# Watchman Superior to Warfarin for Stroke Prophylaxis in Atrial Fibrillation

Written by **Maria Vinall**

Long-term data from the Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation trial [PROTECT AF; NCT00129545] indicate that left atrial appendage (LAA) closure with the Watchman provides superior protection from stroke compared with warfarin. The data, presented by Vivek Y. Reddy, MD, Mount Sinai School of Medicine, New York, New York, USA, also showed that Watchman LAA occlusion filter is associated with a 40% reduction in stroke/systemic embolism (SE)/cardiovascular (CV) death, a 60% reduction in CV mortality, and a 34% reduction in all-cause mortality.

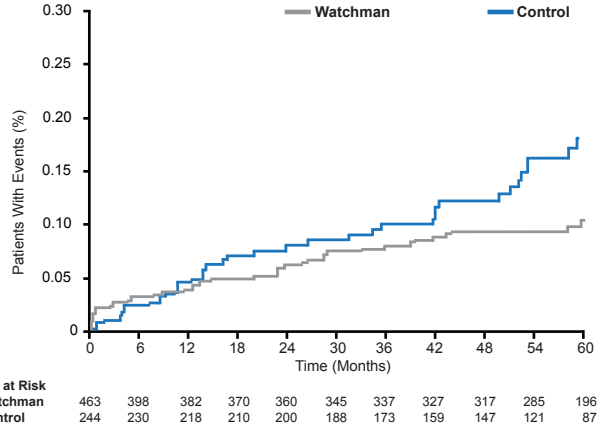
The PROTECT AF trial was a noninferiority/superiority randomized controlled trial conducted to determine whether the Watchman device could replace warfarin for stroke prevention in patients with nonvalvular AF and ≥1 $CHADS_2$ risk factor. A total of 707 patients were randomly assigned in a 2:1 ratio to percutaneous closure of the LAA and subsequent discontinuation of warfarin (intervention; n=463) or to warfarin treatment with a target international normalized ratio (INR) between 2.0 and 3.0 (control; n=244) [Holmes DR et al. *Lancet* 2009]. The composite primary efficacy endpoint included stroke, SE, and CV death. Patients in the study were mostly white (~91%) and male (70%), and the mean $CHADS_2$ score was 2.2. About 20% of patients had experienced a stroke or transient ischemic attack prior to entering the study.

Two prior reports from PROTECT AF suggested that closure of the LAA is noninferior to warfarin and might provide an alternative strategy to chronic warfarin therapy for stroke prophylaxis in this group of patients [Holmes DR et al. *Lancet* 2009; Reddy VY et al. *Circulation* 2013]. However, both reports also indicated more primary safety events in the Watchman group (mainly periprocedural complications) than in the control group. Importantly, the PROTECT AF study also, for the first time, has implicated the LAA in the pathogenesis of stroke in AF [Reddy VY et al. *Circulation* 2013].

In the results presented by Dr. Reddy, the PROTECT AF participants were followed for a mean of 45 months (range, 0 to 77.5; aggregate 2621 patient-years). For the primary efficacy endpoint of stroke, SE, or CV or unexplained death, events per 100 patient-years (95% CI) were 2.3 (1.7 to 3.2) for the Watchman group versus 3.8 (2.5 to 4.9) for the warfarin group. The rate ratio (95% CI) was 0.60 (0.41 to 1.05) indicating not only noninferiority (posterior probability of >0.999) but, for the first time, superiority (posterior probability 96%).

**Figure 1.** PROTECT AF: Primary Efficacy Endpoint

| Event | Watchman Group (n=463) Events/PY | Watchman Group (n=463) Observed Rate (Events/100 PY [95% CI]) | Warfarin Group (n=244) Events/PY | Warfarin Group (n=244) Observed Rate (Events/100 PY [95% CI]) | Rate Ratio (Watchman/ Warfarin [95% CI]) | Posterior Probabilities Non-inferiority | Posterior Probabilities Superiority |
|---|---|---|---|---|---|---|---|
| Primary Efficacy Endpoint | 39/1720.2 | 2.3 (1.7, 3.2) | 34/900.8 | 3.8 (2.5, 4.9) | 0.60 (0.41, 1.05) | >0.999 | 0.960 |

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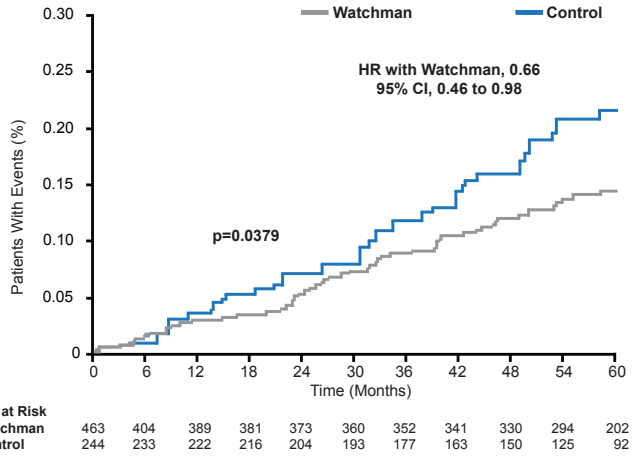
Relative risk according to subgroup analysis showed similar results, all favoring the Watchman group. All-cause mortality in the intent-to-treat population also favored the Watchman group (HR 0.66; 95% CI, 0.45 to 0.98; p=0.0379).

**Figure 2.** Intention-to-Treat: All-Cause Mortality

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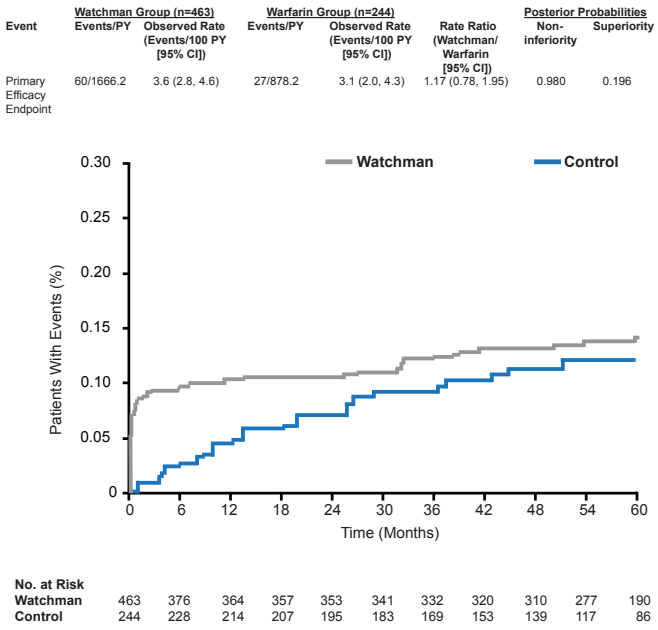
Unlike earlier results, in the 45-month analysis the results for the primary safety endpoint (a composite of serious pericardial effusion, major bleeding, procedure-related stroke, hemorrhagic stroke, and device embolization) were similar for the two approaches but with a bimodal distribution that diminished over time and with operator experience (RR, 1.17; 95% CI, 0.78 to 1.95).

Figure 3. Primary Safety Endpoint

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"Over the course of more follow-up, we see that the amount of benefit hasn't really changed; what has changed is our certainty of this benefit really being true," stated Dr. Reddy.

## First-in-Man Results Show That a Leadless Catheter Pacemaker Is Feasible, Safe, and Effective

Written by **Mary Beth Nierengarten**

Results of a first-in-man study of a novel intracardiac leadless catheter pacemaker (LCP) show its feasibility, safety, and efficacy for right ventricular (RV) pacing, reported study investigators.

Although conventional pacemakers are safe and effective, complications related to lead and generator pocket remain problematic. Each year, it is estimated that chronic lead-related problems affect 65,000 of the over 4.4 million people worldwide with pacemakers.

In an attempt to eliminate the complications related to the lead in conventional pacemakers, a novel percutaneously-delivered LCP was developed for implantation in the right ventricle with a battery life of at least 8 years.

In the prospective, nonrandomized, single-arm LEADLESS study [NCT01700244] conducted at three sites, Vivek Reddy, MD, Mount Sinai School of Medicine, New York, New York, USA, and colleagues evaluated the *in vivo* implantation of the LCP for the first time in 33 patients who required a permanent rate modulated ventricular-based pacemaker. All patients included in the study had documented evidence of chronic atrial fibrillation (AF), normal sinus rhythm with second or third degree atrioventricular block and a low level of physical activity or short expected lifespan, or sinus bradycardia; were aged ≥18 years; had a life expectancy of at least 1 year; and were not pacemaker dependent.

Overall, the mean age of the patients included in the study was 75 years (range, 53 to 91 years), 64% were male, and most had sinus rhythm with low activity or short lifespan (60%) followed by chronic AF and second- or third-degree block (28%) and infrequent pauses or unexplained syncope (24%).

Implantation of the LCP was done by affixing the LCP to the endocardium with a single-turn helix, with a docking feature for repositioning and retrieval capability at the proximal end of the LCP. Implantation was done in the right ventricle by femoral venous access using a deflectable delivery catheter under x-ray guidance. Prior to release, baseline pacing and sensing thresholds were determined and the device was repositioned if these thresholds were suboptimal.

The pacemaker works by increasing the pacing rate with increased metabolic demand by sensing the RV blood temperature.

Evaluation of the primary endpoint (ie, safety) and secondary performance endpoints (ie, RV pacing function, battery longevity, rate response, implant success rate, and implant times) were done at 2 days, 2 weeks, 6 weeks, and 3 months after implantation.

Overall, 32 of the 33 (97%) of the patients were implanted successfully with the LCP. The time from procedure to hospital discharge was a mean of 1 day (range, 1 to 4 days).

The study found no major safety complications related to femoral access, with only one minor groin hematoma that did not require treatment. One patient also had a cardiac perforation and tamponade that was surgically repaired, but the patient had a large right-sided stroke 5 days after surgery and died.

The performance of the device was demonstrated in data that showed pacing threshold changes over time (Figure 1), R-Wave amplitude changes over time, and impedance changes over time, that were similar to those expected to be seen in conventional pacemakers. Overall, pacing was achieved in ~40% of patients.