



## **Call to Action to All Stakeholders Managing Elderly AFib Patients: *Balancing the Risk of Stroke and Bleeding***

### **Introduction**

With the aging population, the prevalence of atrial fibrillation (AFib) is expected to double by 2050. AFib increases stroke risk by five-fold and doubles the risk that a stroke will result in permanent disability. While oral anticoagulation (OAC) is highly effective at reducing stroke risk, elderly patients are often under-anticoagulated owing in part to under-appreciation of the stroke risk associated with AFib, the tendency of some health care professionals to prioritize bleeding risk over stroke prophylaxis, concern over falls and bleeding risk, and growing competency with new treatments. On October 16, 2014 the Alliance for Aging Research convened a symposium with representatives from federal agencies, patient advocacy groups, and medical professional societies to discuss those factors leading to undertreatment of elderly AFib patients and to identify gaps in current clinical practice, outreach, education, research, and policy.

Symposium participants concluded that an integrated, national effort is needed to promote adoption of best practices, develop alternate reimbursement models, expand patient and caregiver education on stroke risk and treatment, leverage existing initiatives, and address gaps in research on stroke and bleeding in AFib.

### **Symposium Recommendations**

#### **Addressing Health Care Professional Barriers/Gaps**

- Develop initiatives that promote broader implementation of current clinical evidence and increase understanding of patient eligibility for OAC
- Improve, and potentially mandate, use of EHRs to flag patients who are candidates for OAC therapy and share information among HCPs
- Create education campaigns targeting HCPs, including appropriate use of new OACs
- Initiate a national campaign to increase awareness among HCPs of the importance of a non-event
- Establish consensus on what information should be shared between HCPs and patients—with emphasis on the importance of shared decision-making with patient preference
- Shift accountability and incentives to emphasize prevention of stroke

## **Symposium Recommendations (Continued)**

### **Addressing Treatment Barriers/Gaps**

- Explore alternative payment mechanisms to compensate HCPs to enable patient self-testing
- Align federal agency priorities to realize benefits of spending on patient self-testing
- Educate HCPs on contraindicated drugs and supplements for anticoagulants
- Define what is needed to encourage adherence over the long-term
- Establish consensus on patient information needed for shared decision-making about the use of OACs
- Development of tools that assist health care professionals and patients in OAC decision making
- Improve protocols for care transitions to improve management and education of DOAC use
- Counteract campaigns related to OAC side-effects and lawsuits

### **Addressing Patient Barriers/Gaps**

- Develop consistent messaging and educational initiatives that empower AFib patients and their family caregivers
- Offer educational materials at various reading levels and include family caregivers in messaging, as well as instruction for individuals who may be cognitively impaired
- Create educational materials that factor in age, gender, ethnicity
- Offer multiple educational formats to appeal to all learning styles
- Educate on a repeated basis to enhance information retention and foster patient adherence

### **Leveraging National Initiatives**

- Integrate the issue of anticoagulation in seniors with existing initiatives such as Million Hearts, the National Action Plan for Adverse Drug Event Prevention, and Healthy People 2020
- Coordinate between federal and state activities on falls prevention, hypertension management, and obesity prevention to leverage and maximize available resources
- Focus a PCORI-led roundtable and targeted funding announcements on anticoagulation decision-making in the elderly

## **Health Care Professional Barriers/Gaps**

At least 2-3 million adult Americans have AFib,<sup>1</sup> with some prevalence estimates as high as 6.1 million.<sup>2</sup> However, 40%-60% of AFib patients are not placed on anticoagulation to reduce their risk of stroke.<sup>3</sup>

According to leading medical guidelines, the decision to anticoagulate or not should reflect the absolute and relative risks of stroke and bleeding.<sup>4</sup> However, when translated to clinical practice, some health care professionals emphasize the risk of bleeding over the risk of stroke, even though warfarin and direct-acting oral anticoagulants (DOACs) have a low incidence of intracranial hemorrhage and fatal bleeding. This likely reflects several factors,

including a feeling of responsibility for an anticoagulation-related bleeding event. In addition, most elderly patients have multiple comorbidities and may be taking several medications—including anti-platelets for acute coronary syndrome and non-steroidal anti-inflammatory drugs—which increase bleeding risk. Further, some health care professionals cite real and perceived falls risk and the potential for a major bleed as a reason for not anticoagulating an elderly patient. In part because of these factors, too many health care professionals have adopted a default position of not anticoagulating elderly AFib patients. With Americans living longer than ever before, this can leave older patients with AFib unprotected for 20 years and more.

Broader implementation of existing stroke and bleeding risk stratification tools could lead to an increase in the number of anticoagulated elderly patients. While such risk assessment has been endorsed by medical societies, it will likely be many years before recommendations have been integrated into general clinical practice, as research has shown a 17-year gap between guidelines and widespread implementation.

In order to realize a meaningful reduction in AFib-related strokes in the nearer term, measures—such as mandating incorporation of risk scores into electronic health records (EHRs)—may be needed to promote formal stroke and bleeding assessment and risk stratification.

However, elderly patients have both higher stroke and bleeding risk, which can complicate the treatment decision and perhaps obscure the utility of comparing a stroke risk score to a bleeding risk score. Creating a single risk stratification tool for elderly patients with AFib should be a priority (see “Research Priorities” later in this report for more detail).

Until such a single scoring tool is available, health care professionals need to understand that addressing stroke risk supersedes bleeding concern for most patients. To achieve this, health care professionals need to be educated on evidence related to falls and major bleeding, as the bulk of clinical evidence shows a net benefit for anticoagulation.<sup>5-7</sup> Health care professionals also need to be able to communicate—and patients need to understand—the importance of a non-event (i.e. no stroke occurred). To achieve this, a consensus of what information should be conveyed to AFib patients is needed so that a consistent message highlighting stroke prevention is disseminated. In addition, a national, well-publicized campaign commemorating years without stroke for AFib patients could be instrumental in shifting the OAC discussion to focus on stroke prevention.

## Recommendations

- Develop initiatives that promote broader implementation of current clinical evidence and increase understanding of patient eligibility for OAC
- Improve, and potentially mandate, use of EHRs to flag patients who are candidates for OAC therapy and share information among HCPs
- Create education campaigns targeting HCPs, including appropriate use of new OACs
- Initiate a national campaign to increase awareness among HCPs of the importance of a non-event
- Establish consensus on what information should be shared between HCPs and patients—with emphasis on the importance of shared decision-making with patient preference
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## Treatment Barriers/Gaps

**Warfarin.** Nearly half of patients taking warfarin do not spend sufficient time in therapeutic range (TTR), which means that patients are not appropriately anticoagulated, despite research that shows improving TTR from 55% to 70% reduces the major adverse event rate by 50%.<sup>8</sup> Anticoagulation clinics are better skilled at keeping patients in TTR compared to community care,<sup>9</sup> reflecting experienced pharmacists and nurses overseeing patient education, monitoring, and follow up. However, one symposium participant noted that even well-run warfarin clinics can have difficulty keeping a sizeable percentage of patients' TTR above 50%.

There are two alternatives to laboratory INR testing—point-of-care testing (POCT) devices and patient self-testing (PST). POCT devices are not widely used, as some centers purport that additional clinic data are needed to ensure that POCT devices have rigor comparable to conventional laboratory testing.

Research has shown that PST can reduce thromboembolic complications and all-cause mortality without increased bleeding events by 60%-80% compared to patients who receive conventional INR laboratory testing.<sup>10</sup> However, the use of PST is largely restricted to patients who do not live close to a coagulation clinic or diagnostic laboratory, as reimbursement for PST is only ~\$9 per month per patient, making it economically unfeasible for most health care professionals to incorporate PST into their clinical practice. According to some estimates, diagnostic centers would have to limit PST use to 20% of their Medicare beneficiaries to make the service economically feasible.

In order to establish adequate reimbursement for PST, federal health agencies' priorities and budgets need better alignment since one agency would incur the cost of the PST device and testing strips but another would see the cost "benefit" in terms of fewer hospitalizations for major adverse events.

**Direct-acting OACs.** Many practitioners lack the knowledge needed to prescribe DOACs in a safe and effective manner. The DOACs offer comparable<sup>11, 12</sup> or superior efficacy<sup>13, 14</sup> to warfarin, and all have demonstrated a lower incidence of intracranial hemorrhage than

warfarin. The DOACs have rapid onset and shorter half-lives (than warfarin), with the latter making it paramount that patients don't skip doses.

Drug-Drug Interactions: The liver's enzyme system which metabolizes many medications, nutrients, and herbal therapies can be inhibited or induced by drugs, and thereby lead to drug-drug interactions. Most health care professionals do not know more than one or two strong inducers/inhibitors and may rely on contraindicated medications listed on target-specific OAC labeling. However, labeling for the new OACs is inconsistent, which could lead some health care professionals to erroneously believe one DOAC can be prescribed without hesitation with concomitant use of St. John's Wart (for instance) while another DOAC cannot. Although the FDA is working to resolve labeling discrepancies among the target-specific agents, education is needed to enable health care professionals to integrate the new OACs into clinical practice.

Patient Monitoring: There is a misperception that once treatment with a DOAC has started, there is no (or little) need for patient management or clinical oversight. Some health care professionals assume the patient doesn't need regular follow-up lab tests. However, renal function declines with age and should be assessed with some frequency so that dose adjustments can be made. Of note, a patient's renal function can affect whether certain drugs are contraindicated. For instance, based on the package insert for rivaroxaban, diltiazem (which is commonly used to treat AFib patients) is contraindicated in AFib patients with mild renal dysfunction. Additionally, medication adherence may be poorly impacted without regular monitoring and feedback. New models of monitoring should be created and implemented in order to improve outcomes and encourage adherence.

Patient Education: Given the DOACs' short half-lives, it's critical that health care professionals who prescribe these agents emphasize the importance of taking all doses as prescribed. However, this is not the only information needed if patients are to share in the decision making of which OAC to take. They must understand all the relative risks and benefits of the target-specific OACs. There is currently no consensus on the granularity of information that needs to be communicated in order for patients to make an informed treatment decision.

Transitions of Care: Strategies to improve care transitions are needed. Patients may be discharged from the hospital to a variety of care settings, including skilled nursing or rehabilitation facilities, a patient-centered medical home, or their own residence. HCPs at the discharging facility need to communicate relevant data with providers in the next-care setting, and patients should leave the hospital with a discharge checklist, including information on medication usage, signs and symptoms of adverse events, and an appointment for a follow-up visit with a physician, and date for lab/blood work (if needed), among others. An HCP at the next-care setting should be designated to reinforce education on anticoagulation and to enhance patient adherence

Concern over Litigation: Some health care professionals may avoid prescribing DOACs owing to concern over possible lawsuits. 1-800-BAD-DRUG and similar advertisements that seek individuals who had bleeding events while on DOACs, to join class action lawsuits, can create fear amongst health care professionals about malpractice suits. These lawsuits are based on the premise that patients were not informed of the risks that the DOACs carry, therefore educated patients cannot make that case. Treatment conversations should include full disclosure of all the risks and benefits.

### **Recommendations**

- Explore alternative payment mechanisms to compensate HCPs to enable patient self-testing
- Align federal agency priorities to realize benefits of spending on patient self-testing
- Educate HCPs on contraindicated drugs and supplements for anticoagulants
- Define what is needed to encourage adherence over the long-term
- Establish consensus on patient information needed for shared decision-making about the use of OACs
- Development of tools that assist health care professionals and patients in OAC decision making
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### **Patient Barriers/Gaps**

The starting point for patient and caregiver education is conveying an understanding of the incidence of AFib-related stroke and the relative risks and benefits of OAC in general. Most patients are not aware of the significant ischemic stroke risk related to AF, nor the risk reduction afforded by OACs. However, patients may have gotten misinformation from friends or relatives, including things such as warfarin being “rat poison” or that herbal remedies offer effective stroke prevention.

Information needs to be communicated in a manner that is easily understood by patients and family caregivers of all reading levels as well as those who may have some cognitive impairment. A patient education program should include several formats (oral, written, infographics, on-line resources,\* etc.) to accommodate different learning styles, and messaging that targets concerns for women and ethnic minorities should be considered. Finally, multiple interactions are often needed to enhance retention of information. This is particularly important during transitions of care, as patients are unlikely to remember instructions provided at hospital discharge two weeks later. Follow-up educational

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\* The ACC’s CardioSmart online resource, which provides information conditions and treatments and prepares patients for discussions with their healthcare provider, is a particularly useful patient education and engagement tool.

interventions will vary depending on the next care setting, e.g., skilled nursing facility, home, etc.

**DOACs.** The direct OACs introduce new patient and family caregiver education needs. In addition to understanding the importance of adherence (including not skipping doses and avoiding double doses), patients also need to appreciate the relationship between renal function, dosing, and safety events. Patients and caregivers should also receive instructions on the signs and symptoms of possible adverse events, such as intracranial or GI bleeding, and understand adverse events unique to each OAC. In order to make an informed decision, patients need to know considerations for all OACs, including warfarin, and be aware that there are no FDA-approved antidotes for target-specific OACs.

Healthcare professionals may also have to dispel misinformation or oversimplification of treatment regimens that patients have “learned” from the Internet and direct-to-consumer marketing. Some patients may also have an exaggerated view of bleeding events associated with some of the DOACs because of advertisements from 1-800-BAD-DRUG and other litigation-oriented concerns. On the other end of the spectrum, some patients may believe that taking a DOAC removes all bleeding risk.

#### **Recommendations**

- Develop consistent messaging and educational initiatives that empower AFib patients and their family caregivers
- Offer educational materials at various reading levels and include family caregivers in messaging, as well as instruction for individuals who may be cognitively impaired
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#### **Federal Efforts**

**Food and Drug Administration(FDA):** The FDA has set a new priority for OACs: Instead of being “as good as warfarin”, the FDA wants OACs to be as good as possible. The FDA believes this higher standard can be achieved through monitoring a specific parameter—perhaps the blood concentration of an OAC or through the use of a clotting test. The potential benefits of active monitoring include better ischemic stroke protection and reduced bleeding events.

**Centers for Disease Control(CDC):** OAC was one of three drug classes studied as part of the National Action Plan on Adverse Drug Events, spearheaded by the U.S. Department of Health and Human Services Office of Disease Prevention and Health Promotion. Analysis showed that about 10% of drug-related adverse outcomes stem from anticoagulation. OAC is responsible for about one in three adverse events in older hospitalized patients as well as one in three emergent hospitalizations. The CDC is involved in Millions Hearts, a national

public-private partnership devoted to preventing one million heart attacks and strokes by 2017. Although Million Hearts does not focus on reducing AFib-related stroke, there may be opportunities to leverage the focus of blood pressure control, as hypertension is a risk factor for both AFib and stroke. The CDC recently awarded \$250 million to state governments to disseminate information on healthy hearts, with a mandate to reduce hypertension, heart disease, and stroke. Efforts need to be made to include AFib and AFib-related stroke risk reduction in these state-directed educational campaigns.

CDC also administers the Healthy People 2020 program, which provides science-based 10-year national objectives for improving the health of all Americans. While there are current objectives to reduce stroke deaths overall and to increase awareness of the signs of stroke, objectives should be developed related to increasing identification of AFib, anticoagulation treatment in individuals with AFib, and adherence.

**National Institute on Aging (NIA):** The NIA is funding several AFib-related programs, including analysis of a 20,000-patient VA cohort, to gain insight into risk factors for major and minor bleeding related to warfarin, and several falls-related research projects. Programs include training for balance and slip recovery, development of a wrist sensor that can tell whether a patient has had a fall or a near fall, and “balance booster” technologies that give feedback to leg muscles to correct balance. The NIA is also collaborating with the Patient-Centered Outcomes Research Institute (PCORI) to evaluate the effectiveness of interventions to prevent falls injury. The study will enroll roughly 6,000 patients aged 75 or more who will be managed by “fall management practitioners”. The NIA’s Behavioral and Social Research division is investigating how seniors process information in order to ascertain the optimal way to communicate information on stroke and bleeding risk.

**National Institute of Neurological Disorders and Stroke (NINDS):** Many of the NINDS’ AFib programs focus on the diagnosis of AFib in the setting of stroke. Approximately 15%-20% of patients who have cryptogenic stroke actually have AFib that has not been detected. When a patient has longer periods of cardiac rhythm monitoring, AFib is usually diagnosed. The NINDS is evaluating outcomes when a health care professional doesn’t place an AFib patient on an OAC because of concern over bleeding-related falls risk to determine if lack of stroke prophylaxis is the appropriate clinical decision.

**National Heart Lung and Blood Institute (NHLBI):** In addition to AFib-related research in the basic and clinical sciences, the NHLBI is funding two AFib-related technology projects. One of these projects is a pilot study involving subcutaneous monitors that assess when patients who currently do not have an indication for anticoagulation, have an AFib episode. This study could offer initial data on whether AFib patients can be monitored remotely for when stroke prophylaxis therapy is needed.

**Agency for Healthcare Research and Quality (AHRQ):** The AHRQ Evidence-based Practice Center program has published several systematic reviews of the evidence for different treatment options for atrial fibrillation. AHRQ’s Innovations Exchange, a searchable database of innovations across the US to improve healthcare delivery, has nearly 60 entries on falls prevention. AHRQ’s Patient Safety division has a safety toolkit on



falls prevention in hospitals, which can be disseminated to hospital facilities and other organizations for implementation. AHRQ's Healthcare Cost and Utilization Project (HCUP), the largest repository of longitudinal data from hospitals in the US, can be used to collect data on the incidence and costs of AFib treatments and hospitalizations.

**Veterans Affairs (VA):** As a closed healthcare system, the VA offers a view of performance-based medicine in which care is not influenced by fees for services. The VA's 21 regional systems have operational control of their domain. Some regional VAs permit routine prescription of DOACs, whereas others may not. Pharmacists oversee the bulk of patient education for warfarin and DOACs in anticoagulation clinics. The VA has also a stroke query program and a variety of AFib-related research projects that overlap with those for heart failure and ischemic heart disease.

### **Recommendations**

- Integrate the issue of anticoagulation in seniors with existing initiatives such as Million Hearts, the National Action Plan for Adverse Drug Event Prevention, and Healthy People 2020
- Coordinate between federal and state activities on falls prevention, hypertension management, and obesity prevention to leverage and maximize available resources
- Focus a PCORI-led roundtable and targeted funding announcements on anticoagulation decision-making in the elderly

### **Research Priorities**

There are a number of areas that require research and development. Priority areas include but are not limited to:

### **Recommendations**

- Create a single risk stratification tool for elderly AFib patients that integrates stroke and bleeding risk to simplify anticoagulant decisions
- Develop coagulation assays and reversal agents for DOACs
- Assess various clinical scenarios (e.g., patient on anticoagulation undergoing surgery or wanting to switch therapies) to inform treatment recommendations
- Evaluate whether DOACs can be used for stroke prophylaxis in patients who have recently had an acute ischemic stroke
- Evaluate OACs in various patient populations to discern relative safety and efficacy of agents based on different patient baseline characteristics (e.g., gender, ethnicity, co-morbidity, etc.)
- Conduct an economic analysis of alternative INR testing modalities to assess potential cost savings
- Economic analysis of stroke hospitalization costs versus additional reimbursement for adherence education or monitoring

## **Conclusion**

An integrated, national effort is needed to raise awareness of the devastating consequences of an AFib-related stroke and the need for prophylactic treatment. Such an effort could create a unified message, standardizing the information on AFib and stroke risk presented to patients who currently hear disparate information from various HCPs. A public service announcement campaign, such as celebrating “years without a stroke”, could shift the OAC discussion to stroke prevention from bleeding risk.

A national initiative, comprised of public and private partners, would be optimal. It would elevate AFib-related stroke reduction in national healthcare priorities and perhaps accelerate the shift in focus to stroke prevention. A national initiative would also facilitate the leveraging of existing initiatives, such as hypertension management, falls prevention, and obesity prevention, which are related to AFib and AFib treatment.

## **Symposium Attendees**

Angie Baker  
National Stroke Association

Jodie Curtis  
District Policy Group at Drinker Biddle

Cynthia Bens  
Alliance for Aging Research

Jessica Deering, MA  
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Mary George, MD, MSPH, FACS  
Centers for Disease Control and  
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Robin Boineau, MD, MA  
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Ilisa Halpern Paul, MPP  
District Policy Group at Drinker Biddle

Elizabeth Brennan  
WomenHeart

Michael Hargrett  
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Susan Campbell, MPH  
WomenHeart

Alan Jacobson, MD  
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## **Symposium Attendees (Continued)**

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National Heart Lung and Blood Institute

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Rebecca Freedman McGrath, JD  
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Martha Nolan, JD  
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Susan Peschin, MHS  
Alliance for Aging Research

Briana Quinn, MPH, BSN, RN  
Emergency Nurses Association

Brittany Reid  
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Christine Welniak  
Upside Communications

Russell Werlinich, CMP  
Heart Rhythm Society

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## References

1. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, et al. Secular trends in the incidence of atrial fibrillation in Olmsted County, Minnesota, 1980-2000, and implications on the projects for future prevalence. *Circ*. 2006;114:199-25.
2. Naccarelli GV, Varker H, Lin J, Schulman KL. Increasing prevalence of atrial fibrillation and flutter in the United States. *Am J Cardiol*. 2009;104:1534-1539.
3. Ogilvie, I, Newton N, Weiner S, Cowell W, Lip G.. Underuse of Oral Anticoagulants in Atrial Fibrillation: A systematic review. *Am J Med*. 2010 123(7):938-45.
4. January CT, Wann S, Alpert JS, Calkins H, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. 2014. [Epub ahead of print]
5. Garwood CL, Corbett TL. Use of anticoagulation in elderly patients with atrial fibrillation who are at risk for falls. *Ann Pharmacother*. 2008;42:523-32.
6. Donze J, Clair C, Hug B, Rodoni N, et al. Risk of falls and major bleeds in patients on oral anticoagulation therapy. *Am J Med*. 2012;125:773-8.
7. Banerjee A, Clementy N, Haguenoer K, Fauchier L, Lip GY. Prior history of falls and risk of outcomes in atrial fibrillation: The Loire Valley Atrial Fibrillation Project. *Am J Med*. 2014;127:972-8.
8. Wan Y, Heneghan C, Perera R, et al. Anticoagulation Control and Prediction of Adverse Events in Patients with Atrial Fibrillation. *Circ Cardiovasc Qual Outcomes*. 2008; 1(2):84-91.
9. Baker WL, Cios DA, Sander SD, Coleman CI. Meta-analysis to assess the quality of warfarin control in atrial fibrillation patients in the United States. *J Manag Care Pharm*. 2009;15:244-52.
10. Bloomfield HE, Krause A, Greer N, et al. Meta-analysis: effect of patient self-testing and self-management of long-term anticoagulation on major clinical outcomes. *Ann Intern Med*. 2011;154:472-482.
11. Patel MR, Mahaffey KW, Garg J, Pan G, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883-91.
12. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369:2093-104.
13. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139-51.
14. Granger CG, Alexander JH, McMurray JJ, Lopes RD, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981-92.