

## Initial Experience With High-Risk Patients Excluded From Clinical Trials Safety of Short-Term Anticoagulation After Left Atrial Appendage Closure Device

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**Background**—The implantation of left atrial appendage closure device (WATCHMAN, Boston Scientific, Natick, MA) is an alternative option to oral anticoagulation (OAC) for stroke prevention in atrial fibrillation. Patients require short-term OAC after implantation to avoid device thrombosis. The 2 clinical trials that assessed this device excluded patients thought not to be candidates for OAC. As such, little is known about the safety of this strategy in patients with previous major bleeding events.

**Methods and Results**—All 20 consecutive patients with history of spontaneous major bleeding while on OAC who had subsequently undergone WATCHMAN device implantation at our institution were included. A newly conceived multidisciplinary Atrial Fibrillation Stroke Prevention Center evaluated patients for candidacy for device implantation and subsequent antithrombotic therapy. The primary outcome was spontaneous major bleeding while receiving short-term postprocedural OAC. Median CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores were 5 (quartiles 5–6) and 5 (quartiles 4–5), respectively. Previous major bleeding events were major gastrointestinal bleeding, intracranial bleeding, spontaneous hemopericardium with cardiac tamponade, and hemarthrosis in 11, 7, 1, and 1 patients, respectively. None of the patients had spontaneous major bleeding during the course of OAC after device implantation. In 1 patient, OAC was discontinued after 40 days because of mechanical fall with head trauma resulting in subdural hematoma with no associated neurological deficits; this was managed conservatively.

**Conclusions**—With careful multidisciplinary evaluation, a short course of OAC after WATCHMAN device implantation in patients with previous spontaneous major bleeding events is associated with low risk of recurrent spontaneous major bleeding. (*Circ Arrhythm Electrophysiol.* 2016;9:e004004. DOI: 10.1161/CIRCEP.116.004004.)

**Key Words:** anticoagulants ■ atrial appendage ■ atrial fibrillation ■ hemorrhage ■ standard of care ■ stroke ■ thromboembolism

Atrial fibrillation (AF) is associated with ≈5-fold increase in the risk of stroke.<sup>1</sup> Long-term oral anticoagulation (OAC) has been the standard of care for patients with AF who are at high risk for thromboembolic events.<sup>2–4</sup>

The left atrial appendage (LAA) is the origin of thromboembolism in ≈90% of cases.<sup>5</sup> Recently, left atrial appendage closure (LAAC) emerged as an alternative stroke prevention strategy for nonvalvular AF patients who cannot be safely managed with long-term OAC.<sup>6</sup> The WATCHMAN device (Boston Scientific Corporation, Natick, MA) was approved by the Food and Drug Administration for the purpose of LAAC.<sup>7</sup>

However, patients who were not eligible for long-term OAC were excluded from the 2 clinical trials that evaluated the safety and efficacy of the device; namely, the PROTECT-AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation)<sup>8</sup> and PREVAIL (Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin Therapy)<sup>9</sup> trials. Furthermore, at least 45 days of OAC are required after device implantation to reduce the risk of thrombus formation on the device and until effective LAA occlusion is achieved.<sup>8,9</sup> As such, little is known about the

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### WHAT IS KNOWN

- The implantation of left atrial appendage closure device (WATCHMAN) is an alternative option to oral anticoagulation for stroke prevention in atrial fibrillation.
- Patients with contraindications to oral anticoagulation were excluded from clinical trials that assessed the safety and efficacy of WATCHMAN device, and a 45-days course of oral anticoagulation is recommended post implantation to avoid device thrombosis.

### WHAT THE STUDY ADDS

- The study shows that in a group of patients who had experienced prior major bleeding events, WATCHMAN device implantation with short term oral anticoagulation was feasible, without significant risks of recurrent spontaneous bleeding events.
- These results were achieved with careful multidisciplinary assessment of rebleeding risk in a dedicated stroke prevention clinic.

safety of this strategy in patients who have history of major bleeding while receiving OAC. In this study, we are reporting our initial experience with this patient population.

## Methods

### Study Population

All consecutive patients referred for LAAC between April and December 2015 at our institution were enrolled in a prospectively maintained LAAC data registry and screened for eligibility for the current study. Major bleeding was defined, in concordance with the International Society on Thrombosis and Hemostasis definition, as fatal bleeding or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome or bleeding causing a fall in hemoglobin level of  $\geq 20$  g L<sup>-1</sup> (1.24 mmol L<sup>-1</sup>) or leading to transfusion of  $\geq 2$  units of whole blood or red cells.<sup>10</sup> Only patients with history of spontaneous major bleeding while receiving OAC were eligible for inclusion and were identified by review of the data registry and medical records for clinical documentation of spontaneous major bleeding. The study excluded any patients with history of only nonmajor or traumatic major bleeding. A total of 20 consecutive patients met the inclusion criteria and subsequently had LAA occlusion using the WATCHMAN device (Boston Scientific Corporation).

In this group of patients, we investigated the occurrence of recurrent spontaneous major bleeding during OAC course post device implantation as a primary outcome. All patients gave written informed consent before the procedures. The Cleveland Clinic Foundation Institutional Review Board approved the study.

### Multidisciplinary Evaluation for Safety of Device Implantation

Given the limited data on safety of resumption of oral anticoagulation after the WATCHMAN device implantation in patients with history of major bleeding, a multidisciplinary team, including the patient's electrophysiologist, neurologist/neurosurgeon (in case of intracranial bleeding) or gastroenterologist (in case of gastrointestinal [GI] bleeding), and primary care physician or primary cardiologist, convened to discuss individual cases. For this purpose, a special AF stroke

prevention Center was established. The risk of rebleeding was assessed and carefully weighed against the benefits of the procedure before proceeding with device implantation. All patients were involved in informed shared decision making. No patient was deemed ineligible after the assessment, and all went on to have the WATCHMAN device implanted.

### Procedural Details

Patients were started on OAC before procedure, allowing enough time to be in therapeutic range; usually 4 to 5 days in case of warfarin and 24 to 48 hours in case of nonvitamin K antagonist OAC (NOACs). For patients receiving warfarin, the international normalized ratios (INRs) had to be therapeutic at the time of implant. Those on nonvitamin K antagonist OAC skipped only 1 dose immediately before the procedure and had their medication restarted immediately after device implantation.

Transesophageal echo (TEE) was performed before the procedure to ensure LAA patency and to rule out intra-atrial thrombi. All procedures were performed under general anesthesia and with TEE and intracardiac echocardiography guidance. Femoral venous access was obtained with ultrasound guidance. A phased-array intravascular ultrasound catheter (Siemens AG, Inc, Malvern, PA) was placed in the right atrium to assist with performing trans-septal punctures, guide location and manipulation of the delivery system within the left atrium, and to monitor for complications during the procedure. Trans-septal access was then obtained with intracardiac echocardiography and fluoroscopy guidance. A pig-tail catheter was advanced to the left atrium and positioned in the LAA. An appendogram was performed to delineate the size and shape of the LAA. The WATCHMAN delivery system was then advanced to the appendage, and an appropriately sized device was deployed at the ostium. Complete isolation/occlusion of the appendage was confirmed by TEE and contrast injection.

### Clinical and Follow-Up Data

All patients received OAC in addition to aspirin for at least 45 days post procedure. Patients were hospitalized for 1 night after the procedure and were discharged on the following day. All patients were assessed for procedural complications immediately after the procedure and before hospital discharge.

On discharge, patients were encouraged to immediately report any bleeding or other complications. All patients returned for follow-up 45 days later and were assessed with a TEE to ensure effective LAA occlusion. If complete exclusion was achieved, patients were advised to stop OAC and continue on aspirin with addition of clopidogrel until 6 months post implantation, and aspirin alone thereafter.

### Statistical Analysis and Outcomes

All statistical analyses were performed by using the statistical software JMP pro version 10.0 (SAS, NC). Descriptive statistics are presented as mean values and SD or median and quartiles for continuous variables and as frequencies and percentages for categorical variables. The primary outcome of interest was spontaneous major bleeding while receiving short-term postprocedural OAC.

## Results

Twenty out of 37 patients with successfully implanted WATCHMAN devices at our institution between April and December 2015 had history of spontaneous major bleeding while receiving OAC and were included in the analysis. Baseline characteristics of the study population are summarized in Table. Patients were  $76.3 \pm 6.9$  years of age, and 65% were men. The median CHADS<sub>2</sub> (congestive heart failure, hypertension, age, diabetes, stroke/transient ischemic attack), CHA<sub>2</sub>DS<sub>2</sub>-VASc (congestive heart failure, hypertension, age  $\geq 75$  years), diabetes, stroke/transient ischemic attack, vascular disease, age [65–74 years], sex [female]), and HAS-BLED

**Table. Baseline Characteristics of Study Population (n=20)**

Characteristic	
Age, y	76.3±6.9
Male	13 (65.0%)
Major bleeding event	
Gastrointestinal bleeding	11 (55.0%)
Intracranial hemorrhage	7 (35.0%)
Hemopericardium with tamponade	1 (5.0%)
Hemarthrosis	1 (5.0%)
Intracranial hemorrhage (n=7)	
Parenchymal hemorrhage	5 (71.4%)
Spontaneous subdural hematoma	2 (28.6%)
CHADS <sub>2</sub> score, median (quartiles)	3.5 (2–4)
CHA <sub>2</sub> DS <sub>2</sub> -VASc score, median (quartiles)	5 (3–6)
HAS-BLED score, median (quartiles)	5 (4–5)
Bleeding-to-implantation interval, median in days (quartiles)	262 (123–796)
INR at the time of device implantation*, median (quartiles)	2.3 (1.9–3.1)
Type of OAC during major bleeding event	
Warfarin	15 (75.0%)
Rivaroxaban	3 (15.0%)
Apixaban	2 (10.0%)
Same OAC started post device implantation	13 (65.0%)
Type of OAC started post device implantation	
Warfarin	18 (90.0%)
Dabigatran	1 (5.0%)†
Apixaban	1 (5.0%)

INR indicates international normalized ratio; OAC, oral anticoagulant

\*For the 18 patients who received warfarin.

†Patient stopped Dabigatran at day 20 after minor transient gastrointestinal bleeding, and 5 days later, he was started on warfarin, which he received for the rest of the course.

(hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly [ $>65$  years], drug or alcohol usage predisposing to bleeding) scores at the time of device implantation were 3.5 (quartiles 2–4), 5 (quartiles 3–6), and 5 (quartiles 4–5), respectively. Previous major bleeding events were major GI bleeding, intracranial hemorrhage, spontaneous hemopericardium with cardiac tamponade, and hemarthrosis in 11, 7, 1, and 1 patients, respectively. Eighteen patients received warfarin for periprocedural anticoagulation, with a median INR of 2.3 (quartiles 1.9–3.1) on the day of device implantation, whereas 1 patient received Apixaban 5 mg BID and 1 patient received Dabigatran 150 mg BID (both patients were taking warfarin at the time of initial major bleeding event). The latter was switched to warfarin targeting an INR value of 2 to 3, after initial 20 days of Dabigatran which resulted in a minor GI bleed. For the purpose of anticoagulation in this study, 13 patients (65%) received the same anticoagulant which had resulted in their previous major

bleeding event. At the time of device implantation, 8 patients (40%) were in normal sinus rhythm and 12 (60%) were in AF; 11 of which (55%) were in long-standing persistent AF.

Importantly, the primary outcome of recurrent spontaneous major bleeding event while receiving OAC post device implantation did not occur in any of the patients in this study. All but 1 patient (95%) completed the planned 45-day course of OAC. In 1 patient, warfarin was discontinued after 40 days because of a mechanical fall with head trauma which resulted in a subdural hematoma with no associated neurological deficits, and this was managed conservatively. In this patient, the initial major bleeding event before device implantation was hemopericardium with cardiac tamponade.

Three patients developed minor transient GI bleed 10, 16, and 25 days post implantation and had to temporarily hold OAC for 3 to 5 days. OAC was subsequently restarted in all 3 patients with no recurrence of bleeding events, and all 3 patients successfully completed the planned 45-day course.

In all but 1 patient (95%), TEE at 45 days post implant showed persistent occlusion of the appendage, and further anticoagulation was switched as previously described to clopidogrel and aspirin for 6 months and aspirin only thereafter. In one patient, TEE showed a residual leak from the appendage, and decision was initially made to continue OAC for a total of 6 months. Yet, after receiving 2 additional weeks of OAC without complications, the TEE images were reviewed with a more experienced TEE operator, and the leak was thought to be 4.7 mm at most. At this point, a decision was made to stop OAC and to continue with antiplatelets as per protocol because this patient had had intracranial hemorrhage in the past.

In this study, no patients experienced procedure-related pericardial effusion, device-related thrombosis, procedure- or device-related stroke, or device embolization.

## Discussion

The current study suggests that in this group of patients who had experienced previous major bleeding events, WATCHMAN device implantation with short-term OAC was feasible, without significant risks of recurrent spontaneous bleeding events. These results were achieved with careful multidisciplinary assessment in a dedicated stroke prevention clinic. The study provides important insights about high-risk patients who were excluded from clinical trials of WATCHMAN implants and are potentially the patients to derive the greatest benefit from atrial appendage closure.

In our study, all patients had a history of spontaneous major bleeding while receiving OAC, including 7 patients with previous intracranial hemorrhage. Remarkably, no patient was deemed ineligible after careful assessment by our multidisciplinary clinic, and all proceeded with device implantation. In 20 successfully implanted patients, there was no recurrence of spontaneous major bleeding and no incidence of device-related thrombosis or procedure-/device-related strokes.

LAAC provides an alternative stroke prevention strategy for nonvalvular AF patients who cannot be otherwise managed with long-term OAC.<sup>6</sup> In real world, most of the patients seeking that option have had bleeding complications while receiving OAC, which are often serious and require discontinuation of therapy. Remarkably, patients who were not eligible for long-term OAC

were excluded from the 2 major clinical trials that evaluated the WATCHMAN device, the only Food and Drug Administration–approved LAAC device to date, mainly to allow randomization against long-term warfarin therapy.<sup>8,9</sup> This lack of evidence poses a challenge to clinicians when faced with AF patients who have history of spontaneous major bleeding when treated with OAC and are at increased risk of thromboembolic events based on their risk profile. This challenge is aggravated by the need for at least 45 days of OAC after device implantation until effective LAA exclusion is achieved. To our knowledge, this is the first study to report the outcomes of the previously described strategy in this patient population.

The ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology) was a nonrandomized, uncontrolled, prospective study that evaluated the safety and efficacy of the WATCHMAN device implantation in 150 nonvalvular AF patients who were ineligible for OAC.<sup>11</sup> Although 93% of the study population had history of bleeding tendencies, the exact number of patients who had history of major bleeding while receiving OAC was not reported. Another main difference is that patients did not receive the recommended course of OAC after device implantation; instead, they received 6 months of dual antiplatelet therapy including aspirin and a thienopyridine antiplatelet agent (clopidogrel or ticlopidine). The caveat is that aspirin monotherapy or aspirin plus clopidogrel both increase the risk of bleeding without appreciable benefit, and their use for stroke prevention in patients with AF is not well supported by clinical trial evidence, and the risks of thromboembolism may be even further potentiated by the presence of a device in the LAA and suboptimal anticoagulation. In ASAP, 6 out of 142 patients (4.2%) had device-related thrombosis, resulting in stroke in 1 patient (0.7%).<sup>11</sup> Another limited evidence suggests ≈5% incidence of Amplatzer Cardiac Plug (St. Jude Medical, St. Paul, MN) thrombosis with antiplatelet therapy in patients with prior intracranial bleeding events.<sup>12</sup>

Our study suggests that a history of spontaneous major bleeding might not be an absolute contraindication for anti-thrombotic therapy after WATCHMAN device implantation. Although antiplatelet therapy has been suggested as an alternative, this strategy remains suboptimal for the prevention of device-related thrombotic complications. Furthermore, previous studies have shown that the rate of spontaneous acute bleeding events resulting in hospitalization secondary to antiplatelet therapy was not significantly different compared with warfarin, especially GI bleeding.<sup>13</sup>

### Study Limitations

The study has the inherent limitations of observational studies and potential for selection bias. INR at the time of previous major bleeding events while receiving warfarin therapy was not available for many patients. Small sample size is another limitation, however, given the challenging decision of prescribing OAC for patients with previous major bleeding and the recent Food and Drug Administration approval of WATCHMAN device for commercial use, larger sample size is difficult to obtain at this point. However, given the importance of the topic, this study can serve as an impetus for future larger studies.

### Conclusion

After careful multidisciplinary evaluation, the standard anticoagulation strategy for WATCHMAN device implantation, including a 45-day course of OAC, may still be safely implemented in patients with previous spontaneous major bleeding while receiving OAC. The rate of recurrence of spontaneous major bleeding in this setting seems to be low. Larger prospective multicenter studies are needed to further evaluate this finding.

### Disclosures

None.

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