Policy

Applied policy, LLC is a health policy consulting group strategically located in the Washington, D.C. metropolitan area. At Applied Policy, our governing principle is transforming intention into action. Taking into account our clients' objectives, we help make our federal system work as it is intended. We partner with our clients to develop strategies to achieve goals that advance their missions. Our tactics are to identify new opportunities, reframe challenges, empower people with information and create mutually beneficial solutions that foster long-term stakeholder relationships. These tactics facilitate our clients' desired outcomes by enabling effective navigation of the complex landscape of legislation, regulations, bureaucracy and diverse interests in Washington, D.C.

The Applied Policy team collaborates with clients to develop and execute strategies that plan for, respond to and resolve legislative, regulatory and other governmental health care opportunities and threats. Based on our full engagement with health policy, we are able to identify and predict conditions that could affect the achievement of our clients' objectives. We have over fifteen years of experience working within the Washington, D.C. health policy community and are positioned to leverage that expertise to utilize the best relationships, medium and strategies to further our clients' missions. As we intimately engage with our clients, we are able to identify and deliver the ideas, tools, skills and resources necessary to achieve results.

About the AFib Optimal Treatment Task Force Members

Anticoagulation Forum

The Anticoagulation Forum is a multidisciplinary nonprofit organization of health care professionals that will improve the quality of care for patients taking antithrombotic medications. The Anticoagulation Forum will minimize the risk and maximize the benefit of strategies used for the prevention and treatment of thromboembolic disease by providing education and networking opportunities for health care professionals, promoting the clinical application of evidence-based practices, and facilitating research aimed at improving health outcomes.

Atrial Fibrillation Association – US

AFA – US is a non-profit organization which focuses on raising awareness of Atrial Fibrillation (AF) by providing information and support materials for patients and medical professionals involved in detecting, diagnosing and managing Atrial Fibrillation.

AFA-US works closely with medical professionals, The American College of Cardiology (ACC), Heart Rhythm Society (HRS), patient advocacy groups and allied professionals. All publications and literature published by AFA-US have been approved by an AF medical panel and endorsed by ACC. The Fact sheets currently available include titles on: Atrial Fibrillation, Blood Thinning and AF, Beta-Blockers, Cardioversion, Warfarin and Diet and Warfarin and Other Medication.

AFA-US is fortunate to have Dr Peter Spector, MD, Dr Hugh Calkins, MD, Dr Kalyanam Shivkumar, MD PhD and Dr. Andrea Natale as Medical Advisory Members. Professor A. John Camm is President and Co-Founder; Mrs Trudie Lobban, MBE is Co-Founder and Director and Mrs Joanne Jerrome is Assistant Director. Lisa Cartin is the Information and Development Officer and Francesca Lobban is the Project Manager.

AFA aims to: provide support and information on atrial fibrillation to those affected by this condition, advance the education of the medical profession and the general public on the subject of atrial fibrillation, and promote research into the management of atrial fibrillation.

ClotCare

ClotCare strives to help others improve lives by providing both patients and health care providers with the most up-to-date information and expert insight on optimal use of antithrombotic and anticoagulant therapy. In achieving this end, ClotCare seeks to be the premier source to which patients and clinicians turn to get information on these therapies used to prevent and/or treat unwanted blood clots that cause heart attacks, strokes, and other potentially catastrophic events.

Heart Rhythm Society

The Heart Rhythm Society is the international leader in science, education and advocacy for cardiac arrhythmia professionals and patients, and the primary information resource on heart rhythm disorders. Our mission is to improve the care of patients by advancing research, education, and optimal health care policies and standards.

Mended Hearts

Mended Hearts has been offering the gift of hope to heart disease patients, their families and caregivers for 60 years. Recognized for its role in facilitating a positive patient-care experience, Mended Hearts partners with 460 hospitals and rehabilitation clinics and offers services to heart patients through visiting programs, support group meetings and educational forums. Our mission is to "inspire hope in heart disease patients and their families."

Because Mended Hearts is made up of the very kinds of people it serves—heart patients, their families, and others impacted by heart disease, its members draw on personal experience as they help others. Mended Hearts support groups help people understand that there can be a rich, rewarding life after heart disease. Members listen, share their experiences, learn from health care professionals and volunteer to talk to other heart patients about what they may face including lifestyle changes, depression, recovery, and treatment. Annually, Mended Hearts volunteers make visits to patients, family members and caregivers in hospitals, online and by phone.

Men's Health Network

Men's Health Network (MHN) is a national non-profit organization whose mission is to reach men and their families where they live, work, play, and pray with health prevention messages and tools,

screening programs, educational materials, advocacy opportunities, and patient navigation. With a network of chapters, affiliates, and health partners, MHN has a presence in every state and over 30 countries. We hope to achieve the following goals:

- To save men's lives by reducing the premature mortality of men and boys.
- To improve the physical and mental health of men so that they can live fuller and happier lives.
- Work with/through women as the family's health care leader to reach men with critical health messages.

For more information about the Men's Health Network please visit www.menshealthnetwork.org – write to info@menshealthnetwork.org – or call 202.543.6461 x 101.

National Forum for Heart Disease and Stroke Prevention

The National Forum for Heart Disease and Stroke Prevention was founded in 2003 to implement A Public Health Action Plan to Prevent Heart Disease and Stroke ("Action Plan"). The Action Plan provides a comprehensive public health strategy and a framework to guide health practitioners and policymakers' action in heart disease and stroke prevention. The National Forum is a 501(c)3 organization. The National Forum's mission is to provide leadership and encourage collaborative action between organizations committed to heart disease and stroke prevention.

The National Forum involves participants from more than 85 national and international organizations representing public and private, health care, advocacy, academic, policy, and community organizations. National Forum Members seek to address the recommendations of the Action Plan by improving cardiovascular health through the prevention, detection, and treatment of risk factors; early identification and treatment of heart attacks and strokes; and prevention of recurrent cardiovascular events. This collaborative effort is designed to guide the nation in taking action, strengthening capacity, evaluating impact, advancing policy, and engaging in partnerships to reverse the epidemic of heart disease and stroke. The National Forum continues to move toward its goal of full implementation of the Action Plan recommendations by convening member organizations, facilitating discussion around topics of need and interest, and driving action amongst the broader stakeholder community. Current efforts are focused on establishing a national comprehensive cardiovascular surveillance system, increasing health equit, and reducing sodium intake in the general population as well as coordinating real world application of the cardiovascular prevention components included in health reform legislation and designing an online policy toolkit.

National Stroke Association

National Stroke Association's mission is to reduce the incidence and impact of stroke by developing compelling education and programs focused on prevention, treatment, rehabilitation and support for all impacted by stroke.

National Stroke Association was formed in 1984 to fill a void as the only national nonprofit health care organization focusing 100 percent of its resources and attention on stroke. In its brief history, National Stroke Association has become a leading national resource on stroke and the driving force behind efforts to improve stroke prevention, treatment and rehabilitation. Based in Englewood, Colorado, National Stroke Association sustains itself through individual donations, memberships and grants.

Preventive Cardiovascular Nurses Association

The current state of health care demands that nurses play a leading role in identifying and implementing cardiovascular risk reduction strategies. PCNA is committed to educating and supporting nurses and advanced Practice nurses so that they may successfully rise to this challenge.

PCNA is the leading nursing organization dedicated to preventing cardiovascular disease (CVD) through assessing risk, facilitating lifestyle changes, and guiding individuals to achieve treatment goals. This is

accomplished through the integration of public and professional education and advocacy, which includes: publishing a bi-monthly, peer reviewed, indexed journal (*Journal of Cardiovascular Nursing*); hosting an active website with our 30 on-line CE programs; distributing a monthly e-newsletter with late-breaking news; holding regional and national meetings throughout the year; conducting research and publishing articles in relevant journal; speaking at national and international cardiology conferences; developing printed and downloadable clinical tools and patient-education materials; and collaborating with industry partners and other health care organizations on educational and advocacy initiatives.

Society for Women's Health Research

The Society for Women's Health Research (SWHR), a national non-profit organization based in Washington DC, is widely recognized as the thought leader in research on sex differences and is dedicated to improving women's health through advocacy, education, and research.

Founded in 1990 by a group of physicians, medical researchers and health advocates, SWHR aims to bring attention to the myriad of diseases and conditions that affect women uniquely. Due to SWHR's efforts, women are now routinely included in most major medical research studies and scientists are beginning to consider biological sex as a variable in their research.

Today, SWHR advocates for greater public and private funding for women's health research and the study of sex differences that: affects the prevention, diagnosis, and treatment of disease; encourages the appropriate inclusion of women and minorities in medical research studies; promotes the analysis of research data for sex and ethnic differences; and informs women, health care providers, and policy makers about contemporary women's health issues through media outreach, congressional briefings, public education campaigns, conferences and special events.

StopAfib.org

StopAfib.org was founded in 2007 to provide information, education, and support to help patients understand and manage their Afib. Founded by Mellanie True Hills, an atrial fibrillation patient who is now afib free, the organization focuses on raising awareness of afib, encouraging diagnosis and treatment, improving the quality of life for patients and families, supporting doctor-patient communication, and decreasing afib-related strokes.

The organization's Global Medical Advisory Board is made up of some of the world's foremost electrophysiologists, surgeons, cardiologists, neurologists, epidemiologists, and researchers, including Professor John Camm and Professor Gregory YH Lip. The site features information about atrial fibrillation and stroke, the latest afib news and videos, patient resources, a newsletter, the Atrial Fibrillation Blog, the StopAfib Discussion Forum and Community, and the StopAfib YouTube Channel that brings top afib doctors to patients.

Among the organization's successes, it created Atrial Fibrillation Awareness Month, recognized every September. StopAfib.org lobbied on Capitol Hill along with other organizations, such as the Heart Rhythm Society, and in 2009, the U.S. Senate passed a resolution officially recognizing September as National Atrial Fibrillation Awareness Month. Through ongoing efforts, the organization continues to make the afib patient voice heard in Washington, D.C., and has been involved in policy and awareness-raising coalitions and partnerships in the United States, Europe, Latin America, and Asia Pacific. In addition, StopAfib.org has represented the afib patient perspective to numerous think tanks and the U.S. Food and Drug Administration.

The AFib Optimal Treatment Task Force and this expert roundtable are brought to you by:

With support from an unrestricted educational grant from:

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