

New device for stroke prevention in atrial fibrillation as an alternative to anticoagulation drugs

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Atrial fibrillation (AF) is a common heart rhythm disorder that causes the upper chamber of the heart to quiver rather than squeeze blood out with each beat. When blood is allowed to pool in the atrium, it can form clots [1]. Anticoagulation with warfarin has been proven effective for the prevention of clot-related strokes in AF. But it is used conservatively, largely because it can cause serious bleeding in some patients [2]. It also necessitates regular blood tests and may require that patients restrict certain physical activities. The Stroke Prevention in Atrial Fibrillation (SPAF) studies have documented the benefits of chronic warfarin therapy in reducing the risk of stroke [3].

The prevention of strokes has traditionally been plagued by the tedious task of continuously adjusting anti-coagulation medicines. The emergence of a new device called Watchman[®] promises to mechanically prevent the formation of dangerous emboli, by occluding left atrial appendage, a place where most thrombi form in patients with AF [4].

The left atrial appendage (LAA) has been identified as a major source of thrombi in patients with AF. Ligation of the LAA surgically has been done for many years. Though this is a very invasive technique, limited data appears to demonstrate a benefit in patients at risk of AF related strokes. Recently, a transcatheter approach to isolate the LAA has been developed [5].

The Watchman[®] LAA system [6] is made of nitinol (a self expanding metal) with the atrial facing surface covered with a thin permeable polyester material. The device is constrained within a catheter until delivery into the LAA and is avail-

able in multiple sizes to accommodate the unique anatomy of each patient (Fig. 1).

The idea behind the Watchman is simply to block the opening of the troublesome appendage with a mesh, squid-resembling stent so that the clots that do form cannot escape and cause trouble elsewhere [7]. To implant the Watchman[®], an interventional cardiologist guides the device into the heart through a catheter inserted in a vein in the upper leg [8, 9]. The catheter is threaded first into the right atrium, then into the left atrium through a puncture in the wall separating the two upper chambers of the heart. Once the catheter is positioned in the opening of LAA, the Watchman[®] is released and left permanently in place to block the formation and release of blood clots. An animation illustrating Watchman's principle of operation can be found at this URL: <http://www.atritech.net/media/deviceanimation.aspx> (Fig. 2).

Clinical trials of the device, however, had until now been small scale (there was a pilot study with about 30 people in 2007) [6]. The new larger Embolic Protection in Patients with Atrial Fibrillation (PROTECT-AF) study was designed to demonstrate the safety and efficacy of the Watchman[®] device in patients with non-valvular AF who require treatment for potential thrombus formation, are eligible for warfarin therapy and who have at least one of the following risk factors: congestive heart failure, hypertension, age 75+ years, diabetes mellitus and/or prior stroke or transient ischemic attack. The results of this study just announced at the 58th Scientific Session of the American College of Cardiology indicate that the device indeed has

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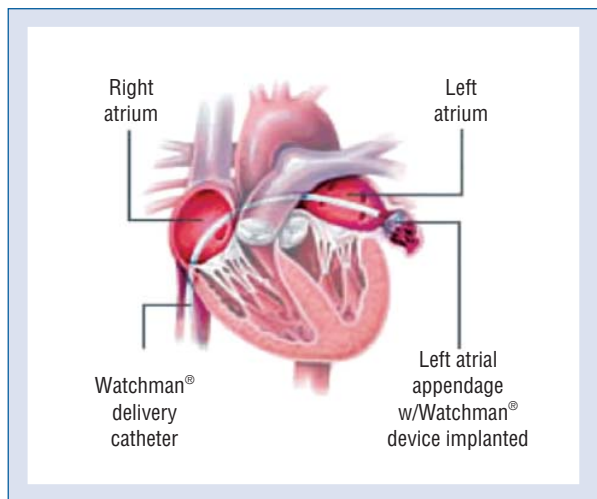


Figure 1. The delivery and placement of the Watchman in the left atrium.

great promise as an alternative to anticoagulant therapy [10].

In the PROTECT-AF trial [11], researchers compared the current standard therapy (anticoagulation with warfarin) to a fabric-covered expandable nitinol cage known as Watchman, which blocks blood clots that typically form in the LAA, an out-pouching of the left atrium. They found that the Watchman reduced by some 30% the combined risk of cardiovascular death and stroke, both ischemic (the type caused by a blood clot) and hemorrhagic (the type caused by excessive bleeding into the brain).

The trial’s principal investigator, David R. Holmes, Jr., MD, Scripps Professor of Medicine at the Mayo Graduate School of Medicine, Rochester, MN, USA, stated that patients with AF have a six-fold increased risk of stroke and therefore require long-term anticoagulation therapy. The placement of this device results in excellent long-term outcomes: effective ischemic stroke prevention with the elimination of hemorrhagic strokes and major bleeding often associated with the use of warfarin [12].

To implant the Watchman, an interventional cardiologist guides the device into the heart through a catheter inserted in a vein in the upper leg. The catheter is threaded first into the right atrium, then into the left atrium through a puncture in the wall separating the two upper chambers of the heart. Once the catheter is positioned in the opening of the LAA, the Watchman is released and left permanently in place to block the formation and release of blood clots.

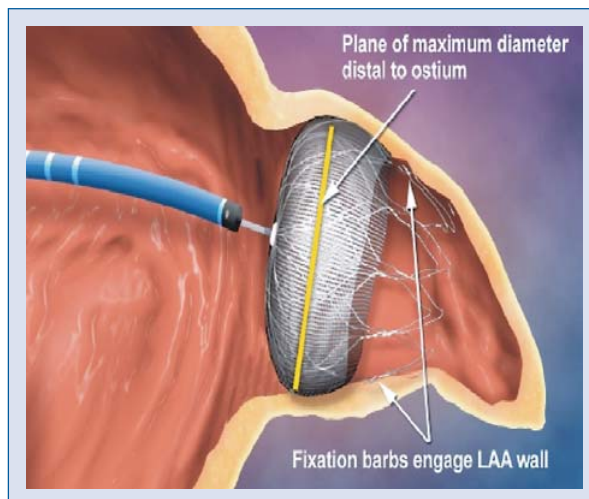


Figure 2. Watchman left atrial appendage (LAA) closure device *in situ*.

For the PROTECT-AF study, 707 patients with non-valvular AF were randomly assigned to closure of the LAA with the Watchman device (463 patients) followed by discontinuation of warfarin, or to long-term treatment with warfarin (244 patients). Of those who got the Watchman, there were 15 strokes and 17 deaths. Of those who didn’t and were treated with coumadin, there were 11 strokes and 15 deaths. This amounts to an approximate 3% risk of clot-related problems with the device, and 5% without. The study found, in more than 900 patient-years of follow-up, that the combined rate of stroke (ischemic and hemorrhagic) and cardiovascular death, the primary measures of effectiveness, was 3.4 per 100 patient-years in the device group *vs.* 5.0 per 100 patient-years in the warfarin group. This was a reduction of 32% (relative risk [RR], 0.68). As for the safety of the device, the researchers observed more procedure-related complications in patients treated with the device (8.7 *vs.* 4.2 per 100 patient-years; RR 2.08). Most complications were related to device implantation. However, after successful implantation of the Watchman and discontinuation of warfarin therapy, complication rates were significantly lower with device therapy (1.7 *vs.* 4.2 per 100 patient-years; RR 0.40).

While the Watchman’s overall advantage met noninferiority criteria [13], the 91% reduction in the hemorrhagic stroke rate (0.2% *vs.* 1.9%) met superiority criteria. However, these benefits in the randomized PROTECT-AF trial came at the price of a doubled risk of complications, predominantly early

Table 1. PROTECT-AF: Primary safety results.

End point	Device events (n)	Device rate (95% CI)	Control events (n)	Control rate (95% CI)	Relative risk (95% CI)
Primary safety results (900 patient-year cohort)	48	8.7 (6.4–11.3)	13	4.2 (2.2–6.7)	2.08 (1.18–4.13)

CI — confidence interval

Table 2. PROTECT-AF: Primary efficacy results.

End point	Device events (n)	Device rate (95% CI)	Control events (n)	Control rate (95% CI)	Relative risk (95% CI)
Primary efficacy results (900 patient-year cohort)	20	3.4 (2.1–5.2)	16	5.0 (2.8–7.6)	0.68 (0.37–1.41)

CI — confidence interval

Table 3. PROTECT-AF: All stroke, hemorrhagic stroke and ischemic stroke by intervention.

End point	Device event rate (95% CI)	Control event rate (95% CI)	Relative risk (95% CI)
All stroke	2.6 (1.5–4.1)	3.5 (1.7–5.7)	0.74 (0.36–1.76)
Ischemic stroke	2.4 (1.3–3.9)	1.6 (0.5–3.1)	1.53 (0.654–5.43)
Hemorrhagic stroke	0.2 (0.0–0.6)	1.9 (0.7–3.7)	0.09 (0.00–0.45)

CI — confidence interval

pericardial effusion. Therefore, there may be a greater up-front risk from the Watchman procedure, but 90% of patients with the device were able to stop coumadin completely, and the device appears to function at least as well as the medication (Table 1).

The primary efficacy end-point included all strokes, including ischemic and hemorrhagic, cardiovascular or unexplained death, and systemic embolization.

Results on primary efficacy were “just the reverse” of the safety end-point, Dr Holmes told the American College of Cardiology. “The patients who received the Watchman device had primary efficacy rates that were improved, and noninferiority criteria were met,” he added, with a relative risk reduction of 32% (Table 2).

Some of the efficacy stroke events were also counted as safety events. There were five periprocedural ischemic strokes, three of which were related to air embolization during the procedure. There were six hemorrhagic strokes in the control group and one in the device group, a stroke that occurred 15 days after the procedure, when the patient was still being treated with warfarin. Of six patients in the control group who had a hemorrhagic stroke, four died.

For all strokes, event-free probability was improved and noninferiority criteria met, he noted.

Ischemic strokes were higher in the device group, 14 events *vs.* five events on warfarin, but hemorrhagic stroke was lower in the device group, meeting superiority criteria (Table 3).

They found a time effect in the frequency of pericardial effusion; although serious effusion occurred in 5.0% overall, it fell from 6.5% in early patients to 4.4% in later patients.

The researchers concluded that the Watchman is an effective alternative to warfarin therapy for preventing stroke in patients with AF. The device has the potential to completely replace blood thinning drugs and bring relief to the patients with AF.

There were some dislodgements during the trial. Two occurred in the pilot phase before improvements in design. Another occurred during the main phase of the trial, several months after placement. In that case, the patient was asymptomatic, and researchers discovered the device missing serendipitously during echocardiography. They later retrieved it from the abdomen. The dislodgement rate was estimated to be one in 350 or 400.

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