Medical Devices: Evidence and Research

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REVIEW

Percutaneous left atrial appendage closure devices: safety, efficacy, and clinical utility

This article was published in the following Dove Press journal:
Medical Devices: Evidence and Research
2 September 2016
Number of times this article has been viewed

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Abstract: Atrial fibrillation (AF) is the most common arrhythmia treated in the clinical practice. One of the major complications of AF is a thromboembolic cerebral ischemic event. Up to 20% of all strokes are caused by AF. Thromboembolic cerebral ischemic event in patients with AF occurs due to atrial thrombi, mainly from the left atrial appendage (LAA). Prevention of clot formation with antiplatelet agents and especially oral anticoagulants (vitamin K antagonists or newer oral anticoagulants) has been shown to be effective in reducing the stroke risk in patients with AF but has several drawbacks with (major) bleedings as the most important disadvantage. Therefore, physical elimination of the LAA, which excludes the site of clot formation by surgical or percutaneous techniques, might be a good alternative. In this review, we discuss the safety, efficacy, and clinical utility of the Watchman™ LAA closure device.

Keywords: stroke, left atrial appendage, prevention, atrial fibrillation

Introduction

Atrial fibrillation (AF) is the most common arrhythmia treated in the clinical practice. Lifetime risk of AF is estimated to be 24% in elderly patients.[1–3] The most devastating complication of AF is a stroke. Patients with AF have a fivefold higher risk of stroke and a twofold increased risk of all-cause mortality.[4] The overall annual stroke risk is 5% in patients with AF, which increases up to 15% in high-risk patients.[5] The percentage of strokes caused by AF increases with age. It has been estimated that 20%–38% are caused directly by AF.[5–10] Furthermore, the prevalence of nondiagnosed ("silent") AF may in fact lead to a higher attributable risk of AF for ischemic stroke.[10] AF-related ischemic strokes are associated with significantly higher morbidity, mortality, and health care expenses compared to stroke from other etiologies.[11,12] Thromboembolic cerebral ischemic event in patients with AF occurs due to the formation of atrial thrombi, especially in the left atrial appendage (LAA). Research has shown that >90% of the atrial thrombi find their origin in the LAA.[13–16] Prevention of clot formation with antiplatelet agents and especially oral anticoagulants (OACs) (vitamin K antagonists [VKAs] or newer oral anticoagulants [NOACs]) has been shown to be effective in reducing stroke risk in these patients but has several drawbacks with (major) bleedings as the most important disadvantage. Therefore, physical elimination of the LAA, which excludes the site of clot formation by surgical or percutaneous techniques, might be a good alternative.

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http://dx.doi.org/10.2147/MDER.S65492

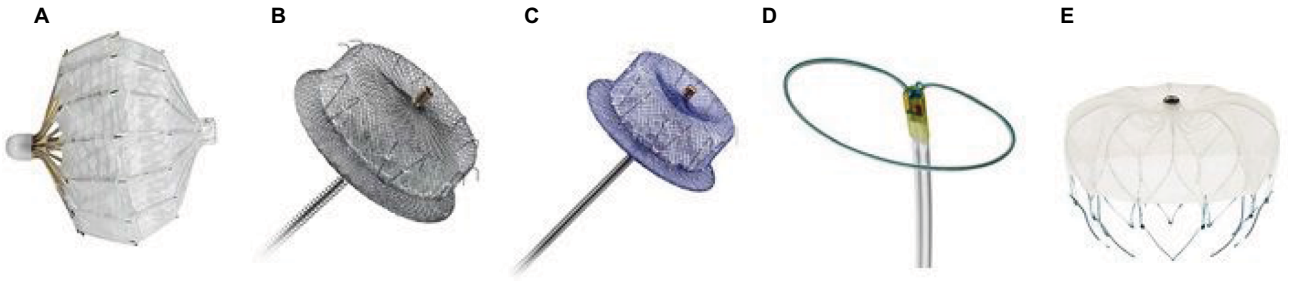

Figure 1 Percutaneous devices for left atrial appendage closure (LAAC)
Notes: (**A**) Plaato™ device. (**B**) Amplatzer™ Cardiac Plug. (**C**) Amplatzer Amulet™ device. (**D**) LARIAT. (**E**) Watchman™.
Abbreviation: Plaato, Percutaneous Left Atrial Appendage Transcatheter Occlusion.

Devices for percutaneous LAA closure

Several devices have been proposed to obtain durable LAA closure (LAAC) by means of a percutaneous approach (Figure 1). The first percutaneous LAA occluder proposed was the Percutaneous Left Atrial Appendage Transcatheter Occlusion (Plaato™; Endovascular 3, Plymouth, MN, USA) device, which was withdrawn from the market in 2006, despite favorable preliminary results in terms of safety and efficacy.[17,18] The Amplatzer™ Cardiac Plug (ACP) and its second generation ACP2 or Amplatzer Amulet™ (St. Jude Medical, St Paul, MN, USA) involve similar implantation techniques and have shown good results in prospective registries in the absence of large-scale randomized clinical trials.[19] The LARIAT suture delivery device (SentreHEART, Palo Alto, CA, USA) excludes the LAA by ligation through a combination of pericardial and transseptal access. Patients with a history of pericarditis or cardiac surgery are considered ineligible for LARIAT implantation. However, periprocedural (N)OAC therapy is not required in LARIAT implantation.[20,21]

Of all available percutaneous techniques for closure of the LAA, the Watchman™ device (Atritech, a subsidiary of Boston Scientific, Plymouth, MN, USA) is the best investigated. After this brief outline on earlier percutaneous LAAC devices, this review focuses in detail on the results of clinical trials of LAAC by means of the Watchman device.

Efficacy of percutaneous LAAC

Table 1 summarizes currently published clinical experience with the Watchman device with regard to efficacy. The initial worldwide experience study showed that LAA occlusion (LAAO) using the Watchman device was safe and feasible. The Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation (PROTECT-AF) trial was the first large randomized clinical trial to test this device.[22,23] This study was designed to assess the non-inferiority of the device against chronic warfarin therapy. The study evaluated 707 patients with non-valvular AF, who were randomly assigned in a 1:2 ratio to either long-term warfarin (international normalized ratio [INR] 2.0–3.0) or the device therapy. Patients allocated to the device group were treated postimplant with warfarin for 45 days to facilitate device endothelialization. Warfarin was discontinued if the follow-up transesophageal echocardiography (TEE) at 45 days showed either complete LAAC or acceptable residual peri-device flow (jet width ≤5 mm). After discontinuation of warfarin, clopidogrel and aspirin were given until 6 months of follow-up. After this period, aspirin alone was continued. The control group received warfarin with target INR between 2.0 and 3.0, which was only accomplished in two-thirds of the time despite close INR monitoring. Implant success rate was 91%. After a mean follow-up of 18 months (1.065 patient-years), the primary efficacy (composite end point of stroke, systemic embolism, and cardiovascular death) event rate was similar in both groups (3.0 vs 4.9 events per 100 patient-years). The PROTECT-AF study successfully demonstrated the non-inferiority of the Watchman device compared with standard therapy with warfarin.[22] A substudy of the PROTECT-AF assessing quality-of-life parameters in a subset of 547 patients (361 device and 186 warfarin patients) showed that patients with non-valvular AF at risk of stroke who underwent LAAC had favorable quality-of-life changes at 12 months vs patients treated with warfarin. A post hoc analysis of the PROTECT-AF and Continuous Access Protocol (CAP) registry assessed the net clinical benefit (NCB) of LAAC combining rates of thromboembolism, intracranial hemorrhage, major adverse events, and death for an objective comparison of LAA device closure vs anticoagulation in AF patients. This study showed that the NCB of LAA device closure is highest for patients at high stroke risk but also showed that the benefit of LAAC

Table 1 Efficacy results with the Watchman™ device

Study	Study design, comments	Total number of patients	Patients randomized, n	Postprocedural medical therapy	Age ± SD (years)	Sex: male (%)	$CHADS_2$ ± SD	CHA_2DS_2-VASc ± SD	Primary efficacy end point	Implant success rate (%)	Efficacy event rate (per 100 patient-years)	Mean FU ± SD (months)
Feasibility study[23]	Open-label non-randomized pilot study for safety and feasibility	75	N/A	45 days VKA and ASA, lifelong ASA	68.5	64	1.8±1.1	N/A	Stroke, CV death, systemic embolism, major bleeding	88.0	No ischemic stroke or systemic embolism during FU	24.3±11.2
PROTECT-AF[22,24,25]	Unblinded RCT, non-inferiority trial	707	463 WM, 244 VKA	45 days VKA and ASA, 6 months DAPT, lifelong ASA	71.7±8.8	70	2.2±1.2	3.4	Stroke, CV death, systemic embolism, major bleeding	90.9	3.022	46±20.4
	Patients eligible for OAC										2.3	46±20.45
PREVAIL[27]	Unblinded RCT, non-inferiority trial	407	269 WM, 138 VKA	45 days VKA and ASA, 6 months DAPT, lifelong ASA	74.0±7.4	68	2.6±1.0	N/A	Stroke, CV death, systemic embolism, major bleeding	95.1	0.71 (ischemic stroke)	11.8±5.8
	Patients eligible for OAC											
CAP Registry[24,28]	Prospective registry	460	N/A	45 days VKA and ASA, 6 months DAPT, lifelong ASA	74±8	65	2.4±1.2	N/A	Stroke, CV death, systemic embolism, major bleeding	95.0	1.8	N/A
ASAP Registry[33]	Prospective registry Patients ineligible lor OAC	150	N/A	6 mo DAPT and lifelong ASA	72.5±7.4	64	2.8±1.2	4.4±1.7	Stoke, CV death, systemic embotican	94.7	2.3 (stroke or systemic ereclism)	14.4±8.6
EWOLUTION[30]	Prospective registry	1021	N/A	Glided through judgement treating physician 27% OAC; 59% DAPT; 7% single APT; 6% without any OAC or APT	73±9	60	2.8±1.3	4.5±1.6	Procedural success, long-term stroke, CV death, systemic embolism, bleedng	98.5	N/A	1

Abbreviations: ASA, acetylsalicylic acid; CV, cardiovascular; DAPT, dual antiplatelet therapy; FU, follow-up; N/A, not applicable; OAC, oral anticoagulation; RCT, randomized controlled study; SD, standard deviation; VKA, vitamin K antagonist; WM, Watchman device.

increased over time. In the PROTECT-AF trial, NCB initially favored anticoagulation due to early procedure-related strokes and tamponades, but after 6–9 months, the NCB changed favorably for the device-based intervention, driven mainly by reductions in intracranial bleedings and death in patients who underwent LAAC. This study also showed that operator experience is an important factor to improve the safety and efficacy outcomes because an NCB of LAA device closure in the CAP registry was already achieved after 3 months due to less procedure-related events.[24]

In 2014, the long-term follow-up data of the PROTECT-AF trial were published. At mean follow-up of 3.8 years or 2,621 patient-years, the primary efficacy event rate (combined end point of all strokes, cardiovascular or unexplained death, and systemic embolism) was lower in the Watchman group (2.3%) than the controls (3.8%), which is a 40% relative risk (RR) reduction, with a 96% posterior probability of superiority. The reduction in the primary efficacy outcome with Watchman was confirmed through a variety of analyses: intention-to-treat (hazard ratio [HR] 0.61; P=0.0348), postprocedure (HR 0.52; P=0.0072), per-protocol (HR 0.50; P=0.0075), and terminal therapy (HR 0.52; P=0.0166). In subgroup analysis, only minor differences were seen for sex (HR 0.45 in males vs 1.03 in females), $CHADS_2$ score (HR 0.29 in patients with a $CHADS_2$ of 1 vs 0.99 in patients with a $CHADS_2$ >1), and AF pattern (HR 0.62 in paroxysmal AF, 0.31 in persistent AF, and 0.84 in permanent AF). No influence was seen in patients with a prior transient ischemic attack (TIA) or stroke (HR 0.66 in patients with a history of TIA/stroke vs 0.61 in patients without a history of TIA/stroke). Secondary analysis also showed a statistical superiority in all-cause mortality (3.2% vs 4.8%), which is a 34% RR reduction (HR 0.66; P=0.0379) and 60% RR reduction in cardiovascular mortality (1.0% vs 2.4%; HR 0.40; P<0.005). The favorable outcomes of the device were driven largely by lower rates of hemorrhagic stroke (0.6% vs 4.0%) as well as hemorrhagic stroke-related deaths (0.4% vs 3.3%) but not by ischemic strokes.[25]

According to the PROTECT-AF study, in most studies, a maximal residual jet <5 mm around the device is allowed after the procedure.[26–28] A substudy of the PROTECT-AF indicated that residual peri-device flow into the LAA after percutaneous closure with the Watchman device was observed in up to 32% of patients at 12-month follow-up. Minimal peri-device flow was not associated with an increased risk of thromboembolism. It needs to be stressed that the event rate in PROTECT-AF was low and therefore this conclusion should be interpreted with caution.[29]

Safety of percutaneous LAAC

Table 2 provides an overview of literature on safety outcomes with the Watchman device. In the initial feasibility study in 75 patients, two device embolizations were observed, and both devices were recaptured by a transcatheter intervention. After modification of the device, no additional embolizations were seen. There were two cardiac tamponades, one air embolism, and one delivery wire fracture with surgical explantation but no long-term sequelae for the patients. At 6-month follow-up in four patients, thrombus formation was seen on the device that resolved with additional anticoagulation. During a mean follow-up of 740±341 days, two patients had a TIA, one of these patients had no apparent thrombus on the device, and there were two non-device-related deaths.[23]

Although in the PROTECT-AF study the device was found at 1,050 patient-years of follow-up to be non-inferior to warfarin in terms of preventing stroke, systemic embolism, and cardiovascular death, its use was accompanied by a higher risk of complications, mostly primarily periprocedural complications such as pericardial effusion and procedural stroke. Primary safety events occurred more frequently in the intervention group than in the control group (7.4 vs 4.4 per 100 patient-years; RR 1.69). A procedure-related stroke was seen in 1.1% of patients in the intervention group. By contrast with the intervention group, in which 55% of the primary safety events occurred on the day of the procedure, the events in the control group usually occurred later, with 50% of events between 45 days and 1 year. Serious pericardial effusion (defined as the need for percutaneous or surgical drainage) with an occurrence of 4.8% was the most frequent complication in the intervention group. The majority of effusions were resolved with pericardiocentesis. There was no mortality in the group of patients with pericardial effusion, although it prolonged hospital stay compared to the patients without pericardial effusion. Effusion rates declined with investigator experience. Device embolization was seen in three patients (0.6%); in one patient, the device was percutaneously removed, while the devices of the other two patients required a surgical procedure, and in one of the these two patients, the aortic valve was damaged requiring concomitant aortic valve replacement. No increased stroke or mortality rates were associated with device embolization.[22] The long-term follow-up data from the PROTECT-AF show that although warfarin was more beneficial with regard to the primary safety end point early on, this difference diminished at 4 years of follow-up (RR 1.17 for Watchman vs warfarin).[25] In view of the learning curve effect, it is expected that the number of complications will decrease with more experience.

Table 2 Safety outcomes with the Watchman™ device

Study	Number of patients assigned to WM	Procedure-related stroke, n (%)	Overall PE, n (%)	PE requiring pericardiocentesis	Device embolization, n (%)	Major bleeding requiring transfusion, n (%)	Serious procedure- or device-related SAEs over 7 days, n (%)	Other complications, n (%)
Feasibility study[23]	75	0 (0.0)	5 (6.7)	2 (2.6)	2 (2.6)	N/A	N/A	Air embolism, 1 (1.3) Delivery wire fracture, 1 (1.3)
PROTECT-AF[28]	542	5 (0.9)	28 (5.2)	24 (4.4)	3 (0.6)	4 (0.7)	42 (7.7)	Arteriovenous fistula, 1 (0.2) Arrhythmia, 1 (0.2) Bruising/hematoma, 2 (0.4)
PREVAIL[27]	269	1 (0.4)	N/A	1 (0.4)	2 (0.7)	1 (0.4)	12 (4.5)	Arteriovenous fistula, 1 (0.4)
CAP Registry[24,28]	460	0 (0.0)	10 (2.2)	10 (2.2)	0 (0.0)	3 (0.7)	17 (3.7)	Arrhythmia, 2 (0.4) Femoral pseudoaneurysm, 1 (0.2) Airway trauma, 1 (0.2)
ASAP Registry[33]	150	1 (0.7)	5 (3.3)	2 (1.3)	2 (1.3)	N/A	13 (8.7)	Femoral pseudoaneurysm (surgically repaired), 1 (0.7) Femoral hematoma, 2 (1.3)
EWOLUTION[30]	1,021	1 (0.1)	7 (0.7)	3 (0.3)	2 (0.2)	7 (0.7)	28 (2.7)	Air embolism, 3 (0.3)

Abbreviations: PE, pericardial effusion; N/A, not applicable; SAEs, serious adverse events; WM, Watchman device.

The influence of the operator's experience on the safety of percutaneous LAAC was assessed in the CAP registry.[28] This was an assessment of safety events in 542 patients from the PROTECT-AF trial who underwent attempted device LAAC and 460 patients from a subsequent nonrandomized registry. The safety end point in this study was bleeding- and procedure-related events (pericardial effusion, stroke, device embolization). A decrease from 7.7% to 3.7% was found across the two studies. When comparing event rates from the first and second halves of PROTECT AF and CAP, there was a decrease from 10.0% to 5.5% and 3.7%, respectively. Moreover, there was a similar improvement in procedure-related stroke (from 0.9% to 0%). These data show that complications associated with Watchman implantation are typically seen early in the peri-/postprocedural period and significantly decrease in frequency with operator experience.[19] These results are supported by the preliminary results of the Prospective Randomized Evaluation of the Watchman LAA Closure Device in Patients with Atrial Fibrillation Versus Long Term Warfarin Therapy (PREVAIL) study. Implant success rate in this study increased to 95%, and safety events (defined as acute occurrence of death, ischemic stroke, systemic embolism, and procedure- or device-related complications requiring major cardiovascular or endovascular intervention) occurred in only 2.2% of patients. Of interest, a minimum of 20% of subjects were enrolled at new centers, and 25% of subjects were enrolled by new operators.[27]

Recently, the clinical data of the multicenter EWOLUTION registry with 1,021 patients were published. The patients in this registry were at high risk of stroke with an average $CHADS_2$ score of 2.8±1.3 and a CHA_2DS_2-VASc score of 4.5±1.6 but also had a moderate-to-high risk of bleeding (an average HAS-BLED score of 2.3±1.2). Almost half of the subjects (45.4%) had a history of TIA, ischemic stroke, or hemorrhagic stroke, and 62% of patients were deemed unsuitable for novel OAC therapy by their physician, based on factors such as comorbidities, the inability to adhere to OAC, and bleeding history or high bleeding risk. Nearly one-third of all subjects had a history of major bleeding (31.2%). In 98.5% of patients, the device was successfully deployed with no flow or minimal residual flow (defined as <5 mm assessed via periprocedural TEE) achieved in 99.3% of implanted patients. In this large real-world registry, the safety profile of the Watchman device was favorably compared to the previous studies. The most common serious adverse event that occurred within 30 days of the procedure was major bleeding requiring transfusion. In particular, the rate of procedural/device-related strokes, with a rate of 0.1% in this study, was substantially lower compared to the 0.9% in PROTECT-AF and 0.4% in

PREVAIL. More generally, the incidence of procedure- or device-related serious adverse events over 7 days occurred at a rate of 2.8%, compared with rates of 8.7% in PROTECT AF, 4.1% in the CAP registry, and 4.2% in PREVAIL. The 30-day procedure- or device-related serious adverse event rate was 3.6%, and the overall 30-day mortality rate was 0.7%.[30]

Finally, many AF patients at highest risk of thromboembolic stroke may also have the greatest risk of hemorrhagic complications of anticoagulation, since some of the risk factors for stroke also increase the risk of bleeding complications, like age, hypertension, and a previous stroke.[6,31,32] Furthermore, there are patient groups where the patients are unable to sustain chronic oral anticoagulation due to a high bleeding risk/tendency, like patients with hereditary hemorrhagic telangiectasia (Rendu–Osler–Weber disease) or patients with a history of major gastrointestinal bleeding or hemorrhagic stroke. Thus, patients with (relative or absolute) contraindications to oral anticoagulation might benefit from LAAC. This was the objective of the ASA Plavix (ASAP) Registry study, which enrolled patients with contraindications to chronic warfarin treatment.[33] This prospective registry enrolled 150 patients with non-valvular AF, a $CHADS_2$ score ≥1, and a contraindication to warfarin use. The mean age of patients was 72.5±7.4 years, mean $CHADS_2$ score was 2.8, and 64% were male. The most common risk factor for stroke was hypertension (94.7%), and 40% of patients had previously experienced an ischemic stroke/TIA. History of hemorrhagic/bleeding tendencies (93%) was the most common reason for warfarin ineligibility. Postimplant, patients were discharged taking clopidogrel for 6 months and aspirin lifelong. The Watchman implantation was successful in 142 of 150 patients (94.7%). At mean follow-up of 14.4±8.6 months, the combined primary efficacy end point (ischemic stroke, hemorrhagic stroke, systemic embolism, and cardiovascular/unexplained death) occurred in eight patients, a rate of 4.6 events per 100 patient-years. Stroke was seen in four patients, a rate of 2.3 events per 100 patient-years. In addition, nine patients died, and three had cardiovascular complications. Furthermore, there were five pericardial effusions, of which only two with tamponade required percutaneous drainage, and six instances of device-related thrombus identified by TEE, only one of which resulted in an ischemic stroke. The observed rate of ischemic stroke was 1.7%, corresponding to a 77% reduction from the expected event rate in patients with a similar $CHADS_2$ score treated with aspirin alone (7.3%) and a 64% reduction vs aspirin and lifelong clopidogrel (5.0%). The authors concluded that Watchman implantation without a warfarin transition might be safe and effective in AF patients with contraindications to even short-term OACs.

Clinical utility and future directions

Current guidelines state that patients with AF at risk of stroke should be treated with (N)OAC based on assessment of both stroke and bleeding risk, indicated as CHA_2DS_2-VASc and HAS-BLED score, respectively.[34–36] According to the European and Canadian guidelines, percutaneous LAAC may be considered in patients with a (very) high stroke risk and contraindications for long-term OAC with a class IIB recommendation.[34,35] Worldwide, over 12,000 Watchman devices have been successfully implanted, and roughly the same number of ACPs and Amulet devices (estimates provided by Boston Scientific and St. Jude Medical, respectively). The most important future perspective is to select the patients who would benefit the most from LAAC, with their benefits far outweighing the risks of the procedure. On the contrary, patients who might benefit the most from LAAC, that is, patients with a history of major bleeding, are underrepresented in the available trials. It needs to be stressed that patients in the two randomized trials were on warfarin treatment and had no specific indication for LAAC. The results are therefore difficult to assess for patients with absolute or relative contraindications for VKA therapy.

Long-term follow-up outcome of the EWOLUTION registry may be valuable and provide more knowledge on the safety and efficacy of LAAC in patients ineligible for (N)OAC therapy.

So, the first patient category would be subjects with a history of cerebral bleeding under VKAs and/or NOACs, irrespective of their HAS-BLED score. Second category could include patients with high stroke risk and bleeding risk according to their CHA_2DS_2-VASc and HAS-BLED scores, respectively. A third category could be identified in which patients with stroke under adequate VKA or NOAC therapy are included. The final group consists of patients who are noncompliant or unwilling to take VKAs or NOACs. Future studies should illuminate the exact role of LAAC in specific patient categories.[37]

In some centers, the LAAC is combined with AF ablation in one procedure. This is because symptomatic AF is more and more being treated with catheter ablation, since significantly better rhythm outcomes are seen with catheter ablation compared to antiarrhythmic drugs.[38–40] However, the long-term efficacy of catheter ablation is disappointing, with success rates <50%.[41] Therefore, combining LAAO with AF ablation might at least decrease the AF-related symptoms, while decreasing the stroke risk and terminating VKA therapy at the same time. The first studies have shown that this combined procedure can be safely performed. Initial complete LAAO was achieved in 94%–100% of the patients. Despite AF recurrence in 23%–44% of the patients, annual

stroke risks of 0.5%–1.7% were observed, which were lower than expected based on mean CHA_2DS_2-VASc scores of 2.6 and 3.0, respectively.[42–44]

Although the long-term follow-up data of the PROTECT-AF have shown that LAAC seems a viable option and might even be superior to warfarin, it is likely that these VKAs are going to be replaced by the NOACs. Until now, no randomized trials have been undertaken to compare NOACs with LAAC devices. Indirect comparisons suggested non-inferiority of LAAC as opposed to NOACs.[45–47] This assumption however is largely speculative and should be verified in head-to-head randomized controlled studies.[48]

Future trials should not only compare LAAC with the NOACs but also compare closure of the appendage with the device alone vs device closure of the appendage plus anticoagulation. Moreover, various postimplant antithrombotic regimens have been applied in the studies. Future clinical studies should address the appropriate antithrombotic therapy in both immediate postprocedural and long-term phase.

Conclusion

The long-term efficacy data from PROTECT-AF coupled with safety results of PREVAIL and CAP provide strong evidence that Watchman, the most studied device for LAAC and the only one with randomized and long-term clinical data, may be a viable alternative to chronic warfarin therapy for stroke reduction in non-valvular AF patients.

Disclosure

The Department of Cardiology receives proctoring fees for training/educational services from Boston Scientific. The authors report no other conflicts of interest in this work.

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