Do Improvements in Anticoagulation Therapy Obviate the Need for Left Atrial Appendage Occlusion Therapies?

Left Atrial Appendage Occlusion Addresses the Tremendous Unmet Needs of Stroke Prevention in Atrial Fibrillation That Persist Despite Recent Advances in Anticoagulation Therapy

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Oral anticoagulation is the standard of care for stroke prevention in atrial fibrillation but falls short of providing an adequate solution to this common threat when considered from both efficacy and safety perspectives. Anticoagulation-associated treatment deficits include major and minor bleeding, refusal of anticoagulation based on anticoagulation risk, lack of medication adherence, personal and physician preference, and a persistent risk of ischemic stroke and major adverse cardiovascular events despite use. The challenges of contemporary anticoagulation management are highlighted in a recent large national assessment of warfarin therapy use involving 138,319 patients and 2,683,674 international normalized ratio results with reported mean time in therapeutic range of only 53.7%. Even in the setting of optimal management without clinically relevant major bleeds, emerging data regarding long-term risk of cerebral microbleeds prompt the need to explore risk and benefits of long-term anticoagulation use in patients with atrial fibrillation.

Response by Ezekowitz and Kent on p 1524

Among atrial fibrillation patients who experience a stroke, the large majority are felt to originate from left atrial appendage (LAA) thromboembolism. Accordingly, despite the lack of randomized data, LAA ligation is a frequent adjunct to cardiac surgery in patients with atrial fibrillation. Invasive transcatheter occlusion systems are now available and minimize the invasive nature of open and thorascopic surgical approaches. The long-term outcomes from multiple trials using the Watchman LAA occlusion system (Boston Scientific, Natick, MA) have demonstrated that endocardial left atrial appendage closure provides similar protection against stroke, systemic embolism, and cardiovascular mortality as warfarin, and by extension provides proof of concept of LAA closure. LAA closure is an upfront treatment without the bleeding risks inherent to lifelong anticoagulation. As such, with long-term efficacy similar to anticoagulation without the need for chronic drug dependence, percutaneous transcatheter LAA closure meets the tremendous unmet needs of patients with reasons to not take oral anticoagulants.

The Persistent Unmet Needs of Traditional and Novel Anticoagulants

Risk of Major and Minor Bleeding

Anticoagulation therapy use is directed by characterizing an individual patient’s stroke risk with either the CHADS2 or CHA2DS2-Vasc score. Anticoagulation has traditionally been recommended in patients with a CHADS2 score ≥2 and selected patients with a CHADS2 score of 1. More recent guidelines have recommended moving from CHADS2 to the more accurate
CHA$_2$DS$_2$-Vasc scoring system, whereas others have advocated anticoagulation in patients with a CHADS$_2$ score of ≥2.6 In addition to stroke risk consideration, individualized use of anticoagulation also requires an assessment of bleeding risk. For risk of bleeding, the HAS-BLED score is often used.7 A comparison of the efficacy scores (CHA$_2$DS$_2$, CHA$_2$DS$_2$-Vasc) and risk scores (HAS-BLED) highlights the challenge with anticoagulation as the risk assessments share overlapping risk variables including age, hypertension, and previous stroke. Patients with the highest risk of stroke often have the highest risk of bleeding. Because atrial fibrillation is a chronic condition, even patients with an initial low risk of stroke and bleeding will become higher risk over time with aging and the acquisition of cardiovascular and renal diseases (Figure 1).

The novel anticoagulants (NOACs) have generally demonstrated a statistically significant reduction in major bleeding when compared with warfarin, including an important reduction in intracranial hemorrhage, but bleeding remains a clinically significant issue. The lowest rate of major bleeding in any of the NOAC trials was reported in the Apixaban arm of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial with a major bleeding rate of 2.13% per year. The median follow up in the ARISTOTLE Trial was 1.8 years, during which 327/9088 (3.6%) experienced major bleeding. Clinically relevant bleeding was observed in 613 (6.9%) of patients, and any bleeding was reported by 2356 (25.8%) of patients in ARISTOTLE.8 Among patients receiving 20 mg of rivaroxaban in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET) trial, 5.6% (3.6/100 patient-years) experienced major bleeding. In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Trial, the risk of major bleeding on the higher dose was 3.11% per year. This major bleeding risk increased with age, decreased creatinine clearance, and concomitant aspirin use. Among patients aged ≥75 years the yearly risk of major bleeding was 5.1% with high-dose dabigatran and 4.4% with warfarin (P<0.001).9 The NOACs represent a small incremental gain in terms of bleeding risk when compared with warfarin but nevertheless convey a risk of major bleeding between 2.13% and 5.1% per year. The fundamental challenge of long-term stroke prevention in atrial fibrillation patients that does not simultaneously result in a persistent significant risk of major bleeding remains unanswered with the NOACs.

**Patient Tolerance and Nonadherence to Long-Term Anticoagulation**

Patients on long-term warfarin are well aware of the numerous drug–drug, drug–supplement, and drug–food interactions and the need for frequent international normalized ratio assessments. Although bleeding is commonly cited as the reason for long-term warfarin nonadherence, the majority of warfarin discontinuations stem from other reasons. In the Anticoagulation and Risk Factors in Atrial Fibrillation Trial (ATRIA) 2.3% of patients were hospitalized for bleeding at 1 year, but 26.3% had discontinued warfarin therapy.10 Nonadherence is especially pronounced in elderly patients with higher risks of atrial fibrillation–mediated stroke.11 In the Birmingham Atrial Fibrillation Treatment of the Aged Trial (BAFTA) over a follow-up period of 2.7 years, 33% of the elderly patients discontinued warfarin.12

Although the NOACs have a more predictable pharmacokinetic profile, fewer drug–drug and drug–food interactions, and do not require frequent international normalized ratio assessments, their discontinuation rates remain significant. In the RELY trial at 1 year 15.5% discontinued dabigatran compared with 10.2% that discontinued warfarin. At 2 years these rates increased to 21.2% and 16.6%, respectively. In the ROCKET trial, 23.9% of patients discontinued rivaroxaban compared with 22.4% that discontinued warfarin. These results were surprising given the multiple challenges with warfarin monitoring.

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**Figure 1. Shared stroke and bleeding risks increase with age.** The risk scores used to predict long-term stroke and bleeding share many clinical factors in common. Aging and the effects of atrial fibrillation on the genesis and worsening of cardiovascular and other disease states result in an evolving risk for both stroke and bleeding that directly influence the efficacy and safety of anticoagulant strategies. INR indicates international normalized ratio; and TIA, transient ischemic attack.
and adherence. The NOACs compete with warfarin among patients who otherwise would be taking warfarin but their availability has not resulted in an increase in overall anticoagulation utilization among patients at high risk for stroke with atrial fibrillation. The inability to monitor anticoagulation with the NOACs is of particular concern among patients with extremes of body weights and varying degrees of renal dysfunction.

Competing Needs for Antiplatelet Therapy
It may be considered a paradox that the CHA2DS2-VASc scoring system identifies atherosclerosis patients for anticoagulation therapy when antiplatelet therapy is preferable to anticoagulation for the prevention of atherosclerotic events. Up to a quarter of the strokes in patients with atrial fibrillation are caused by cerebrovascular disease and complex atheromatous plaques involving the aorta. Antiplatelet therapy is recommended over anticoagulation for the prevention of stroke in patients with cerebrovascular and peripheral vascular disease. Previous myocardial infarction was noted among 16.6% of patients in the RELY trial and 17.5% of patients in the ROCKET trial, demonstrating the frequency with which the clinician must balance the competitive indications and risks for anticoagulation and antiplatelet therapy. The concern of major bleeding with exposure to dual or triple antithrombotic agents often results in discontinuation of ≥1 of the agents. However, premature discontinuation of thienopyridine therapy is associated with a marked increase in the risk of stent thrombosis and is also the subject of an American College of Cardiology (ACC)/American Heart Association (AHA) guideline. Among patients receiving coronary stents in the What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting (WOEST) Trial, 44.4% of patients randomized to triple therapy with aspirin and clopidogrel in addition to anticoagulation experienced bleeding compared with 19.4% randomized to double therapy with anticoagulation and clopidogrel. Mortality was also increased with triple therapy (6.3% versus 2.5%, P=0.027).

Stroke Prevention in “Lower Risk” Patients With a CHADS2 Score of <2
Atrial fibrillation patients considered low or moderate risk with a CHADS2 score of 0 or 1 have a still concerning annualized stroke rate between 1.8 and 4%. OAC therapy is considered optional according to current ACC/AHA guidelines for patients with a CHADS2 score of 1 because of the significant risk of OAC-associated bleeding which mitigates the benefit of stroke reduction. Although the CHA2DS2-VASc score provides additional risk factor based stratification, stroke prevention among these lower risk patients represents yet another unmet clinical need. In the ATRIA study, lower risk, including younger patients, were the most likely to discontinue warfarin. With less self-perceived risk of stroke and lengthening duration of treatment, nonadherence to anticoagulation increases.

The Accumulative Risk of Persistent Stroke Events With Traditional and Novel Anticoagulation Strategies
The randomized trials comparing the NOACs with warfarin for the prevention of stroke in atrial fibrillation have demonstrated a reduction in thrombotic and hemorrhagic stroke when compared with warfarin. However, the persistent stroke risk leaves room for enhanced efficacy and the exploration of novel approaches. The annualized rate of stroke and systemic embolism exceeded 1.5% with warfarin and 1.1% with the NOACs in each of these trials (Table 1). Although these events occurred relatively infrequently in a given year, their cumulative risk over a lifetime is sobering. For example, among the patients randomized to high-dose Edoxaban in the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation (Engage AF) Trial, the annualized rate of stroke or systemic embolism was 1.18%. With a median treatment exposure of 907 days, 4.2% of the high dose Edoxaban patients experienced a stroke or systemic embolism and 11.8% experienced a major adverse cardiac event. RE-LY observed the net clinical benefit defined as a composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major bleed at a rate of 6.91% per year with high-dose dabigatran and 7.64% per year with warfarin. With a mean follow-up of 2 years, 832/6076 (13.7%) of patients randomized to high-dose dabigatran experienced this net clinical benefit.

LAA Closure: The Evidence of Efficacy
The WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation (PROTECT AF) Trial is the pivotal trial demonstrating the efficacy of the Watchman device and proving the benefit of LAA closure. The PROTECT AF Trial randomized 707 patients in a 2:1 ratio to LAA closure versus warfarin and was designed to prove noninferiority with a primary combined end point of all stroke, systemic embolism,
and cardiovascular mortality. When first published with 1065 patient-years of follow-up, the primary efficacy event rate was 3.0 per 100 patient-years in the device group and 4.9 per 100 patient-years in the warfarin group (probability of noninferiority >99.9%). In the subsequent publication with 1588 patient years of follow-up, the primary efficacy event rates continued to remain noninferior to warfarin (3% with the device and 4.3% for warfarin, probability of noninferiority >99.9%). Addressing some of the early criticisms of PROTECT AF, the 1588 patient-year publication demonstrated that when the analysis was restricted to patients with a CHADS\(_2\) score ≥2, the primary efficacy event rates were 3.9% per year in the device group and 5.0% per year in the control group (probability of noninferiority = 99.9%). Among the 131 patients with a history of previous stroke or TIA, the primary efficacy event rate was 5.3% with device and 8.2% with warfarin (probability of noninferiority = 98.7%). The most recent data from the PROTECT AF Trial were presented at the December 11, 2013 Food and Drug Administration (FDA) panel meeting and are available on the www.fda.gov website. With 2621 patient years of follow-up, the primary efficacy event rate has decreased to 2.3/100 patient-years with the Watchman device while remaining largely unchanged at 3.8/100 patient-years with warfarin. The stroke rate among patients randomized to Watchman (1.5/100 pt. yrs.) compared favorably with warfarin (2.2/100 patient-years). The lower rate of stroke with the Watchman device when compared with warfarin in PROTECT AF was attributable to a reduction in hemorrhagic stroke (Table 2). Once the procedural risk has been accounted for, the long-term risk of ischemic stroke was similar with both LAA closure and warfarin. (Figure 2)

The nonrandomized Continued Access to Protect (CAP) registry included 566 Watchman patients with a mean CHADS\(_2\) score of 2.5 during the transition from completion of PROTECT AF to the initiation of the PREVAIL Trial. The CAP registry demonstrated improved safety compared with PROTECT AF, particularly related to lower periprocedural complications and events that were reduced from 8.7% to 4.4%, a finding felt to reflect operator experience and improved training. The efficacy results were presented at the European Society of Cardiology meetings in 2013 and reviewed at the December 11, 2013 FDA panel meeting. In spite of enrolling a higher risk group than in PROTECT, the CAP primary efficacy end point (stroke, systemic embolism, and cardiovascular death) rate was slightly better: 2.0 events per 100 patient-years (27 events/1328 patient-years). There were 14 ischemic strokes and 1 hemorrhagic stroke during the 1328 patient-years of follow-up, yielding a composite stroke rate of 1.13 strokes per 100 patient-years.

The Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy (PREVAIL) Trial randomized 407 patients in a 2:1 fashion to the Watchman device (n=269) and warfarin (n=138). The PREVAIL Bayesian statistical design incorporated previous patients from PROTECT AF as well as newly randomized patients in PREVAIL while discounting the contribution of the PROTECT AF patients. PREVAIL was designed with 3 coprimary end points. A mechanism of action end point comparing ischemic events >7 days after Watchman implantation demonstrated noninferiority with warfarin. The safety end point also achieved its performance goal with a low rate of procedural complications. However, at 18 months, the rate of the first coprimary efficacy end point (composite of stroke, systemic embolism, and cardiovascular/unexplained death) was 0.064 in the device group versus 0.063 in the control group (rate ratio, 1.07; 95% credible interval [CrI], 0.57–1.89) and did not achieve the prespecified criteria for noninferiority (upper boundary of 95% CrI, 1.75; Figure 3). With a relatively small sample size and a mean follow-up of <1 year in PREVAIL, the FDA encouraged its panel members to consider the totality of data when evaluating the Watchman device. High procedural success and infrequent complications confirmed the safety of the procedure and that the experienced gained in previous years could be transferred to new operators.

Not only did LAA closure compete well with warfarin in the Watchman Trials, the cumulative LAA closure experience provides convincing evidence of LAA closure efficacy. When PROTECT AF and CAP are combined to provide 3503 patient years of follow-up in 1122 device-treated patients, the combined primary end point (stroke, systemic embolism, and cardiovascular death) event rate was 2.14 events per 100 patient-years, and the combined ischemic stroke rate was 1.26 events per 100 patient-years. These absolute event rates compare favorably with the NOAC Trials (Table 1), compare favorably with the stroke rates from the historical warfarin efficacy trials, and are dramatically less than would be expected in the absence of anticoagulation according to the CHADS\(_2\) and CHA\(_2\)DS\(_2\)-VASc scores of the enrolled cohort.

### Table 2. Watchman Trials – Stroke, Systemic Embolism, and Cardiovascular Mortality

<table>
<thead>
<tr>
<th></th>
<th>PROTECT AF(^{27,29,30})</th>
<th>CAP(^{33})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Device</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Mean enrolled CHADS(_2) score</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Stroke &amp; systemic embolism (%/yr)</td>
<td>2.6</td>
<td>3.2</td>
</tr>
<tr>
<td>1065 pt yrs</td>
<td>2.3</td>
<td>2.7</td>
</tr>
<tr>
<td>1588 pt yrs</td>
<td>1.7</td>
<td>2.2</td>
</tr>
<tr>
<td>2621 pt yrs</td>
<td>1.0</td>
<td>2.8</td>
</tr>
<tr>
<td>CV Death (%/yr)</td>
<td>3.4</td>
<td>5.0</td>
</tr>
<tr>
<td>1065 pt yrs</td>
<td>3.0</td>
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<td>2621 pt yrs</td>
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pt yrs indicates patient-years.
The favorable incidence of cardiovascular mortality in PROTECT AF and CAP when compared with warfarin and the NOACs may be considered hypothesis-generating and warrants additional investigation (Figure 4, Tables 1 and 2). Annualized cardiovascular mortality in the combined PROTECT AF and CAP cohort was <1%, whereas annualized cardiovascular mortality in RE-LY and Engage AF was >2% (Table 1). The WOEST Trial randomized coronary stent patients taking anticoagulants to either double therapy with clopidogrel or triple therapy with clopidogrel and aspirin. Although the primary outcome of any bleeding was more common with triple therapy than double therapy (44.4 versus 19.4%, \( P = .001 \)), the secondary end point of all-cause mortality was also more common with triple therapy (6.3% versus 2.5%, \( P = .027 \)). One may hypothesize various mechanisms whereby anticoagulant associated bleeding may have translated into excess mortality in these various trials.

LAA closure has demonstrated significant benefits in stroke reduction, bleeding risk, and cardiovascular mortality. Additional outcomes have also been favorably influenced. For example, warfarin as discussed previously requires frequent anticoagulation monitoring and lifestyle and dietary restrictions that impact quality of life. Although dabigatran-associated quality of life is not significantly different from warfarin, patients treated with LAA closure have favorable quality of life changes versus patients treated with warfarin.37

The totality of data supporting the efficacy and safety of the Watchman Left atrial appendage closure device was closely scrutinized and strongly endorsed by a FDA advisory panel in December 2013. The panel members voted 13 to 1 in favor of safety, efficacy, and the overall benefit versus risk of the Watchman LAA occluder to prevent stroke, systemic embolization, and death in patients with nonvalvular atrial fibrillation. The nearly unanimous favorable vote is a powerful endorsement of the hypothesis that LAA closure prevents atrial fibrillation-associated ischemic events.

**Patient Selection for LAA Closure in 2014**

The greatest unmet clinical need for stroke prevention in the setting of atrial fibrillation is among patients who cannot or choose to not take oral anticoagulants. A successful randomized trial comparing LAA closure with antiplatelet therapy or no therapy in patients contraindicated to oral anticoagulants would provide a mandate to treat such patients and definitively demonstrate the efficacy of LAA closure. However, many perceive such a trial to be unethical in light of the overwhelming efficacy of the available Watchman trials. The yearly incidence of atrial fibrillation-mediated stroke without oral anticoagulation is well documented in excess of 5% in the both the numerous trials comparing warfarin with aspirin or no therapy39 as well as the large stroke trials that have validated the CHADS and CHA\(_2\)DS\(_2\)-VASc scoring systems.19,20 The long-term yearly
stroke rate of 1.26/100 patient-years in PROTECT AF and CAP, with 1122 Watchman allocated patients and 3503 patient-years of follow-up, has demonstrated that the Watchman device not only competes favorably with warfarin but is dramatically less than predicted without oral anticoagulation.\(^{31,32}\) The European Society of Cardiology (ESC) therefore seems justified in suggesting LAA closure be considered for patients with a high stroke risk and contraindications for long-term oral anticoagulation.\(^{26}\) Although the PROTECT AF Trial included only patients who were candidates for warfarin and required 6 weeks of warfarin after device deployment, The Aspirin Plavix Feasibility Study with Watchman Left Atrial Appendage Closure Technology (ASAP) included 150 patients considered ineligible for warfarin. After Watchman deployment, antiplatelet therapy was administered without oral anticoagulation. With a mean duration of follow-up of 14.4 months, there were 4 stroke or systemic embolism primary end point events. This translated to an event rate of 2.3% per year, which was less than expected based on the CHADS\(_2\) scores of the patient cohort.\(^{28}\)

The FDA panel seemed to largely support the ESC guidelines endorsing LAA closure for contraindicated patients while further recognizing and extending support to those who would prefer to avoid long-term anticoagulation. Boston Scientific proposed the following indication for use at the December 2013 panel meeting: “Watchman LAA Closure Therapy is indicated to prevent thromboembolism from the left atrial appendage. It may be considered for use in patients with nonvalvular atrial fibrillation who are eligible for warfarin therapy to reduce the risk of stroke and systemic embolism based on CHADS\(_2\) or CHA\(_2\)DS\(_2\)-VASC scores.” The panel suggested emphasizing a personalized approach including consideration of patient preference regarding long-term anticoagulation therapy and suggested adding the statement “and who have reason not to remain on chronic warfarin therapy” to the proposed indications for use.\(^{34}\)

Potential of LAA Closure

Technological progress is inevitable. The Watchman device is an early generation device, and the Watchman trials represent the first experience of most physicians closing the left atrial appendage. Among the 463 patients randomized to device in the PROTECT AF Trial, 12% failed to receive a device and many continued to take warfarin after receiving a device secondary to incomplete closure. The intention-to-treat results discussed thus far are most appropriate when considering using the Watchman device today. However, additional analyses are equally appropriate when considering the potential of LAA closure. After excluding adverse procedural events in the PROTECT AF Trial, the yearly primary efficacy event rate was 2.5/100 patient-years with the Watchman and 4.3/100 patient-years with warfarin (probability of superiority = 95.3%).\(^{27,28}\) A prespecified per-protocol analysis comparing patients who received a device and discontinued warfarin with patients randomized to warfarin who took warfarin as prescribed revealed an annual primary event rate of 2.3/100 patient-years with the Watchman device versus 4.1/100 patient-years with warfarin (probability of superiority = 95.5%).\(^{27,28}\) Once the procedural risk of implantation is accounted for, the ischemic stroke rate in both device and warfarin arms of PROTECT AF was similar.\(^{29}\) The Watchman Trials have answered the fundamental proof of concept question, does elimination of the left atrial appendage prevent atrial fibrillation–mediated stroke, with resounding success and demonstrated that after successful deployment, the Watchman device was more effective than chronic warfarin therapy. Evolving physician experience and next-generation devices including iterative designs of the Watchman device will lead to improved outcomes with diminished procedural complications and enhanced closure. The anticipated FDA approval of the Watchman device represents a pivotal but nevertheless early step in the quest to minimize the risk of atrial fibrillation–mediated stroke through LAA closure. Physicians and the medical device industry will now march toward the goal of eliminating the LAA with ever-improving outcomes. Procedures will become less invasive, more efficacious, and safer.

Although eliminating the LAA as a source of thrombus diminishes the incidence of atrial fibrillation–mediated stroke, much work remains to individualize care and identify the role of LAA closure as an adjunct to additional therapies. LAA closure does not exclude adjunctive pharmacology or atrial fibrillation ablation. Additional investigations will refine the role of antiplatelet and anticoagulation after device placement. The synergistic role of pulmonary vein isolation and other ablative therapies will be investigated. Strategies will be tailored to individual patients based on anatomy, stroke risk, and bleeding risk.

Conclusion

The NOACs provide many advantages compared with warfarin and have demonstrated efficacy in large randomized trials. However, many patients cannot or will not be exposed to the potential hazards of antithrombotic therapy. Chronic systemic anticoagulation is inherently undesirable given risks of bleeding that increase with aging. Oral anticoagulation is associated
with a significant persistent risk of thrombotic stroke, hemorrhagic stroke, and adverse cardiovascular events including death and is associated with diminished quality of life. The shortcomings of chronic systemic anticoagulation leave a major unmet clinical need.

Clinical trials have proven the LAA to be critical to the pathogenesis of atrial fibrillation-mediated stroke and have demonstrated LAA closure to represent an alternative to chronic anticoagulation for patients with a reason to avoid chronic anticoagulation. One-time procedural elimination of the LAA nidus for thrombus and stroke has inherent advantages when compared with chronic systemic anticoagulation. LAA closure may also prove synergistic to antithrombotic and rhythm management strategies. The proven efficacy of LAA closure challenges the medical community to refine our techniques and devices with safer and more efficacious LAA closure. Additional research is indicated to confirm the efficacy of the Watchman Trials and to extend our understanding of how to incorporate LAA closure into our stroke prevention strategies.

Disclosures
Dr Whisenant is a director and stockholder of Coherex Medical and has consulted for Boston Scientific. Dr Kar has research grants from Boston Scientific and has modest equity in Coherex Medical. Dr Bunch has consulted for Boston Scientific. Dr Kar has research grants from NABOR (National Anticoagulation Benchmark and Outcomes Report) Steering Committee. Antithrombotic therapy practices in US hospitals in an era of practice guidelines. Arch Intern Med. 2009;165:1458–1464.

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The authors highlight important limitations of anticoagulation therapy for stroke prevention in patients with atrial fibrillation (AF). Left atrial appendage (LAA) exclusion devices, although theoretically an attractive alternative, currently fall short of resolving these limitations. We acknowledge bleeding and the fear of bleeding leads to an ≈40% permanent discontinuation rate of anticoagulation at ≈6 years (RELY-ABLE), however the need for anticoagulation to prevent device thrombosis and in patients who develop peri-device leaks does not preclude risk of bleeding. If devices could overcome the need for anticoagulation or at best achieve effective LAA closure using a single antiplatelet regimen with an acceptable bleed rate, their role for stroke prevention in patients with AF would be more appealing. Life-threatening procedural complications also pose a unique barrier to LAA device placement. Technical experience is essential, and subsequent device monitoring using transesophageal echocardiography is needed. Compared with warfarin, the risk of ischemic stroke is similar or elevated with LAA devices. Dabigatran 150 mg BID and apixaban 5 mg BID are superior to warfarin and represent the new standard. Direct comparisons between novel anticoagulants and LAA devices are needed. Cardiovascular mortality is reduced in comparison with warfarin for both novel anticoagulation and LAA devices. The largest clinical trial testing the devices had 770 patients compared with a total of ≈70000 for the trials evaluating novel anticoagulants. The efficacy and safety of LAA devices over the long-term has not been established, whereas novel anticoagulation has been evaluated for up to 6.7 years (RE-LY and RELY-ABLE). Thus, although LAA exclusion devices are of interest, improvements in efficacy, procedural safety, and device surfaces are needed to adequately address the limitations of anticoagulation.
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