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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)

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Objectives The purpose of this study was to assess the safety and efficacy of left atrial appendage (LAA) closure in nonvalvular atrial fibrillation (AF) patients ineligible for warfarin therapy.

Background The PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) trial demonstrated that LAA closure with the Watchman device (Boston Scientific, Natick, Massachusetts) was noninferior to warfarin therapy. However, the PROTECT AF trial only included patients who were candidates for warfarin, and even patients randomly assigned to the LAA closure arm received concomitant warfarin for 6 weeks after Watchman implantation.

Methods A multicenter, prospective, nonrandomized study was conducted of LAA closure with the Watchman device in 150 patients with nonvalvular AF and $CHADS_2$ (congestive heart failure, hypertension, age $\geq$75 years, diabetes mellitus, and prior stroke or transient ischemic attack) score $\geq$1, who were considered ineligible for warfarin. The primary efficacy endpoint was the combined events of ischemic stroke, hemorrhagic stroke, systemic embolism, and cardiovascular/unexplained death.

Results The mean $CHADS_2$ score and CHA_2DS_2-VASc ($CHADS_2$ score plus 2 points for age $\geq$75 years and 1 point for vascular disease, age 65 to 74 years, or female sex) score were 2.8 $\pm$ 1.2 and 4.4 $\pm$ 1.7, respectively. History of hemorrhagic/bleeding tendencies (93%) was the most common reason for warfarin ineligibility. Mean duration of follow-up was 14.4 $\pm$ 8.6 months. Serious procedure- or device-related safety events occurred in 8.7% of patients (13 of 150 patients). All-cause stroke or systemic embolism occurred in 4 patients (2.3% per year): ischemic stroke in 3 patients (1.7% per year) and hemorrhagic stroke in 1 patient (0.6% per year). This ischemic stroke rate was less than that expected (7.3% per year) based on the $CHADS_2$ scores of the patient cohort.

Conclusions LAA closure with the Watchman device can be safely performed without a warfarin transition, and is a reasonable alternative to consider for patients at high risk for stroke but with contraindications to systemic oral anticoagulation. (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology [ASAP]; NCT00851578)
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Atrial fibrillation (AF) is the most common sustained arrhythmia, and increases the risk of ischemic stroke 5-fold (1). AF-related ischemic stroke is associated with significant morbidity, mortality, and healthcare expenditures (2–4). Thus, prevention of cardioembolic stroke remains clinically and economically important (5). Although oral anticoagulation with either warfarin or the more recently introduced factor II/Xa inhibitors can significantly reduce the risk of stroke in at-risk patients with AF, these medications are associated with the potential for severe hemorrhagic complications (6–9). As an alternative to systemic anticoagulant therapy, the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With AF) clinical trial examined the hypothesis that the "local" therapy of left atrial appendage (LAA) closure could recapitulate the benefits in stroke prevention observed with

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Abbreviations and Acronyms

$CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or transient ischemic attack

CHA_2DS_2-VASC = $CHADS_2$ score plus 2 points for age ≥75 years and 1 point for vascular disease, age 65 to 74 years, or female sex

LAA = left atrial appendage

TEE = transesophageal echocardiogram

TIA = transient ischemic attack

warfarin. The Watchman device proved to be noninferior to warfarin in preventing stroke in nonvalvular AF patients with a $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or transient ischemic attack) score ≥1 (10). However, PROTECT AF only included patients who were candidates for either therapy, and in patients randomized to the LAA closure arm, patients received concomitant warfarin after Watchman implantation for 6 weeks (11). Thus, there are no data on the potential use of the Watchman device in patients with contraindications to warfarin. The nonrandomized ASAP (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology) study was conducted to assess the safety and efficacy of LAA closure in nonvalvular AF patients with a contraindication for warfarin therapy (12,13). Patients only received antiplatelet agents after Watchman implantation.

Methods

This was a multicenter prospective nonrandomized study of LAA closure with the Watchman device (Boston Scientific, Natick, Massachusetts) in patients with nonvalvular AF and a $CHADS_2$ score ≥1, who were ineligible for oral anticoagulation. Patients (N = 150) were enrolled at 4 centers between January 2009 and November 2011. The inclusion criteria were age >18 years, nonvalvular AF (paroxysmal, persistent, or permanent), $CHADS_2$ score ≥1, a contraindication for even short-term oral anticoagulation therapy, and eligibility for 6 months of treatment with a thienopyridine antiplatelet agent (clopidogrel or ticlopidine) and lifelong aspirin. Contraindications for oral anticoagulant use (based on the warfarin labeling) were categorized as: 1) hemorrhagic/bleeding tendencies—defined as active peptic ulcer disease or history of overt bleeding of the gastrointestinal, genitourinary, or respiratory tract; central nervous system hemorrhage, cerebral aneurysms, dissection of the aorta, pericarditis/pericardial effusions or bacterial endocarditis; 2) blood dyscrasias; 3) unsupervised patients with senility and/or high fall risk; and 4) other documented reason (including hypersensitivity to warfarin). Similar to the PROTECT AF trial, the key exclusion criteria included left ventricular ejection fraction <30%, intracardiac thrombus/dense spontaneous contrast by transesophageal echocardiography (TEE), a patent forman ovale with atrial septal aneurysm, complex atheroma with mobile plaque in the ascending aorta/aortic arch, significant mitral stenosis, or an existing pericardial effusion >3 mm (10). After approval by the institutional review board, patients were enrolled with written informed consent.

Implantation and follow-up. Heparin was administered to a recommended active clotting time of 200 s to 300 s. Under TEE and fluoroscopic guidance, Watchman implantation was performed as previously described (10). After device implantation, subjects were followed up at 3, 6, 12, 18, and 24 months. A TEE was performed at 3 and 12 months to assess device position, peri-device LAA flow, and device-related thrombus. The National Institutes of Health stroke scale was administered by a neurologist at baseline, and at 3, 12, and 24 months (14). The Barthel index and modified Rankin scale were administered at baseline and all follow-ups. Following the Watchman implant, patients were administered 6 months of a thienopyridine antiplatelet agent (clopidogrel or ticlopidine) and lifelong aspirin.

Definitions. The $CHADS_2$ score (scale 0 to 6) includes congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or transient ischemic attack (TIA [2 points]) (15). The CHA_2DS_2-VASc score (scale 0 to 9) includes the same components but with 2 points for age ≥75 years and the addition of 1 point for vascular disease, age 65 to 74 years, or female sex (16). The composite primary efficacy endpoint includes ischemic stroke, hemorrhagic stroke, systemic embolism, and cardiovascular/unexplained death. A serious adverse event includes any untoward medical condition that results in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, or resulted in persistent or significant disability/incapacity. An independent clinical events committee adjudicated all adverse events.

Statistical methods. A sample size of as many as 150 enrolled subjects was determined based on the feasibility nature of the study and was not calculated by statistical means. The pre-defined analysis reported here consists of all subjects completing the 3-month follow-up visit. Incidence rates are expressed as percentages or rates (per 100 patient-years). Patient-years were calculated from the date of implant attempt to either the event date, date of last known status, or date of death.

Results

Patient demographics, cardioembolic risk factors, and follow-up compliance. The baseline characteristics of the study population are shown in Table 1. The mean age was 72.5 ± 7.4 years, 64% (n = 96 of 150) were male. The most common risk factor for stroke was hypertension (94.7%), and 40% of patients previously had an ischemic stroke/TIA. The mean $CHADS_2$ score was 2.8 ± 1.2, and 85% of patients were $CHADS_2$ ≥2. The mean CHA_2DS_2-VASC score was 4.4 ± 1.7, and 95% of patients were CHA_2DS_2-VASC ≥2. History of hemorrhagic/bleeding tendencies (93%) was the most common reason for warfarin ineligibility. The mean duration of follow-up was 14.4 ± 8.6 months, and the overall compliance with follow-up visits

Table 1 Clinical Characteristics and Stroke Risk (N = 150)

Clinical	
Age, yrs	72.5 ± 7.4
Male	96 (64.0%)
Stroke risk factors*	
Heart failure or reduced LVEF	43 (28.7%)
Hypertension	142 (94.7%)
Age ≥75 yrs	64 (42.7%)
Diabetes mellitus	48 (32.0%)
Prior stroke or TIA	61 (40.7%)
Vascular disease	27 (18.0%)
Age 65 to74 yrs	64 (42.7%)
Female	54 (36.0%)
$CHADS_2$ score	
1	22 (14.7%)
2	39 (26.0%)
3	52 (34.7%)
4	23 (15.3%)
5	13 (8.7%)
6	1 (0.7%)
Mean $CHADS_2$ score (entire cohort, N = 150) = 2.8 ± 1.2	
CHA_2DS_2-VASC score	
1	7 (4.7%)
2	12 (8.0%)
3	25 (16.7%)
4	42 (28.0%)
5	28 (18.7%)
6	18 (12.0%)
7	13 (8.7%)
8	5 (3.3%)
9	0 (0.0%)
Mean CHA_2DS_2-VASC score (entire cohort, N = 150) = 4.4 ± 1.7	
Reasons for warfarin ineligibility*	
History of hemorrhagic/bleeding tendencies	140 (93.0%)
Blood dyscrasia	11 (7.3%)
Unsupervised senility/high fall risk	6 (4.0%)
Other	8 (5.3%)

Values are mean ± SD and n (%). *Risk factors/reasons not mutually exclusive.

$CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or transient ischemic attack; CHA_2DS_2-VASC = $CHADS_2$ score plus 2 points for age ≥75 years and 1 point for vascular disease, age 65 to 74 years, or female sex; LVEF = left ventricular ejection fraction; TIA = transient ischemic attack.

was 98% (96 of 98) at 12 months and 100% at 24 months (43 of 43). Two patients (1.3%) were lost to follow-up, and another 2 patients (1.3%) withdrew consent.

Procedural details. The mean procedure time was 51.5 ± 27.7 min. Successful device implantation occurred in 94.7% (n = 142 of 150) (Table 2). Failure to implant (n = 8, 5.3%) was due to anatomical considerations (n = 7) or pericardial tamponade (n = 1). Of the former, the devices were introduced but did not meet the device release criteria so were removed. The distribution of successfully deployed devices is shown in Table 2; the majority (60.6%) were either 24 mm or 27 mm.

Procedure and device-related serious adverse events. Serious procedure- or device-related safety events occurred in 8.7% of patients (13 of 150) (Table 3). There were 2 cases of pericardial effusion with tamponade requiring percutaneous drainage (500 cc and 600 cc of blood were removed, respectively). Neither patient required surgical intervention. One of these patients subsequently underwent a successful LAA closure procedure; in the other case, the procedure was simply aborted. There were 3 additional cases of small/mild pericardial effusion without tamponade not requiring intervention. Device embolization occurred in 2 patients, both immediately within the procedure itself. In both, the devices embolized to the descending aorta, and were successfully retrieved percutaneously with a vascular loop snare; neither patient experienced immediate or long-term complications. After removal, 1 patient subsequently underwent successful implantation of a larger Watchman device.

There were 6 cases of device-related thrombus; only 1 was adjudicated as a serious adverse event because only it was associated with a stroke (341 days post-implant). The remaining 5 cases were discovered during surveillance TEEs (mean 164 ± 135 days post-implant) without clinical sequela. These 5 cases were conservatively managed: 4 received 4 to 8 weeks of low-molecular-weight heparin, and 1 received no treatment.

Primary efficacy outcomes. As shown in Table 4, after 176.9 patient-years of follow-up, all-cause stroke or systemic embolism occurred in 4 patients (2.3% per year), ischemic stroke in 3 patients (1.7% per year), and hemorrhagic stroke

Table 2 Procedural Details (N = 150)

Procedure time, min	51.5 ± 27.7
Implant success	142 (94.7%)
Implant failure	8 (5.3%)
Anatomical considerations*	7
Discontinued procedure (pericardial effusion)	1
Implanted device sizes	
21 mm	23 (16.2%)
24 mm	46 (32.4%)
27 mm	40 (28.2%)
30 mm	26 (18.3%)
33 mm	7 (4.9%)

Values are mean ± SD and n (%). *In these 7 cases, the devices were deployed but not released as they did not meet the device release criteria, which include the following: 1) the implant is positioned at or slightly distal to and spans the entire left atrial appendage ostium; 2) the implant is stable (by gentle tug test); 3) the implant size is appropriate once deployed; and 4) the implant seals off the left atrial appendage from the left atrium (jet around the device <5 mm) and all lobes are distal to implant.

Table 3 Procedure and Device-Related Serious Adverse Events (N = 150)

Device embolization	2 (1.3%)
Pericardial effusion with tamponade (percutaneous drainage)	2 (1.3%)
Pericardial effusion, no tamponade (no intervention required)	3 (2.0%)
Device thrombus with ischemic stroke*	1 (0.7%)
Femoral pseudoaneurysm (surgically repaired)	1 (0.7%)
Femoral hematoma/bleeding	2 (1.3%)
Other†	3 (2.0%)
Total patients with procedure- and device-related SAEs	13 (8.7%)

Values are n (%). *Device thrombus and stroke occurred in a single patient, but is counted as 2 adverse events. †Oral bleeding, n = 1, and intraprocedural hypotension, n = 2.

SAE = serious adverse event(s).

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in 1 patient (0.6% per year). The strokes occurred in patients with a prior history of stroke or TIA. A total of 9 patients (5.0% per year) died during the follow-up period (cardiovascular, n = 3; cancer, n = 2; other, n = 4); none were device or procedure related. The cardiovascular and noncardiovascular deaths occurred at a median of 406 and 209 days post-implant, respectively.

Comparison to expected annual stroke/TIA risk. The mean $CHADS_2$ score in the ASAP study population was 2.8, which equates to a predicted ischemic stroke rate of 7.4% per year using data from a cohort of hospitalized AF patients, and assuming no aspirin use (17). If this expected stroke rate of 7.4% per year is averaged with data in which aspirin was used (15), the expected ischemic stroke of the ASAP population is approximately 7.3% (Fig. 1). Thus, the observed ischemic stroke rate of 1.7% per year (1-sided exact upper 95% bound rate of 4.4%) represents 77% fewer events than expected.

Clopidogrel has been reported to reduce ischemic stroke by 32% (13). Thus, if one discounts the 7.3% rate by 32% (though clopidogrel or ticlopidine were only used for 6 months in the ASAP study), the expected stroke rate would be 5.0% per year. But the observed rate of 1.7% per year would still represent a 64% reduction in the ischemic stroke rate.

Discussion

This represents the first prospective study of LAA closure with the Watchman device in the clinically important population of patients with contraindication to even short-term oral anticoagulation therapy (18,19).

Main findings. On the basis of the thromboembolic risk profile ($CHADS_2$ score 2.8) of the ASAP registry population, the annualized ischemic stroke rate was expected to be 7.3% if treated with aspirin alone (15). However, the observed rate in ASAP was only 1.7%, representing 77% fewer events than expected. Patients in the ASAP study also received concomitant treatment with clopidogrel for 6 months, and the ACTIVE A (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events) study demonstrated that AF patients additionally treated with life-long clopidogrel sustained fewer ischemic strokes that those treated with aspirin alone (relative risk: 0.68; 95% confidence interval: 0.57 to 0.80) (13,15). Accordingly, if one discounts the expected stroke rate of this $CHADS_2$ score population by this 32% stroke benefit (even though the ASAP study patients did not receive life-long clopidogrel, but rather, only 6 months), this would still result in an expected ischemic stroke rate of 5.0%—again, the observed stroke rate of 1.7% represents 64% fewer events than expected.

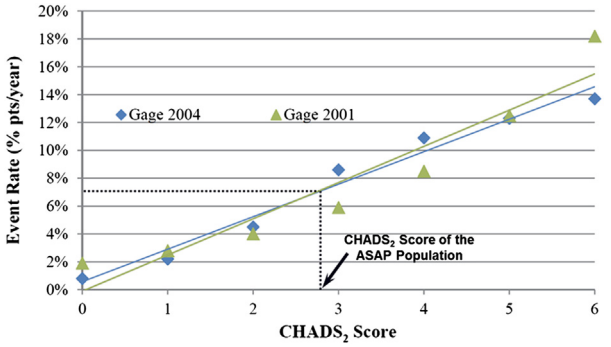

Figure 1 Expected Annual Rate of Stroke Based on $CHADS_2$ Score

Gage 2004 **(blue diamonds)** (15); Gage 2001 **(green triangles)** (17). ASAP = ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology; $CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or transient ischemic attack.

For patients randomly assigned to the device arm in the PROTECT AF study, the annualized rates of all-cause stroke and ischemic stroke were 2.3% and 2.2%, respectively. If one excludes the procedure-related ischemic strokes observed in PROTECT AF, this would translate to an annualized ischemic stroke rate of 1.34% in the Watchman group. (Although these procedure-related strokes are certainly relevant when assessing the risk/benefit ratio of Watchman implantation in any given patient, these are technical issues that are operator experience-related and when removed, allow for a better understanding of the underlying scientific question of the antistroke potential of LAA closure using various periprocedure anticoagulation strategies.) Interestingly, the annualized rates of all-cause stroke and ischemic stroke in the ASAP registry (2.3% and 1.7%, respectively) was similar despite the fact that the patients in the device arm of the PROTECT AF study were additionally prescribed warfarin during the 45-day transition period until the follow-up TEE. This raises the possibility that this initial warfarin transition may not provide a significant benefit even in those patients able to tolerate short-term oral anticoagulation therapy. Of course, this is only a hypothesis based on shorter-term follow-up in the ASAP registry, and must be assessed in a prospective clinical trial.

Stroke reduction in warfarin-ineligible patients. Until recently, pharmacological strategies of reducing the risk of stroke in high-risk patients considered unsuitable for warfarin therapy have been only modestly effective. The combination of aspirin and clopidogrel reduces the risk of ischemic stroke (2.4% per year), compared with aspirin alone

Table 4 Clinical Outcomes

	Entire Cohort Events/Patient-Years*
Primary efficacy	8/175.0 (4.6%)
Death, all cause	9/180.0 (5.0%)
All stroke	4/176.0 (2.3%)
Ischemic stroke	3/176.9 (1.7%)
Hemorrhagic stroke	1/179.1 (0.6%)

The primary efficacy endpoint was defined as the combined events of ischemic stroke, hemorrhagic stroke, systemic embolism, and cardiovascular/unexplained death. *Events per 100 patient-years.

(3.3% per year), but at the cost of an increased major bleeding risk (2.0% vs. 1.3% per year, respectively) (13). These results were reflected in the 2011 American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society focused update on the management of AF patients, which assigned a Class IIB recommendation to the addition of clopidogrel in warfarin-ineligible patients (20).

But this may change with the advent of novel oral anticoagulants. In the AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Strokes in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) study, warfarin-ineligible patients were randomly allocated to either aspirin or the factor Xa inhibitor, apixaban (21). The primary efficacy endpoint of stroke or systemic embolization was significantly lower in patients randomly assigned to apixaban (1.6% per year) versus aspirin (3.7% per year; hazard ratio: 0.45, 95% confidence interval: 0.32 to 0.62; $p < 0.001$). Furthermore, there were similar rates of major bleeding in the apixaban (1.4% per year) and aspirin groups (1.2% per year; hazard ratio: 1.13, 95% confidence interval: 0.74 to 1.75; $p = 0.57$). Although apixaban has not yet been approved for clinical use, on the one hand, this raises the question of exactly which patients will be ineligible for oral anticoagulation therapy and require LAA closure; and on the other hand: 1) the patients in the AVERROES study had a lower $CHADS_2$ score than those in the ASAP study (2.0 vs. 2.8, respectively)—a factor known to correlate with bleeding risk; and 2) in the AVERROES study, even in the carefully monitored setting attendant with a clinical trial, the rate of permanent discontinuation of apixaban was 17.9% per year.

In addition, there are prior studies of percutaneous LAA closure with the PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) device in warfarin-ineligible patients. This device, which is no longer commercially available, also supported the notion that LAA closure in the absence of a warfarin transition can reduce strokes in high-risk AF patients. The European PLAATO study was a prospective, multicenter, nonrandomized study of 180 nonrheumatic AF patients with $CHADS_2$ scores ≥ 2 and contraindications to warfarin (22). After 129 patient-years of follow-up, the annualized stroke rate in this patient cohort was 2.3%, as compared with an expected rate of 6.6%. Although the mean follow-up of this study was only 9.6 months, there are 2 single-center reports of 5-year follow-up data after LAA closure with the PLAATO device. In the first cohort of 64 patients, the annualized stroke rate was 3.8% after PLAATO device implantation, as compared with an expected stroke rate of 6.6%; in the second cohort of 22 patients, the annualized stroke rate was 3.6% after PLAATO device implantation, as compared to an expected stroke rate of 6.8% (23,24). It remains to be seen whether this preservation of antistroke benefit over longer follow-up with the PLAATO device will also be realized with the Watchman device.

Safety. Serious procedure- or device-related safety events occurred in 8.7% of patients (13 of 150 patients), which is lower than that in the early PROTECT AF study cohort (10.0%). The 2 most significant safety events in the PROTECT AF trial were pericardial tamponade related to trauma during device implantation and procedure-related stroke due to inadvertent introduction of air or thrombus into the systemic circulation during device implantation. The incidence of pericardial tamponade requiring intervention was 5.0% in the PROTECT AF study, but with operator experience, this decreased in the subsequent nonrandomized multicenter CAP (Continued Access Protocol) registry to 2.2% (11). The ASAP tamponade rate (1.3%) compares favorably; importantly, both patients were successfully managed percutaneously. Procedure-related stroke occurred in 1.1% of patients in the PROTECT AF trial, but with operator experience, there were no procedure-related strokes in the CAP registry (11) or in the ASAP study. With careful sheath management during implantation, this complication appears to have largely been eliminated.

Of the 150 patients enrolled in the ASAP registry, there were 6 cases (4%) of device-related thrombus on the device face, but only 1 resulted in clinical sequela (an ischemic stroke). The remaining 5 thrombi were detected during routine TEE screening. For comparison, in the PROTECT AF study, device-associated thrombus was observed in 4.2% (20 of 473) of successfully implanted patients, but only 3 had an ischemic stroke; the other patients were either asymptomatic or the thrombus resolved with anticoagulation therapy. That translated to a device thrombus-associated annualized stroke rate of 0.3% (11).

In the ASAP study, there were 2 instances (1.3%) of device embolization to the aorta—both of which occurred during the procedure—and were percutaneously snared and removed. For comparison, of the 542 and 460 Watchman patients enrolled in the PROTECT AF trial and the CAP registry, the device embolized in 3 (0.6%) and 0 (0%) patients, respectively. When all trials are combined, this translates to an overall device embolization rate of 0.4% (5 of 1,152 patients).

Similar to what was observed in the PROTECT AF and CAP studies, there were no deaths related to the procedure or to the device in the ASAP registry. For comparison, in the European PLAATO study, 2 patients (1.1%) died within 24 h of the procedure, and there were 6 cases of cardiac tamponade (3.3%), of which 2 required surgery (22).

Study limitations. The prospective, nonrandomized design of this study is inherently limited by the absence of a control or alternative treatment group, and like all observational studies is prone to selection bias. A randomized controlled trial would be necessary to confirm the favorable reductions in ischemic stroke seen with LAA closure in warfarin-ineligible patients. Furthermore, because newer oral anticoagulant agents (e.g., apixaban, rivaroxaban, and dabigatran) may be better tolerated by certain patients, a randomized

controlled trial comparing LAA closure to 1 of these newer drugs is necessary (25). The complication rate of Watchman implantation may be higher in centers during their initial learning curve than observed in this study. As with other studies that have enrolled patients considered unsuitable for warfarin, clinical judgment is often the final determination of whether a patient can safely or adequately take warfarin, which can result in an overestimation of bleeding risk, especially in the elderly. Finally, although the ASAP registry was a prospective multicenter study with rigorous monitoring and independent adjudication of all clinical events, it was nonetheless not randomized and utilized historical control data to predict the expected stroke rates.

Conclusions

Building upon the demonstration in the PROTECT AF study that "local" therapy with LAA closure using the Watchman device recapitulates the stroke prophylactic effect of "systemic" therapy with oral anticoagulation therapy, the ASAP registry has demonstrated that the Watchman device can be safely implanted without a warfarin transition. That allows the application of this therapy to the patient population at greatest clinical need for an alternative to oral anticoagulation therapy: AF patients at high risk for stroke but with contraindications to systemic oral anticoagulation. Indeed, the recent 2012 European Society of Cardiology guidelines for AF management have, for the first time, included percutaneous LAA closure therapy for stroke prophylaxis in AF patients—particularly patients with contraindications to chronic anticoagulation therapy (26).

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REFERENCES

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22:983–8.
2. Kim MH, Johnston SS, Chu BC, Dalal MR, Schulman KL. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. Circ Cardiovasc Qual Outcomes 2011;4:313–20.
3. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. Circulation 2012;125:e2–220.
4. Hylek EM, Go AS, Chang Y, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N Engl J Med 2003;349:1019–26.
5. Mercaldi CJ, Ciarametaro M, Hahn B, et al. Cost efficiency of anticoagulation with warfarin to prevent stroke in Medicare beneficiaries with nonvalvular atrial fibrillation. Stroke 2011;42:112–8.
6. Mant J, Hobbs FD, Fletcher K, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet 2007;370:493–503.
7. Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. Circulation 2007;115:2689–96.
8. Lip GY, Andreotti F, Fauchier L, et al. Bleeding risk assessment and management in atrial fibrillation patients: a position document from the European Heart Rhythm Association. Europace 2011;13:723–46.
9. Flaherty ML, Kissela B, Woo D, et al. The increasing incidence of anticoagulant-associated intracerebral hemorrhage. Neurology 2007;68:116–21.
10. Holmes DR, Reddy VY, Turi ZG, et al. 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.
11. Reddy VY, Holmes D, 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.
12. Lee WC, Lamas GA, Balu S, Spalding J, Wang Q, Pashos CL. Direct treatment cost of atrial fibrillation in the elderly American population: a Medicare perspective. J Med Econ 2008;11:281–98.
13. Connolly SJ, Pogue J, Hart RG, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med 2009;360:2066–78.
14. Kasner SE. Clinical interpretation and use of stroke scales. Lancet Neurol 2006;5:603–12.
15. Gage BF, van Walraven C, Pearce L, et al. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. Circulation 2004;110:2287–92.
16. 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.
17. 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.
18. Connolly S, Yusuf S, Budaj A, et al. Rationale and design of ACTIVE: the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events. Am Heart J 2006;151:1187–93.
19. Onalan O, Crystal E. Left atrial appendage exclusion for stroke prevention in patients with nonrheumatic atrial fibrillation. Stroke 2007;38 Suppl:624–30.
20. Wann LS, Curtis AB, January CT, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2011;57:223–42.
21. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. N Engl J Med 2011;364:806–17.
22. Bayard YL, Omran H, Neuzil P, et al. PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) for prevention of cardioembolic stroke in non-anticoagulation eligible atrial fibrillation patients: results from the European PLAATO study. EuroIntervention 2010;6:220–6.
23. Block PC, Burstein S, Casale PN, et al. Percutaneous left atrial appendage occlusion for patients in atrial fibrillation suboptimal for warfarin therapy: 5-year results of the PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) study. J Am Coll Cardiol Intv 2009;2:594–600.
24. Viles-Gonzalez JF, Reddy VY, Petru J, et al. Incomplete occlusion of the left atrial appendage with the percutaneous left atrial appendage transcatheter occlusion device is not associated with increased risk of stroke. J Interv Card Electrophysiol 2012;33:69–75.
25. Lopes RD, Al-Khatib SM, Wallentin L, et al. Efficacy and safety of apixaban compared with warfarin according to patient risk of stroke and of bleeding in atrial fibrillation: a secondary analysis of a randomised controlled trial. Lancet 2012;380:1749–58.
26. 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.

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