The Assessment of the Watchman Device in Patients Unsuitable for Oral Anticoagulation (ASAP-TOO) trial

David R. Holmes, MD,[a] Vivek Y. Reddy, MD,[b] Maurice Buchbinder, MD,[c] Kenneth Stein, MD,[d] Myriah Elletson[d] Martin W. Bergmann, MD,[e] Boris Schmidt, MD,[f] and Jacqueline Saw, MD, FRCPC[g] *Rochester, Minneapolis, MN; New York, NY; Stanford, CA; Hamburg, Frankfurt, Germany; and British Columbia, Canada*

Background Oral anticoagulants (OACs) reduce stroke risks with nonvalvular atrial fibrillation (AF); however, they are underused because of absolute or relative contraindications due to real or perceived risk of bleeding. Although left atrial appendage closure is increasingly performed in OAC-ineligible patients, this has not been studied in a randomized controlled trial.

Study objectives The ASAP-TOO study is designed to establish the safety and effectiveness of the Watchman left atrial appendage closure device in patients with nonvalvular AF who are deemed ineligible for OAC. The primary effectiveness end point is the time to first occurrence of ischemic stroke or systemic embolism. The primary safety end point includes all-cause death, ischemic stroke, systemic embolism, or device- or procedural-related event requiring open cardiac surgery or major endovascular intervention.

Study design This is a multinational, multicenter prospective randomized trial. Patients meeting the inclusion criteria with CHA_2DS_2-VASc score ≥ 2 and who are deemed by 2 study physicians to be unsuitable for OAC will be randomized in a 2:1 allocation ratio to Watchman versus control. Control patients will be prescribed single antiplatelet therapy or no therapy at the discretion of the study physician. Up to 888 randomized subjects will be enrolled from up to 100 global investigational sites. Both device group and control patients will have follow-up visits at 3, 6, and 12 months and then every 6 months through 60 months.

Summary This trial will assess the safety and efficacy of Watchman in this challenging population of high–stroke risk AF patients. (Am Heart J 2017;189:68-74.)

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia both in the United States and worldwide. As populations age with increasing morbidity, the incidence increases.[1] The relationship between increasing age, AF, and stroke is well documented. AF is associated with a 5-fold increase in stroke rates, and these cardioembolic events are typically associated with marked increases in both mortality and morbidity.[2-4]

The pathophysiology of stroke in the setting of nonvalvular AF has been well studied in pathologic and echocardiographic studies and has been confirmed in the randomized controlled Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation (PROTECT-AF) study with left atrial appendage closure (LAAC), which documented equivalent reduction in stroke with Watchman LAAC compared with warfarin. The field continues to evolve based primarily on the introduction and increasing application of non–vitamin K oral anticoagulants (NOACs) and the subsequent approval of LAAC with the Watchman device. The former has been documented in multiple randomized trials to be superior to conventional warfarin therapy for reduction of hemorrhagic stroke, with attenuated reduction in all-cause stroke as well as a reduction in ischemic stroke. Yet NOACs do not or only marginally reduce major bleeding, specifically gastrointestinal, bladder, and skin bleeding events.[5-9] In contrast, LAAC has been documented in randomized clinical trials and registries to be associated with a marked reduction in

From the [a]Mayo Clinic, Rochester, MN, [b]Icahn School of Medicine at Mount Sinai, New York, NY, [c]Stanford University, Stanford, CA, [d]Boston Scientific Corp., Minneapolis, MN, [e]Herzkatheter Asklepios Wandsbek, Hamburg, Germany, [f]Cardioangiologisches Centrum Bethanien, Frankfurt, Germany, and [g]Vancouver General Hospital, Vancouver, British Columbia, Canada.

RCT# NCT02928497
Clinicaltrials.gov Identifier: NCT02928497
Submitted December 19, 2016; accepted March 3, 2017.
Reprint requests: Jacqueline Saw, MD, FRCPC, 2775 Laurel St, Level 9, Vancouver General Hospital, Vancouver, British Columbia, Canada V5Z1M9.
E-mail: jsaw@mail.ubc.ca
0002-8703

http://dx.doi.org/10.1016/j.ahj.2017.03.007

hemorrhagic stroke and postprocedural longer-term rates of overall bleeding.[10,11]

The field of stroke prevention in nonvalvular AF has been complicated by several factors. Although anticoagulants, both warfarin and NOACs, have been the standard of care and proven to reduce stroke in nonvalvular AF, particularly a reduction in hemorrhagic stroke, they are underused particularly in those patients at highest stroke risk.[12] This is related to the presence of either absolute or relative contraindications to anticoagulation due to real or perceived risk of bleeding. Accordingly, patients at high risk for stroke are not treated with drugs proven to reduce the risk of stroke. Furthermore, the only randomized control trials of LAAC as an alternative to anticoagulation for stroke prevention mandated that patients be treated with short-term (45 days) warfarin to facilitate rapid endothelialization of the device, potentially limiting this technology in patients at the highest risk for bleeding.[10,11] Although there is an increasing amount of information on LAAC in patients treated only with single or dual antiplatelet therapy, it has not been studied in randomized controlled trials. The ASAP-TOO trial has been developed to scientifically address these issues.

Study objectives

The primary study objective of ASAP-TOO (NCT02928497) is to establish the safety and effectiveness of the Watchman LAAC device (Boston Scientific Corp, Minneapolis, MN) in reducing the risk of thromboembolic ischemic stroke and systemic embolism in patients with nonvalvular AF who are deemed not eligible for anticoagulant therapy. This is in contradistinction to the current manufacturer's instruction for use that mandates patients receiving the Watchman device be eligible for warfarin therapy and that warfarin therapy be administered for at least 45 days based upon the study protocol of PROTECT-AF and Prospective Randomized Evaluation of the Watchman LAA Closure Device in Patients with Atrial Fibrillation Versus Long Term Warfarin Therapy (PREVAIL).[10,11]

The Watchman device has been studied in 2 randomized clinical trials and multiple national and global registries.[10,11,13] As previously described, it is a self-expanding nitinol-framed structure with fixation barbs and a permeable polyester fabric, which covers the ostium of the LAA. The Watchman device (generation 2.5) is available in 5 sizes, with diameters that range from 21 to 33 mm, and chosen depending upon the LAA size. It is implanted by a catheter-based delivery system using a transseptal approach and positioned at or slightly distal to the ostium of the LAA.[14]

The primary effectiveness end point of this current study is the time to first occurrence of ischemic stroke or systemic embolism. The primary safety end point is the occurrence of one of the following events between the time of implant and within 7 days following the procedure or by hospital discharge, whichever is later: all-cause death, ischemic stroke, systemic embolism, or device- or procedural-related event requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair or arteriovenous fistula repair. *Percutaneous* catheter drainage of a pericardial effusion, *percutaneous* retrieval of an embolized device, or thrombin injection to treat femoral pseudoaneurysm and nonsurgical treatments of access site complications are excluded from this safety end point. Secondary end points include the time to first occurrence of the individual components of the primary end point, the composite occurrence of stroke (ischemic and/or hemorrhagic), systemic embolization and cardiovascular death, the occurrence of *major bleeding* (defined as bleeding academic research consortium [BARC] $\geq$3), and characterization of the stroke events (fatal; disabling; or nondisabling). In addition, net clinical benefit (combining all-cause stroke, systemic embolism, cardiovascular death, and major bleeding) and weighted net clinical benefit analyses will be performed. Procedural outcomes including implant success rate, procedural duration, number of devices and sizes used, and residual peridevice leak will be evaluated.

Patient selection criteria

Patients with documented paroxysmal, persistent, permanent, or long-term/long-standing persistent nonvalvular AF are candidates if they (Table I):

1. have a CHA_2DS_2-VASc score $\geq$ 2;
2. are deemed by 2 study physicians to be unsuitable for oral anticoagulation; and
3. are deemed to be suitable for the defined pharmacologic regimen of aspirin and/or clopidogrel and are willing to follow the required protocol for follow-up visits and examinations.

The exclusion criteria include prior stroke/transient ischemic attack within 30 days prior to randomization; BARC type 3 or 4 bleeding within 14 days of randomization; a history of atrial septal aneurysm or patent foramen ovale (PFO) repair; any mechanical heart valve; New York Heart Association class 4 congestive heart failure; life expectancy <2 years; left ventricular ejection fraction <30%; preexisting pericardial effusion >5 mm; and the presence of an intracardiac thrombus, LAA sludge, or dense spontaneous echo contrast within 2 days prior to implant (Tables II and III).

The acceptable reasons for patients to be considered unsuitable for oral anticoagulation include the following (Table IV):

1. History of overt bleeding related or unrelated to oral anticoagulants: prior intracranial hemorrhage or subdural hematoma, major organ bleeding

Table I. ASAP-TOO inclusion criteria

Clinical inclusion criteria
1. The subject is of legal age to participate in the study per the laws of their respective geography.
2. The subject has documented paroxysmal, persistent, permanent, or long-term/long-standing persistent nonvalvular AF (ie, the subject has not been diagnosed with rheumatic mitral valvular heart disease).
3. The subject has a calculated CHA_2DS_2-VASc score of 2 or greater.
4. The subject is deemed by 2 study physicians to be unsuitable for oral anticoagulation.
5. The subject is deemed by a study physician to be suitable for the defined protocol pharmacologic regimen of aspirin and clopidogrel* therapy following Watchman implant.
6. The subject or legal representative is able to understand and willing to provide written informed consent to participate in the trial.
7. The subject is able and willing to return for required follow-up visits and examinations.

*Ticagrelor or prasugrel may be used in place of clopidogrel if patient has another indication or a known resistance to clopidogrel. Prasugrel should only be used if neither clopidogrel nor tricagrelor can be used because of bleeding risk.

Table II. ASAP-TOO clinical exclusion criteria

Clinical exclusion criteria
1. The subject is unable or unwilling to return for required follow-up visits or examinations.
2. The subject had or is planning to have any invasive cardiac procedure within 30 d prior to randomization (eg, cardioversion, ablation).
3. The subject is planning to have any cardiac or noncardiac invasive or surgical procedure that would necessitate stopping or modifying the protocol required medication regimen within 90 d after the Watchman implant (eg, cardioversion, ablation, cataract surgery, endoscopy).
4. The subject had a prior stroke (of any cause) or TIA within the 30 d prior to randomization.
5. The subject had a prior major bleed (BARC bleeding score of ≥3) within the 14 d prior to enrollment. Lack of resolution of related clinical sequelae, or planned and pending interventions to resolve bleeding/bleeding source are a further exclusion regardless of timing of major bleed.
6. The subject has a history of atrial septal repair or has an atrial septal defect/patent foramen ovale device.
7. The subject has implanted mechanical valve prosthesis in any position.
8. The subject suffers from New York Heart Association class IV congestive heart failure.
9. The subject has left ventricular ejection fraction <30%.
10. The subject is of childbearing potential and is, or plans to become, pregnant during the time of the study (method of assessment upon study physician's discretion).
11. The subject is currently enrolled in another investigational study or registry that would directly interfere with the current study, except when the subject is participating in a mandatory governmental registry or a purely observational registry with no associated treatments.
12. The subject has a life expectancy of <2 y.
13. The subject has a known or suspected hypercoagulable state.

Table III. ASAP-TOO echocardiographic exclusion criteria

Echocardiographic exclusion criteria
1. The subject has intracardiac thrombus, LAA sludge (gelatinous, nonadherent, intracavitary echodensity more layered than dense spontaneous echo contrast seen continuously throughout cardiac cycle) or dense spontaneous echo contrast visualized by TEE within 2 d prior to randomization.
2. The subject has an existing pericardial effusion with a circumferential echo-free space >5 mm, and/or the subject has signs/symptoms of acute or chronic pericarditis, and/or there is evidence of tamponade physiology.
3. The subject has a high-risk PFO with an atrial septal aneurysm excursion >15 mm or length ≥ 15 mm.
4. The subject has a high-risk PFO with a large shunt defined as early, within 3 beats, and/or substantial passage of bubbles.
5. The subject has significant mitral valve stenosis (ie, mitral valve < 1.5 cm^2).
6. The subject has complex atheroma with mobile plaque of the descending aorta and/or aortic arch.
7. The subject has a cardiac tumor.

(eg, gastrointestinal; genitourinary; ocular; spinal; pulmonary; retroperitoneal; pericardial; or ear, nose, and throat), or epistaxis requiring hospital visit or intervention.

2. Increased risk of bleeding or bleeding tendencies: gastrointestinal lesions (eg, diverticular disease, esophageal varices, inflammatory bowel disease, peptic ulcer disease), history of falls/seizures with likelihood of recurrent falls, cerebral amyloid angiopathy, significant thrombocytopenia, need for lifelong dual antiplatelet therapy.
3. Contraindications to warfarin and/or direct oral anticoagulant: severe renal failure (glomerular filtration rate <30), allergy to these agents.
4. Other contraindications including lifestyle or occupational bleeding risk, poor control on warfarin (time in therapeutic range < 50%), and intolerance to direct anticoagulants.

Table IV. Acceptable reasons for unsuitability for oral anticoagulation

Reasons for unsuitability for oral anticoagulation
1. History of overt bleeding related or unrelated to oral anticoagulants:
• Prior history of intracranial or subdural hemorrhage
• Other clinically relevant organ bleeding as defined by requiring hospitalization, transfusion or medical intervention, including the following: gastrointestinal; genitourinary; ocular; spinal; pulmonary; retroperitoneal; pericardial; or ear, nose, and throat. Last event must be within the 6 m prior to randomization.
• Epistaxis requiring emergency department visit, hospitalization, or physician intervention. Last event must be within the 6 m prior to randomization.
2. Increased risk of bleeding or bleeding tendencies:
• Gastrointestinal lesions resulting in clinically relevant bleeding as defined by requiring hospitalization, transfusion, or medical intervention (eg, esophageal varices, diverticular disease with a history of bleeding in which the site was not identified and presumed to be diverticular). Last event must be within the 6 m prior to randomization.
• Active inflammatory bowel disease
• Peptic ulcer disease with gastrointestinal bleeding in which it is deemed that anticoagulation cannot be safely initiated or restarted following healing of the peptic ulcer
• Uncontrolled seizures
• History of traumatic falls with the likelihood of recurrence
• Cerebral amyloid angiopathy
• Significant thrombocytopenia (defined as platelet count <50 × 109/L)
• Need for lifelong dual antiplatelet therapy
3. Contraindications to warfarin and/or direct OAC
• Severe renal failure (glomerular filtration rate <30 mL/[min/1.73 m^3])
• Allergy to the above agents
4. Other contraindications including:
• Lifestyle or occupational bleeding risk (ie, anyone who is at risk of trauma as a result of their occupation or their lifestyle. For example, high-voltage electrical line workers, airline pilots, manual laborers, extreme sports enthusiasts)
• Poor control on warfarin (time in therapeutic range < 50%) and intolerance to the direct OACs
• Other medical or social reasons that make OACs unsuitable (eg, an elderly patient with poor social support and a high risk of bleeding resulting in the use of aspirin alone despite a high stroke risk)

Study design

This is a multinational, multicenter prospective randomized clinical trial. Patients meeting the inclusion criteria (Table I) will be randomized stratified by study site to a 2:1 allocation ratio of Watchman versus control. Up to 888 randomized subjects will be enrolled in this study from up to 100 global investigational sites. The protocol and informed consent will have been approved by each investigator's institutional review board before trial initiation.

All subjects will have their screening criteria assessed (Figure 1) such that the baseline transesophageal echocardiogram (TEE) will be the final study for confirming eligibility. Randomization will be performed electronically to either the device or the control group. Following enrollment and randomization, the device group patients will undergo the implant procedure, and both device group and control patients will have follow-up visits at 3, 6, and 12 months and then every 6 months through 60 months. Both device and control group subjects will be evaluated by a study neurologist blinded to randomization at baseline, 12 months, and 24 months.

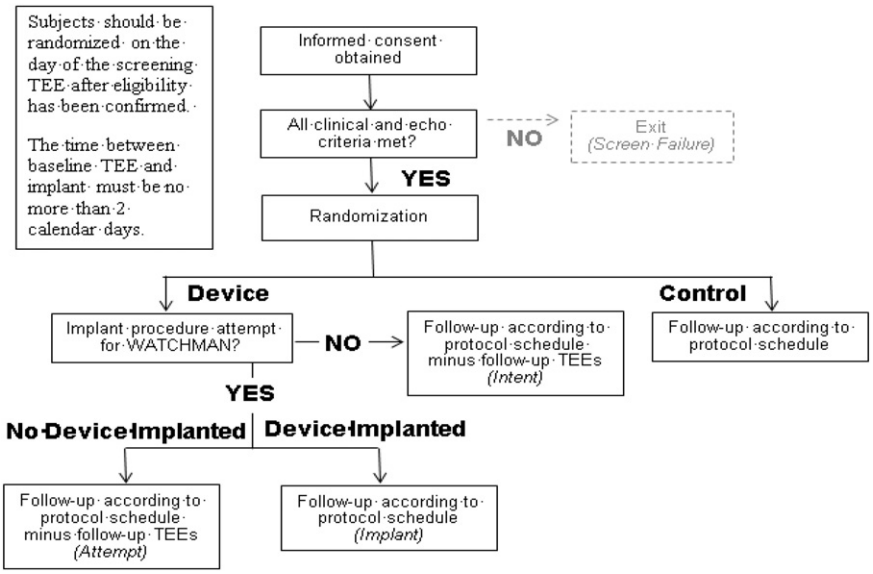
Control patients will be prescribed single antiplatelet therapy or no therapy for the entire duration of the trial at the discretion of the study physician. Depending on the clinical setting, patients may be on dual antiplatelet therapy if indicated.

Patients randomized to the device will undergo implantation within 2 days of the baseline TEE. No other concomitant procedures such as AF ablation will be performed. The implant should be performed using standard-of-care methods established by each investigational site using sterile technique by study physicians trained in percutaneous and transseptal procedures who have completed the manufacturer's physician training program. Information collected will include device release criteria, duration of procedure and fluoroscopy, type of anesthesia, device deficiencies, and device and procedural adverse events. Aspirin should be started 1 day prior to the scheduled implant date and then continued daily for the study duration. Depending on the patient's individual bleeding risk profile, the patient should be heparinized throughout the procedure with a recommended activated clotting time of 200-300 seconds throughout the procedure. Follow-up TEEs will be performed at 3 and 12 months or if a neurologic event has occurred suggesting either transient ischemic attack (TIA) or stroke.

Statistical methods

The statistical objective is to determine if LAAC with Watchman is superior to the control group of patients

Figure 1



ASAP-TOO study flowchart.

treated with single antiplatelet therapy with respect to the primary effectiveness composite end point of ischemic stroke and systemic embolism. The primary method of analysis will be a group sequential design based on the log-rank test to test the null hypothesis of identical time-to-event curves across the device and control groups.

The primary analysis for the primary effectiveness end point will be done on an intent-to-treat basis, with each subject analyzed as being part of their randomized group regardless of the actual treatment received. Additional analysis sets, such as the inclusion of only LAAC patients who undergo an implant attempt, will be used for the primary effectiveness end point as sensitivity analyses. The analysis of the primary safety end point will include all data from subjects randomized to the device who undergo an implant attempt. Statistical analyses of the primary efficacy end point between the device and control groups will occur at periodic intervals. The overall type I and type II errors will both be controlled using a power error spending function ($\rho = 2$). The timing of each analysis will be based on the total number of adjudicated primary effectiveness end point events across both treatment groups; therefore, the exact timing of each analysis cannot be known in advance.

The primary safety end point definition as described above and the event rate will be calculated as the percentage of all implanted or attempted subjects randomized to the device arm who experience a primary safety end point event. The observed primary safety end point event rate in the combined PREVAIL and CAP2 device arms was 1.65%. We estimated a slightly higher rate of 3.30% for ASAP-TOO patients randomized to the device given the increased frailty and lack of alternative anticoagulation options for these patients. A delta of 2.50% was added to this expected rate to establish the performance goal of 5.80%. This performance goal corresponds to a maximum observable rate of 4.16% and is deemed to be clinically acceptable based on the observed rates of procedural complications in comparable procedures, the magnitude of benefit required to pass the efficacy end point, and the absence of an approved alternative for reduction in the risk of ischemic stroke in this population. A 1-sided exact binomial test will be used to test the assumption that the rate of subjects experiencing a primary safety end point event is $\geq$5.80%. The null hypothesis will be rejected if the resulting *P* value is less than .05.

Sample size justification

For the primary effectiveness end point of ischemic stroke and systemic embolization, power calculation was performed using group sequential design log-rank test. With an expected annual event rate of 2.25% with WATCHMAN and expected treatment effect with hazard ratio 0.5 (WATCHMAN vs control), and with 85% power and 2-sided $\alpha < .05$, a maximum sample size of 870 patients is required. For the primary safety end point, a sample size of 592 device subjects is required, representing an overall study sample size of 888 subjects. This provides 90% power with 1-sided α of 5% and accommodating expected attrition rate of 2.5%. Therefore, the overall study sample size (N = 888) will be driven by the

primary safety end point analysis. This sample size provides slightly more than 86.5% power for the primary effectiveness end point analysis. This sample size was calculated using exact binomial methodology using SAS version 9.4.

Study organization

Clinical Events Committee

A Clinical Events Committee (CEC) consisting of an independent group of individuals with pertinent expertise including neurology, neuroradiology, interventional cardiology, and electrophysiology will review and adjudicate the events that have been included in the primary and secondary end points. The events that the CEC will review for this study include all strokes, TIA, all-cause death, systemic embolism, bleeding events, and device- and/or procedure-related events which resulted in open cardiac/endovascular surgery. The CEC will review a safety event dossier, which may include copies of subject source documents provided by study sites, and confirm inclusion of the event into the primary and secondary end points.

Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be established to review the data and safety parameters for the study. The DMC will develop a charter and stopping rules for the study. Members will consist of at least 3 physicians in specialties of electrophysiology, interventional cardiology, or neurology. At least 1 member of the committee will be a biostatistician. Periodic meetings will be held by the DMC to review study data and evaluate the impact of identified adverse events. The DMC may recommend revising the study protocol or stopping the study early if an unacceptable rate of adverse events is experienced to maintain the safety and welfare of the involved subjects.

Funding

The study was designed by the principal investigators (J. S., M. C., V. Y. R.) in collaboration with the sponsor and with consultation and approval by the Federal Drug Administration. The study was sponsored by Boston Scientific Corporation.

Discussion

Cardioembolic stroke in patients with non-valvular atrial fibrillation is a major clinical problem that can result in markedly increased morbidity and mortality. Given the well-documented relationship between increasing age, increasing incidence of AF, and the associated increased stroke hazard, it has significant public health issues. In this patient population, anticoagulant therapy either with warfarin or increasingly more often with NOACs has been shown to significantly reduce both overall stroke and more specifically hemorrhagic stroke.[5] This information has formed the basis for guideline therapy recommendations of these agents in patients at increased risk for stroke. In this group, therapeutic strategies are selected based upon assessment of the risk-benefit ratios using a variety of risk prediction models, most prominently CHA_2DS_2-VASc and HAS-BLED, which are used in combination to select options. There are however several elements identical to both stroke and bleeding risk scores so that patients at increased risk of stroke are also at increased risk of bleeding. Accordingly, some patients do not receive guideline-based medical therapy with an OAC because of concerns of bleeding.[12] In addition, up to 25% of patients discontinue such guideline-based therapy within the first 24 months of administration.[6-8] Such patients then remain unprotected from the standpoint of stroke prevention.

The pathophysiology of stroke in this setting has been well studied; the source of the thrombus responsible for the stroke has been found to be the LAA in approximately 90% of these patients.[12] This finding has led to the development of local site-specific therapy with LAA occlusion. Only 1 endovascular device (Watchman) has been approved by the FDA for stroke prevention in this setting, which has been tested in 2 randomized studies and multiple registries, and these data formed the basis for device approval. The PROTECT-AF study showed Watchman to be noninferior to warfarin for overall stroke prevention but superior in respect to a decrease in hemorrhagic stroke and long-term bleeding, and to be associated with a reduction in all-cause mortality. The meta-analysis of PROTECT-AF and PREVAIL also showed similar all-cause stroke or systemic embolization rates between Watchman and warfarin, with lower hemorrhagic stroke and cardiovascular mortality with Watchman. For the randomized controlled trials and US registries, a condition of approval was that patients had to be eligible for long-term warfarin.[10,11,15,16] Accordingly, the instruction for use reflected that, and currently, patients receiving this device must be felt clinically able to take anticoagulants, although there must be a reason for concern on the part of either the physician or patient about long-term use of these agents.

The issue has become complicated by the fact that in large non-US registries, the device is implanted in patients who have either a relative or absolute contraindication to oral anticoagulants. In the EWOLUTION Registry of 1,022 patients treated with Watchman, 72% were felt to be in the category of "contraindication" to anticoagulation.[13] In a smaller study, ASAP,[17] 150 patients in whom anticoagulation therapy was contraindicated underwent device implantation. In this population, the rate of ischemic stroke or systemic embolism (1.7% annualized) was 77% less than would be expected for this population if only treated with aspirin (7.3% annualized based on the

$CHADS_2$ score); this imputed benefit was observed up to 5 years of follow-up.[18] In both of these experiences as well as in other registries, the device was safe and efficacious without anticoagulation.

The current trial ASAP-TOO is aimed at resolving the issues by randomizing a predicted 888 patients in a 2:1 mode to either Watchman without any oral anticoagulation or a comparison group of control patients with similar CHA_2DS_2-VASc scores who will be treated with either single antiplatelet or no antiplatelet therapy.

Summary

The ASAP-TOO study is a multicenter randomized controlled trial comparing Watchman LAA closure to single or no antiplatelet therapy in nonvalvular AF patients who are deemed ineligible for OAC. This trial will assess the safety and efficacy of Watchman in this challenging population of high–stroke risk AF patients.

Disclosures

Dr Holmes reports that both he and Mayo Clinic have a financial interest in technology related to this research. That technology has been licensed to Boston Scientific. Dr Reddy has received grant support from and has served as a consultant to Boston Scientific, Coherex, and St Jude Medical. Dr Buchbinder has received research grant support from and has been a consultant for Boston Scientific. Dr Stein and Ms Elletson are employees of Boston Scientific. Dr Bergmann has served as a consultant for Biosense Webster and Boston Scientific, and has received honorarium from Bayer Pharma Ag, Biotronik, Boehringer Ingelheim, Daiichi Sankyo, Eli-Lilly, Novartis, and St Jude Medical. Dr Schmidt has served as a consultant to and received speaker honoraria from Boston Scientific and St Jude Medical. Dr Saw has received grant supports from AstraZeneca, Abbott Vascular, St Jude Medical, Boston Scientific, and Servier; has served as consultant for AstraZeneca, St Jude Medical, Boston Scientific, Abbott Vascular, and Bayer; and has served as proctor for St Jude Medical and Boston Scientific.

References

1. Colilla S, Crow A, Petkun W, et al. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. Am J Cardiol 2013;112(8):1142-7.
2. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22(8):983-8.
3. Wolf PA, D'Agostino RB, Belanger AJ, et al. Probability of stroke: a risk profile from the Framingham Study. Stroke 1991;22(3):312-8.
4. Lamassa M, Di Carlo A, Pracucci G, et al. Characteristics, outcome, and care of stroke associated with atrial fibrillation in Europe: data from a multicenter multinational hospital-based registry (The European Community Stroke Project). Stroke 2001;32(2):392-8.
5. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383(9921):955-62.
6. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365(11):981-92.
7. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365(10):883-91.
8. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361(12):1139-51.
9. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369(22):2093-104.
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(9689):534-42.
11. Holmes Jr DR, Kar S, Price MJ, et al. Prospective randomized evaluation of the watchman left atrial appendage closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. J Am Coll Cardiol 2014;64(1):1-12.
12. Camm AJ, Accetta G, Ambrosio G, et al. Evolving antithrombotic treatment patterns for patients with newly diagnosed atrial fibrillation. Heart 2016.
13. Boersma LV, Schmidt B, Betts TR, et al. Implant success and safety of left atrial appendage closure with the WATCHMAN device: peri-procedural outcomes from the EWOLUTION registry. Eur Heart J 2016;37(31):2465-74.
14. Saw J, Lempereur M. Percutaneous left atrial appendage closure: procedural techniques and outcomes. JACC Cardiovasc Interv 2014;7(11):1205-20.
15. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg 1996;61(2):755-9.
16. Reddy VY, Holmes D, Doshi SK, et al. 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(4):417-24.
17. Reddy VY, Mobius-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(25):2551-6.
18. Sharma D, Reddy VY, Sandri M, et al. Left atrial appendage closure in patients with contraindications to oral anticoagulation. J Am Coll Cardiol 2016;67(18):2190-2.