Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.
Vol. 63, No. 4, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.08.1631

STATE-OF-THE-ART PAPER

Left Atrial Appendage Occlusion

Opportunities and Challenges

David R. Holmes, Jr, MD,* Dhanunjaya R. Lakkireddy, MD,† Richard P. Whitlock, MD, PhD,‡ Ron Waksman, MD,§ Michael J. Mack, MD‖

Rochester, Minnesota; Kansas City, Kansas; Hamilton, Ontario, Canada; Washington, DC; and Dallas, Texas

Stroke prevention in patients with atrial fibrillation is a growing clinical dilemma as the incidence of the arrhythmia increases and risk profiles worsen. Strategies in patients with nonvalvular atrial fibrillation have included anticoagulation with a variety of drugs. Knowledge that stroke in this setting typically results from thrombus in the left atrial appendage has led to the development of mechanical approaches, both catheter-based and surgical, to occlude that structure. Such a device, if it were safe and effective, might avoid the need for anticoagulation and prevent stroke in the large number of patients who are currently not treated with anticoagulants. Regulatory approval has been difficult due to trial design challenges, balance of the risk-benefit ratio, specific patient populations studied, selection of treatment in the control group, and specific endpoints and statistical analyses selected. Accumulating data from randomized trials and registries with longer-term follow-up continues to support a role for left atrial appendage exclusion from the central circulation as an alternative to anticoagulation in carefully-selected patient populations. (J Am Coll Cardiol 2014;63:291–8) © 2014 by the American College of Cardiology Foundation

By virtue of its increasing incidence and the increased potential for embolic stroke, atrial fibrillation (AF) is among the most complex and difficult challenges in the field of modern cardiovascular disease, and it represents a major health concern (1–5). The projected number of patients in the United States will be approximately 10 million by 2050 (3). In the setting of nonvalvular AF, two-thirds of strokes are cardioembolic. Echocardiographic and pathologic studies suggest that when a source can be identified, approximately 90% of such strokes can be attributed to thrombus in the left atrial appendage (LAA) (6).

The relationship between the increased burden of AF with advancing age and the increased incidence of related stroke has been well described (1,2,5). This is a cause for concern because of the attendant increased mortality and morbidity from AF-related stroke; cardioembolic strokes are particularly catastrophic, resulting in the worst prognosis among the various causes of stroke (1,7–9). The search for strategies to prevent or at least decrease stroke frequency in this setting has drawn considerable attention; this review provides an overview of these strategies with a focus on nonpharmacological approaches.

From the *Department of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota; †Section of Electrophysiology, Bloch Heart Rhythm Center, KU Cardiovascular Research Institute, Mid America Cardiology, University of Kansas Hospital, Kansas City, Kansas; ‡Department of Surgery, Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada; §Department of Interventional Cardiology, MedStar Washington Hospital Center, Washington, DC; and the ‖Department of Cardiovascular Medicine, Baylor Healthcare System, Dallas, Texas. Dr. Holmes and the Mayo Clinic have a financial interest in technology related to this research. That technology has been licensed to Atritech. Dr. Lakkireddy has received speaker's honoraria from Boehringer Ingelheim, St. Jude Medical, Jansen, Pfizer, and Bristol-Myers Squibb; consulting fees from St. Jude Medical; and a research grant from SentreHEART. Dr. Waksman has received honoraria for his service on the speakers' bureaus of Boston Scientific, Medtronic, AstraZeneca, Biotronik, and Abbott Vascular; nonroyalty payments from Biotronik; and research grants from Boston Scientific, Medtronic, Volcano, Lilly Daiichi Sankyo, AstraZeneca, and Abbott Vascular. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received July 10, 2013; revised manuscript received August 23, 2013, accepted August 27, 2013.

Risk Prediction Models

Prediction of stroke. Models for prediction of stroke risk most commonly have relied on clinical variables (10–14). Evaluation and comparison of multiple models have documented relatively poor performance, with inability to predict central nervous system events. In a study of 79,884 patients followed for an average of 4 years, risk prediction models were found to have only modest discriminatory ability, with C-statistics of approximately 0.60 (12). The most commonly used model has been $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack) score (Table 1), although this has now been largely supplanted by the CHA_2DS_2 VASC ($CHADS_2$ plus vascular disease, age 65 to 74 years, and female sex) score (Table 1), which has the advantage of discriminating the potential for stroke in lower-risk patient groups, and thereby might facilitate the selection of preventive strategies that are more specific (11,12).

Prediction of bleeding risk. A variety of bleeding risk scores have also been developed. Recently, 3 scoring systems

Abbreviations and Acronyms

AF = atrial fibrillation
CI = confidence interval
INR = international normalized ratio(s)
LAA = left atrial appendage
NOAC = novel oral anticoagulant
RR = rate ratio

have been evaluated in patients with AF (15). These included ATRIA (anticoagulation and risk factors in AF), HEMORR$_2$HAGES (hepatic or renal disease, ethanol abuse, malignancy, older age, reduced platelet count or function, rebleeding, hypertension, anemia, genetic factors, excessive fall risk, and stroke), and HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or pre-disposition, labile international normalized ratio [INR], >65 years, drug or alcohol use) (15). The latter score has become perhaps the most widely used. When applied in 2,293 patients with AF who were randomized to either fixed-dose Idraparinux (sanofi-aventis, Bridgewater, New Jersey) or adjustable-dose oral vitamin K, the HAS-BLED score performed best in predicting any clinically-relevant bleeding. In addition, the HAS-BLED score was the only one that demonstrated significant prediction for intracranial hemorrhage. However, all 3 scores demonstrated only modest performance in predicting any clinically-relevant bleeding, with C-indexes below 0.70 (15).

Anticoagulant therapy. Anticoagulant therapy has been the mainstay of therapy for stroke prevention in AF (1,16–24). Limited initially to warfarin, several important observations and conclusions have been drawn. Although warfarin therapy is very effective in reducing ischemic stroke (in contrast to acetylsalicylic acid, which has very limited effectiveness), several issues with it have been identified (1,24–31):

1. Less than 50% of patients at risk for stroke are prescribed or fill a prescription for warfarin on presentation with AF. This relates to several factors, including patient preference and real or perceived relative or absolute contraindications that are typically related to concerns for bleeding hazard (9,28–30).
2. Of those patients prescribed warfarin, there is ongoing attrition of its use to approximately 40% by 4 years (31).
3. During periods where warfarin must be withheld, such as for surgery or significant bleeding, patients are exposed to a window of thromboembolic risk.
4. Variable control of INR is frequent, with only approximately 60% of serial INR in randomized clinical trials being within therapeutic range (24–27,32).
5. There is patient inconvenience and cost with long-term monitoring of INR, dose adjustments, and multiple drug-to-drug interactions.
6. The risk of bleeding is increased when warfarin is administered along with dual antiplatelet therapy for associated conditions such as drug-eluting stents (33–35). When bleeding occurs in this setting, both warfarin and the dual antiplatelet therapy may be withheld, increasing the risk of stent thrombosis.

Table 1 $CHADS_2$ Scores

$CHADS_2$ Score		CHA_2DS_2 VASC Score	
Risk Factor	Score	Risk Factor	Score
CHF	1	CHF/LF dysfunction	1
Hypertension	1	Hypertension	1
Age ≥75 yrs	1	≥75 yrs	2
Diabetes mellitus	1	Diabetes mellitus	1
Stroke/TIA	2	Stroke/TIA	2
		Vascular disease	1
		65–74 yrs	1
		Female sex	1

Two commonly used scores for risk prediction of stroke in patients with nonvalvular atrial fibrillation. With these scores, there is an increase in the incidence of stroke with an increasing additive score.

$CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack; CHA_2DS_2 VASC = $CHADS_2$ plus vascular disease, age 65 to 74 years, and female sex; CHF = congestive heart failure; LF = labile factor; TIA = transient ischemic attack.

Because of these issues, novel oral anticoagulants (NOACs) have been developed and tested in large-scale randomized clinical trials in aggregate enrolling >50,000 patients (36–43) (Table 2). Although most studies with NOACs have shown them to be either noninferior or superior to warfarin for stroke reduction, bleeding rates have been somewhat variable. Compared with warfarin, both factor Xa inhibitors and 2 doses of the direct thrombin inhibitor dabigatran showed a large reduction in hemorrhagic strokes (36–44). Major bleeding rates with these agents, however, still exceeded 2% to 3% per year, and minor bleeding rates were over 10% per year (36). Thus, although improved, hemorrhagic complications remain a significant and serious limitation of new oral anticoagulants. When major bleeding occurs, it is associated with increased risk of death that, although less than with warfarin, is still substantial. As previously mentioned, a major complication with bleeding is that it often leads to discontinuation of antithrombotic therapy at least until the bleeding risk is minimized, leaving the patient exposed to the underlying thromboembolic risk. Consequently, within 2 years of initiating therapy with NOACs, approximately 20% of patients have discontinued them (36). One advantage of the NOACs is that they do not require monitoring, which makes them more clinically acceptable than warfarin, but this paradoxically limits the physician's ability to ensure patient compliance, particularly with the short half-lives of these NOACs. Furthermore, the lack of widely available antagonists renders management problematic when emergency surgical procedures are necessary or when bleeding occurs.

There are no direct head-to-head trials comparing the NOACs. A recent meta-analysis (40) included 44,733 patients from 4 studies that included apixaban, dabigatran, and rivaroxaban versus warfarin. Using adjusted indirect comparisons, there was significant heterogeneity in results. Dabigatran lowered the composite of systemic emboli or

Table 2 Results of Large RCTs of New Anticoagulants Versus Warfarin

Clinical Events and RCTs	Novel Drug and Dose	Novel Agent (%/yr)	Warfarin (%/yr)	HR (95% CI)	p Value
Stroke or systemic embolism					
RE-LY	Dabigatran 110 mg twice daily	1.53	1.69	0.91 (0.74–1.11)	0.34
	Dabigatran 150 mg twice daily	1.11	1.69	0.66 (0.53–0.82)	<0.001
ROCKET-AF	Rivaroxaban 20 mg daily	2.12	2.42	0.88 (0.75–1.03)	0.12
ARISTOTLE	Apixaban 5 mg twice daily	1.27	1.60	0.79 (0.66–0.95)	0.01
Hemorrhagic stroke					
RE-LY	Dabigatran 110 mg twice daily	0.12	0.38	0.31 (0.17–0.56)	<0.001
	Dabigatran 150 mg twice daily	0.10	0.38	0.26 (0.14–0.49)	<0.001
ROCKET-AF	Rivaroxaban 20 mg daily	0.26	0.44	0.59 (0.37–0.93)	0.02
ARISTOTLE	Apixaban 5 mg twice daily	0.24	0.47	0.51 (0.35–0.75)	<0.001
Major bleeding					
RE-LY	Dabigatran 110 mg twice daily	2.71	3.36	0.80 (0.69–0.93)	0.003
	Dabigatran 150 mg twice daily	3.11	3.36	0.93 (0.81–1.07)	0.31
ROCKET-AF	Rivaroxaban 20 mg daily	3.60	3.45	1.04 (0.90–1.20)	0.58
ARISTOTLE	Apixaban 5 mg twice daily	2.13	3.09	0.69 (0.60–0.80)	<0.001
Death					
RE-LY	Dabigatran 110 mg twice daily	3.75	4.13	0.91 (0.80–1.03)	0.13
	Dabigatran 150 mg twice daily	3.64	4.13	0.88 (0.77–1.00)	0.051
ROCKET-AF	Rivaroxaban 20 mg daily	4.5	4.9	0.92 (0.82–1.03)	0.15
ARISTOTLE	Apixaban 5 mg twice daily	3.52	3.94	0.89 (0.80–0.998)	0.047

The RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy) trial (36) included 18,113 patients with AF. Two doses of dabigatran were compared with open-label warfarin with both safety and efficacy endpoints. ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) (41) randomized 14,264 patients with nonvalvular AF at increased risk for stroke to either rivaroxaban or dose-adjusted warfarin. Both safety and efficacy endpoints as noted were assessed. The ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial (42) randomized 18,201 patients with AF and a greater or equal additional risk factor for stroke to apixaban or warfarin. As per the other studies of novel oral anticoagulants, both safety and efficacy endpoints were assessed as noted. Modified with permission from Granger and Armaganijan (39).

AF = atrial fibrillation; CI = confidence interval; HR = hazard ratio; RCT = randomized clinical trial.

stroke versus rivaroxaban, and apixaban versus both rivaroxaban and dabigatran lowered the risk of major gastrointestinal bleeding. Of interest, in terms of gastrointestinal bleeding, not all studies documented less bleeding than with warfarin use. There was increased gastrointestinal bleeding with dabigatran and rivaroxaban in the RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy) trial (36) and the ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) (41) but not with apixaban in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial (42).

Device therapy. Given that the LAA has been found to be the nidus of thrombus, resulting in stroke in approximately 90% of cases, approaches aimed at occlusion continue to be explored (45–54). Although intuitively attractive, evaluation of this strategy has proven difficult. In contrast to the multitude of large pharmaceutical trials that have randomized over 50,000 patients to either warfarin or an NOAC, only a single randomized trial of an LAA occlusion device has been published, and it included approximately 800 patients randomized in a 2:1 fashion device to warfarin (47). Device evaluation has been difficult because any device strategy for occlusion of the LAA necessarily includes an invasive procedure with its inherent attendant up-front procedural risks compared with initiating drug therapy alone. Furthermore, blinding common with pharmaceutical trials is very challenging with device trials. The PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) trial, which compared the Watchman (Boston Scientific, Natick, Massachusetts) LAA occlusion device to warfarin, identified an early safety hazard mainly related to procedural pericardial effusion occurring in approximately 5% of patients. Although the pericardial effusion did not result in either mortality or longer-term disability, it did prolong hospital stay and was considered a serious adverse event. Other procedural risks that occur with devices but not with initiation of pharmacologic therapy include anesthetic-related and peripheral vascular complications, as well as early embolic events. Although device embolization is an obvious risk, it is extremely rare. In addition, the long-term implications of leaving a permanent implant and the risk of erosion are largely unknown. In small trials, such events and concerns represent important imbalances in comparing strategies. Another important issue relates to the fact that some patients randomized to the device continue to also receive anticoagulant therapy longer term either for a new medical problem, such as the development of pulmonary emboli, or for a residual leak around the device at the LAA ostium, thereby making it difficult to attribute any reduction in stroke solely to the device itself. Peridevice leaks probably related to variations in the anatomy, device-LAA ostial mismatch, and heterogeneous remodeling of the LAA tissues around the device remain a potential issue. They have

been demonstrated after attempts at surgical ligation as well as percutaneous LAA closure in the PROTECT AF trial. In PROTECT AF, high-flow narrow leaks were not associated with increased risk of systemic thromboembolism (53); however, the specific size of a peridevice leak that might increase complications remains unclear. Improvements in implantation-guided imaging, for example, with 3-dimensional transesophageal echocardiography or new device iterations, might help to decrease this issue.

The PROTECT AF trial demonstrated that device placement was noninferior to warfarin for the primary efficacy endpoint of stroke (either ischemic or hemorrhagic), cardiovascular death, or systemic thromboembolism using a noninferiority margin of 2. This noninferiority finding was offset by the increase in adverse safety events in the device group, the majority of which occurred within the first 7 days. Longer-term information on safety of the Watchman has become available. This data combines information from the PROTECT AF trial with the CAP (Continued Access Protocol) registry (48). In these 2 studies, 542 patients had been treated in PROTECT AF and 460 in CAP. There was a significant decrease in procedure- or device-related safety events. The rate of serious pericardial effusion decreased from 5.0% in PROTECT AF to 2.2% ($p = 0.019$) in the CAP registry, whereas periprocedural stroke decreased from 0.9% to 0% ($p = 0.039$). There was also a reduction in safety events from the first one-half of enrollment in the PROTECT AF trial to the second one-half, reflecting among other things, improved operator experience and technique (48). The most recent data evaluates outcomes out to 2.3 ± 1.1 years (Table 3). At this time, the primary efficacy event rates with the device remained noninferior to warfarin control: 3.0% per 100 patient-years with device versus 4.3% in the control group (rate ratio [RR]: 0.71, 95% confidence interval [CI]: 0.44% to 1.30% per year). The effect was similar across multiple pre-defined subsets (Fig. 1). The previously mentioned early safety hazard related to periprocedural events, though improved, was still higher with device placement (50).

The outcome of PROTECT AF has now been reported, and the findings and conclusions have changed significantly. A total of 707 patients had a mean follow-up of 45 months, and, in aggregate, 2,621 patient-years. Superiority criteria for the composite efficacy endpoint were now achieved. Using the Cox proportional hazards model, there were 2.3 events per 100 patient-years in the Watchman group versus 3.8 in the warfarin group (hazard ratio: 0.61, 95% CI: 0.38 to 0.97; $p = 0.0348$). There were fewer fatal or disabling strokes in the device group (RR: 0.37). The efficacy results were consistent across subgroups based on age, sex, $CHADS_2$ score, and previous warfarin use. In this final analysis, the composite primary safety events between the 2 groups were now noninferior (RR: 1.17, 95% credible interval: 0.78 to 1.95).

A second randomized pivotal trial has now been completed (PREVAIL [Evaluation of the Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy]; NCT01182441) that aimed at documenting continued improved safety and at confirming the efficacy demonstrated in the PROTECT AF trial.

Current issues compromising the implementation of procedural approaches for stroke prevention in AF are discussed herein and include: 1) lack of multiple randomized clinical trials; 2) lack of consensus regarding the appropriate target population to study; and 3) ability to obtain approval of devices for outcome measures of unconfirmed clinical importance, such as, the use of complete closure of the LAA at the time of the index procedure as a surrogate for clinical efficacy.

Randomized Clinical Trials and Target Populations

As previously mentioned, there is only a single randomized clinical trial of percutaneous closure that has been completed and published (47). The major criticisms of this initial pivotal trial include the following: small sample size compared with the pharmacologic trials in similar patient groups; a mean $CHADS_2$ score of 2.2 ± 1.2; the boundaries of noninferiority; the initial use of 45 days of warfarin in the device group, which was designed to enhance endothelialization but also possibly contributed to improved early outcome in the device group or alternatively improved safety

Table 3 Efficacy and Safety Results at 2.3-Year Follow-Up of the PROTECT-AF Trial

	Device		Control		Posterior Probabilities		
	Events/Pt-Yrs	OR/100 Pt-Yrs (95% CI)	Events/Pt-Yrs	OR/100 Pt-Yrs (95% CI)	RR* (95% CI)	Noninferior	Superior
Primary efficacy	31/1,025.7	3.0 (2.1–4.3)	24/562.7	4.3 (2.6–5.9)	0.71 (0.44–1.30)	>0.99	0.88
Ischemic stroke	19/1,026.3	1.9 (1.1–2.9)	8/564.9	1.4 (0.6–2.4)	1.30 (0.66–3.60)	0.76	0.18
CV/unexplained death	11/1,050.4	1.0 (0.5–1.8)	16/573.2	2.8 (1.5–4.2)	0.38 (0.18–0.85)	>0.99	0.99
Hemorrhagic stroke	3/1,050.3	0.3 (0.1–0.7)	7/571.0	1.2 (0.5–2.3)	0.23 (0.04–0.79)	>0.99	0.99
Systemic embolism	3/1,049.8	0.3 (0.1–0.7)	0/573.2	0	—	—	—
All stroke	21/1,026.3	2.0 (1.3–3.1)	15/562.7	2.7 (1.5–4.1)	0.77 (0.42–1.62)	>0.99	0.73
All-cause mortality	34/1,050.4	3.2 (2.3–4.5)	26/573.2	4.5 (2.8–6.2)	0.71 (0.46–1.28)	>0.99	0.85
Primary safety	54/979.9	5.5 (4.2–7.1)	2/554.6	3.6 (2.2–5.3)	0.53 (0.95–2.70)	—	—

Endpoint data in the PROTECT-AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) trial at 2.3-year follow-up. The composite primary endpoint remains noninferior to warfarin. *Rate ratio (RR) (intervention/control). Modified with permission from Reddy et al. (50).

CI = confidence interval; CV = cardiovascular; OR = odds ratio; Pt-yrs = patient-years; — = data not available.

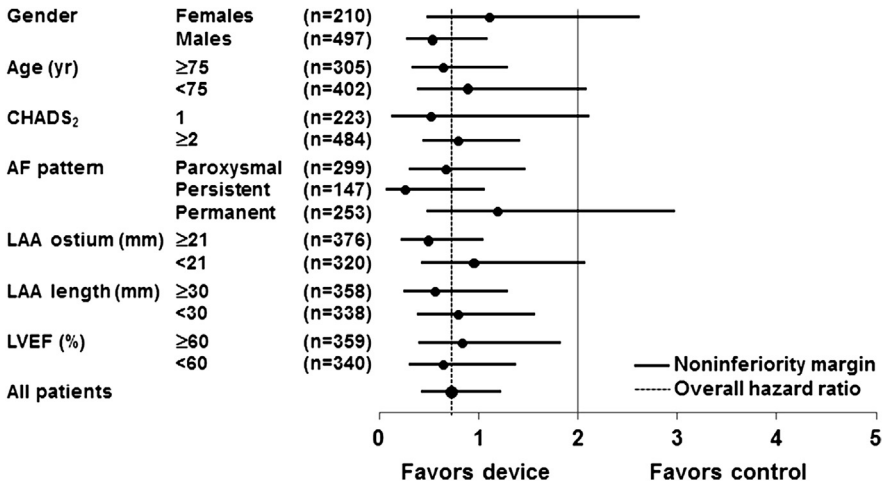

Figure 1 Percutaneous LAA Closure for Stroke Prophylaxis

Follow-up at 2.3 years of the PROTECT AF trial. Reproduced with permission from Reddy et al. (50). AF = atrial fibrillation; $CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack score; LAA = left atrial appendage; LVEF = left ventricular ejection fraction; PROTECT AF = Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation trial.

risks; the reintroduction of warfarin later during the follow-up period for other reasons; restricting the trial to patients who were candidates for warfarin; time in therapeutic range in the warfarin arm; and inclusion of both ischemic and hemorrhagic strokes as an efficacy endpoint. An additional important limitation is the restriction of the anticoagulant only to warfarin, thereby excluding the NOACs.

An important consideration to be addressed in this regard is the need for a randomized trial in a patient population not treated with anticoagulants. The current and planned randomized clinical trials have as their focus patients who are candidates for oral anticoagulant therapy either warfarin or an NOAC. This excludes approximately 50% of patients who are at risk for stroke but are not felt to be candidates for oral anticoagulants. Such candidates are at increased risk for complications; approval of a device in this group would add an important alternative therapeutic strategy. There are problems with the design of such a trial in terms of definition of criteria for "an absolute or relative contraindication to oral anticoagulants," as well as the specific treatment in the control group—either aspirin alone or dual antiplatelet therapy, neither of which has been proven effective for stroke prevention. The closest data available in patients who were not candidates for warfarin include the Watchman (ASAP [ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology]) registry (54) of 150 patients in whom the device was implanted. Patients were treated only with either aspirin or dual antiplatelet therapy, despite the fact that acetylsalicylic acid and clopidogrel might also be associated with increased bleeding similar to warfarin. In this trial, patients had a mean $CHADS_2$ score of 2.8, which would predict an event rate of approximately 7%; in contrast to what was expected, stroke and transient ischemic attack occurred in only 1.7%, a reduction of approximately 75%. Although statistically underpowered for clinical events, the ASAP registry offers data that might affect patient care and outcome.

A current randomized clinical trial, the ACP (Amplatzer Cardiac Plug Clinical Trial; NCT01118299) (Amplatzer, St. Jude Medical, St. Paul, Minnesota), which has taken approximately 1 year for investigational device exemption approval, has been affected greatly with changes in inclusion/exclusion criteria as well as in endpoints. For example, either current or anticipated use of any thienopyridine is a contraindication for participation. Whereas the inclusion of patients taking a thienopyridine could introduce confounding bias, making interpretation of results difficult, the current selection criteria exclude patients who might benefit the most: those with a need for dual antiplatelet therapy, for example, patients with drug-eluting stents in addition to oral anticoagulation for stroke prevention who are at a greatly increased risk for hemorrhage. This study will include control patients on dabigatran.

Alternative Devices

A final related issue comes after approval of a single device in a new category of devices. Do subsequent trials of either new iterations of the initial devices or new designs have to be randomized against the initial device (Watchman) or against the control group in the initial protocol trials (warfarin)? The approval of devices currently used for LAA occlusion but only approved for nonstroke prevention indications is problematic (52). The prototypical device in this category is the Lariat device (SentreHEART, Inc., Redwood City, California), which received 510(k) approval for opposing

tissue planes. The concept is unique and is based on an external transpericardial approach to occlude the LAA by a suture. Both transvenous and direct pericardial access are required. Magnetically-tipped guidewires are positioned to meet at the tip of the dominant lobe of the LAA. A suture fashioned as a "lasso or lariat" is positioned over the pericardial access wire and then tightened to occlude the LAA.

The largest series of Lariat cases reported to date is 85 patients, so information sufficient to evaluate device and procedure safety and effectiveness is very limited (52). Although eligibility criteria included "a poor candidate or ineligible for warfarin," at 1-year follow-up (52), 55% of patients were receiving warfarin. The rate of closure of the appendage with this device was approximately 95%. Even though closure documented on transesophageal echocardiograms with this particular device is very compelling, closure alone has not been validated as a surrogate for stroke prevention and should not be used as such. Pericarditis, which can be quite severe and anecdotally appears to occur with some frequency, typically results in prolongation of the initial hospital stay. Whether severe pericarditis will have lasting sequelae remains unknown. Although this approach looks promising, in the absence of controlled scientific data, very limited conclusions can be drawn.

Exclusion of the LAA can also be performed at the time of concomitant cardiac surgery. Currently-available surgical methods to isolate the LAA include: 1) suture ligation; 2) excision and suture closure; and 3) stapling exclusion with or without excision. These techniques remain limited by issues of incomplete closure and residual flow in up to one-third of patients (55,56) and trauma to the appendage.

New devices for surgical approaches have been developed. The Atriclip Device System (Atricure, Inc., West Chester, Ohio), a self-closing, sterile, implantable clip with a reusable deployment tool, is applied epicardially by either an open surgical or a minimally-invasive technique and is available in 4 sizes (35, 40, 45, and 50 mm). In the European trial that led to CE mark approval, 34 patients underwent successful clip placement; there were no device-related complications (57). LAA occlusion was confirmed by intraoperative transesophageal echocardiography and by serial computed tomography at 3 months in all patients. In the U.S. regulatory trial of the same device, 71 patients undergoing open cardiac surgery at 7 U.S. centers were enrolled (58). In 1 patient, the LAA was too small and did not meet eligibility criteria; the remaining 70 patients had successful placement of the device. Intraprocedural successful exclusion was confirmed in 67 of 70 patients (95.7%). There were no adverse events related to the device, and at 3 months, 60 of 61 patients (98.4%) who underwent imaging had successful LAA exclusion by computed tomography angiography or transesophageal echocardiography.

The Tiger Paw System (Terumo Cardiovascular Systems, Ann Arbor, Michigan) is another device approved for commercial use in the United States (59). In the regulatory study, 60 patients were enrolled. Transesophageal echocardiograms at 90 days were available in 54 patients, and no leaks were detected.

Summary and Recommendations

The issues of stroke prevention in patients with AF are extremely important. Although there is an abundant dataset on the use of warfarin and now new anticoagulant strategies, many problems remain—for example, long-term chronic therapy, incremental lifetime risk of bleeding, cost, and drug-drug interactions—as well as the fact that approximately 50% of patients at risk are not treated with these agents. With the increasing data that occlusion of the LAA results in an outcome that is at least noninferior and is now documented to be superior to warfarin, what can be done to enhance regulatory approval of these devices? The answer is continued data with well-controlled efficient studies adequately powered with important clinical endpoints in multiple groups of patients who could benefit.

One option would be to expedite the approval of LAA occlusion devices once they have passed the regulatory safety tests and to subsequently demonstrate efficacy as compared with currently effective anticoagulants. This could be accomplished by combining well-conducted randomized clinical trials with rigorous post-marketing registries that include standardized data forms, detailed inclusion criteria, procedural outcome, and clinical follow-up focusing on stroke events and bleeding. The TVT (Transcatheter Valve Therapy) registry (60) for post-market surveillance of transcatheter aortic valve replacement is an example of such a registry. A similar registry could be initiated by the professional societies that focus on LAA occlusion devices. These registries should include monitoring and rigorous surveillance up to 5 years to establish the knowledge of the risks and benefits of such devices for a broad study population. Although post-market surveillance studies have their own set of issues, such as relying on site-reported outcomes and limited complete rigorous monitoring, the data generated will serve as a guide for physicians to tailor the optimal therapy for the treatment of nonvalvular AF.

Reprint requests and correspondence: Dr. David R. Holmes, Jr., Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905. E-mail: holmes.david@mayo.edu.

REFERENCES

1. Alli O, Holmes DR Jr. Left atrial appendage occlusion for stroke prevention. Curr Probl Cardiol 2012;37:405–41.
2. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. JAMA 2001;285:2370–5.
3. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for further prevalence. Circulation 2006;114:119–25.

4. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. Stroke 1991;22:983–8.
5. Lloyd-Jones DM, Wang TJ, Leip EP, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart study. Circulation 2004;110:1042–6.
6. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg 1996;61:755–9.
7. Holmes DR. Atrial fibrillation and stroke management: present and future. Semin Neurol 2010;30:528–36.
8. Tu HT, Campbell BC, Christensen S, et al., for the EPITHET Investigators. Pathophysiological determinants of worse stroke outcome in atrial fibrillation. Cerebrovasc Dis 2010;30:389–95.
9. Patel TK, Yancy CW, Knight BP. Left atrial appendage exclusion for stroke prevention in atrial fibrillation. Cardiol Res Pract 2012;2012:610827.
10. Lip GY, Frison L, Halperin JL, Lane DA. Identifying patients at high risk for stroke despite anticoagulation: a comparison of contemporary stroke risk stratification schemes in an anticoagulated atrial fibrillation cohort. Stroke 2010;41:2731–8.
11. Olesen JB, Lip GY, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ 2011;342:d124.
12. Van Staa TP, Setakis E, Di Tanna GL, et al. A comparison of risk stratification schemes for stroke in 79,884 atrial fibrillation patients in general practice. J Thromb Haemost 2010;9:39–48.
13. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864–70.
14. Coppens M, Eikelboom JW, Hart RG, et al. The CHA_2DS_2-VASc score identifies those patients with atrial fibrillation and a $CHADS_2$ score of 1 who are unlikely to benefit from oral anticoagulant therapy. Eur Heart J 2013;34:170–6.
15. Apostolakis S, Lane DA, Guo Y, Buller H, Lip GY. Performance of the HEMMOR(2)HAGES, ATRIA, and HAS-BLED bleeding risk-prediction scores in patients with atrial fibrillation undergoing anticoagulation: the AMADEUS (Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients with Atrial Fibrillation) study. J Am Coll Cardiol 2012;60:861–7.
16. Ezekowitz MD, Bridgers SL, James KE, et al., for the Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. N Engl J Med 1992;327:1406–12.
17. Stroke prevention in atrial fibrillation study: final results. Circulation 1991;84:527–39.
18. EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. Lancet 1993;342:1255–62.
19. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II study. Lancet 1994;343:687–91.
20. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASAK study. Lancet 1989;1:175–9.
21. 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.
22. Fuster V, Ryden LE, Cannom DS, et al. 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. J Am Coll Cardiol 2011;57:e101–98.
23. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. Eur Heart J 2012;33:2719–47.
24. Singer DE, Albers GW, Dalen JE, et al. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest 2008;133 Suppl 6:546S–92S.
25. Wysowski DK, Nourjah P, Swartz L. Bleeding complications with warfarin use: a prevalent adverse effect resulting in regulatory action. Arch Intern Med 2007;167:1414–9.
26. Landefeld CS, Beyth RJ. Anticoagulant-related bleeding: clinical epidemiology, prediction, and prevention. Am J Med 1993;95:315–28.
27. Fang MC, Go AS, Chang Y, et al. Death and disability from warfarin-associated intracranial and extracranial hemorrhages. Am J Med 2007;120:700–5.
28. Sudlow M, Thomson R, Thwaites B, Rodgers H, Kenny RA. Prevalence of atrial fibrillation and eligibility for anticoagulants in the community. Lancet 1998;352:1167–71.
29. Brass LM, Krumholz HM, Scinto JM, Radford M. Warfarin use among patients with atrial fibrillation. Stroke 1997;28:2382–9.
30. Go AS, Hylek EM, Borowsky LH, Phillips KA, Selby JV, Singer DE. Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the Anticoagulation and risk Factors in Atrial Fibrillation (ATRIA) study. Ann Intern Med 1999;131:927–34.
31. Gallagher AM, Rietbrock S, Plumb J, van Staa TP. Initiation and persistence of warfarin or aspirin in patients with chronic atrial fibrillation in general practice: do the appropriate patients receive stroke prophylaxis? J Thromb Haemost 2008;6:1500–6.
32. White HD, Gruber M, Feyzi J, et al. Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: results from SPORTIF III and V. Arch Intern Med 2007;167:239–45.
33. Hansen ML, Sorensen R, Clausen MT, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. Arch Intern Med 2010;170:1433–41.
34. Karjalainen PP, Porela P, Ylitalo A, et al. Safety and efficacy of combined antiplatelet-warfarin therapy after coronary stenting. Eur Heart J 2007;28:726–32.
35. Orford JL, Fasseas P, Melby S, et al. Safety and efficacy of aspirin, clopidogrel, and warfarin after coronary stent placement in patients with an indication for anticoagulation. Am Heart J 2004;147:463–7.
36. Connolly SJ, Ezekowitz MD, Yusuf S, et al., for the RE-LY Steering Committee and Investigators. Dabigatran versus warfarin inpatients with atrial fibrillation. N Engl J Med 2009;361:1139–51.
37. Connolly SJ, Wallentin L, Ezekowitz MD, et al. The Long-Term Multi-Center Observational Study of Dabigatran Treatment in Patients With Atrial Fibrillation (RELY-ABLE) study. Circulation 2013;128:237–43.
38. Verheugt FW. New oral anticoagulants in atrial fibrillation forever? Circulation 2013;128:200–2.
39. Granger CB, Armaganijan LV. Should newer oral anticoagulants be used as first-line agents to prevent thromboembolism in patients with atrial fibrillation and risk factors for stroke or thromboembolism? Circulation 2012;125:159–64.
40. Baker WL, Phung OJ. Systematic review and adjusted indirect comparison meta-analysis of oral anticoagulants in atrial fibrillation. Circ Cardiovasc Qual Outcomes 2012;5:711–9.
41. Patel MR, Mahaffey KW, Garg J, et al., for the ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883–91.
42. Granger CB, Alexander JH, McMurray JJ, et al., for the ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981–92.
43. Connolly SJ, Eikelboom J, Joyner C, et al., for the AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. N Engl J Med 2011;364:806–17.
44. Majeed A, Hwang HG, Brueckmann M, et al. Management and outcomes of major bleeding on dabigatran or warfarin. Abstract presented at: American Society of Hematology Annual Meeting; December 8–11, 2012; Atlanta, GA.
45. Sievert H, Lesh MD, Trepels T, et al. Percutaneous left atrial appendage transcatheter occlusion to prevent stroke in high-risk patients with atrial fibrillation: early clinical experience. Circulation 2002;105:1887–9.
46. Sick PB, Schuler G, Hauptmann KE, et al. Initial worldwide experience with the WATCHMAN left atrial appendage system for stroke prevention in atrial fibrillation. J Am Coll Cardiol 2007;49:1490–5.
47. Holmes DR, Reddy VY, Turi ZG, et al., for the PROTECT AF Investigators. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. Lancet 2009;374:534–42.

48. Reddy VY, Holmes DR, Doshi SK, Neuzil P, Kar S. Safety of percutaneous left atrial appendage closure: results from the Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF (PROTECT AF) clinical trial and the Continued Access Registry. Circulation 2011;123:417–24.
49. Park JW, Bethencourt A, Sievert H, et al. Left atrial appendage closure with Amplatzer cardiac plug in atrial fibrillation: initial European experience. Catheter Cardiovasc Interv 2011;77:700–6.
50. Reddy VY, Doshi SK, Sievert H, et al., for the PROTECT AF Investigators. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-year follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) trial. Circulation 2013;127:720–9.
51. Singh SM, Dukkipati SR, d'Avila A, Doshi SK, Reddy VY. Percutaneous left atrial appendage closure with an epicardial suture ligation approach: a prospective randomized pre-clinical feasibility study. Heart Rhythm 2010;7:370–6.
52. Bartus K, Han FT, Bednarek J, et al. Percutaneous left atrial appendage suture ligation using the LARIAT device in patients with atrial fibrillation: initial clinical experience. J Am Coll Cardiol 2013;62:108–18.
53. Viles-Gonzalez JF, Kar S, Douglas P, et al. The clinical impact of incomplete left atrial appendage closure with the Watchman device in patients with atrial fibrillation: a PROTECT AF (Percutaneous Closure of the Left Atrial Appendage versus Warfarin Therapy for Prevention of Stroke in Patients with Atrial Fibrillation) substudy. J Am Coll Cardiol 2012;59:923–9.
54. Reddy VY, Möbius-Winkler S, Miller MA, et al. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology). J Am Coll Cardiol 2013;61:2551–6.
55. Katz ES, Tsiamtsiouris T, Applebaum RM, Schwartzbard A, Tunick PA, Kronzon I. Surgical left atrial appendage ligation is frequently incomplete: a transesophageal echocardiographic study. J Am Coll Cardiol 2000;36:468–71.
56. Kanderian AS, Gillinov AM, Pettersson GB, Blackstone E, Klein AL. Success of surgical left atrial appendage closure: assessment by transesophageal echocardiography. J Am Coll Cardiol 2008;52:924–9.
57. Salzberg SP, Plass A, Emmert MY, et al. Left atrial appendage clip occlusion: early results. J Thorac Cardiovasc Surg 2010;139:1269–74.
58. Ailawadi G, Gerdisch MW, Harvey RL, et al. Exclusion of the left atrial appendage with a novel device: early results of a multicenter trial. J Thorac Cardiovasc Surg 2011;142:1002–9.
59. Slater DA, Tatooles AJ, Coffey A, et al. Prospective clinical study of a novel left atrial appendage occlusion device. Ann Thorac Surg 2012;93:2035–40.
60. Carroll JD, Edwards FH, Marinac-Dabic D, et al. The STS-ACC Transcatheter Valve Therapy National Registry: a new partnership and infrastructure for the introduction and surveillance of medical devices and therapies. J Am Coll Cardiol 2013;62:1026–34.

Key Words: left atrial appendage occlusion ■ nonvalvular atrial fibrillation ■ stroke prevention ■ Watchman device.