Left Atrial Appendage Closure Device in Atrial Fibrillation

Michael C. Giudici, MD, FHRS*, Prashant D. Bhave, MD, FHRS

KEYWORDS

• Left atrial appendage closure • Anticoagulation • Embolic stroke

KEY POINTS

- Left atrial appendage closure is an attractive, but unproven technology.
- Warfarin has a 50-year track record of success in prevention of embolic stroke.
- If it ain't broke, don't fix it.

There are known knowns. These are things we know that we know. There are known unknowns. That is to say, there are things that we know we don't know. But there are also unknown unknowns. These are things we don't know we don't know.

—Donald Rumsfeld

Case History

A 76 y/o patient has been on anticoagulation with warfarin for thromboembolic prophylaxis for atrial fibrillation for the past 3 years and has had no complications. The CHADS2 score is 3 for HTN and DM and age. There has not been a thromboembolic event and no bleeding complications. The INR measurements, however, have fluctuated over the years. You recommend placement of a WATCHMAN left atrial appendage closure device and discontinuation of warfarin.

I have been asked to make a case against implanting a Watchman device (Boston Scientific Corporation, Natick, MA) at this time in this asymptomatic 76-year-old man who seems to be getting along well on warfarin, albeit with some lability in international normalized ratio (INR) values.

When we as physicians consider any therapy for a patient, we evaluate the therapy on the basis of its safety, its efficacy, and its cost.

SAFETY

Let's start with the known knowns. Warfarin has been used as an oral anticoagulant for more than half a century. If you try to list medications that have been widely used as long as warfarin, only penicillin and aspirin come to mind. The number of patients treated with warfarin over the years would be in the millions. To list all the trials over the years in which investigators tried to find something as safe and efficacious as warfarin is beyond the scope of this article. The Stroke Prevention in Atrial Fibrillation Trials (SPAF)[1] and the ACTIVE trials[2] were among the largest that failed to bump warfarin off the top step of the podium. It was not until the new "novel" anticoagulants came along that we have a therapy that is potentially as safe and effective as warfarin.[3–5] Warfarin is an easy drug to dislike. The issues with drug and diet interactions, the need for constant monitoring,

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Division of Cardiovascular Medicine, Department of Internal Medicine, University of Iowa Hospitals and Clinics, 200 Hawkins Drive, Iowa City, IA 52242, USA
* Corresponding author. 200 Hawkins Drive, 4426JCP, Iowa City, IA 52242.
E-mail address: michael-c-giudici@uiowa.edu

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and its relatively narrow therapeutic range drive the search for potential alternatives.[6,7] And there is still a residual risk of stroke despite optimal anticoagulation.[8]

That is not to say that there are no safety issues. In SPAF, there was a 1.2% per year risk of "relevant hemorrhage" on warfarin. That was not significantly different from aspirin or placebo, however. In the PROTECT-AF WATCHMAN Trial[9] there was 7.4% risk of major bleeding in the warfarin group over 2612 patient-years (45 months) of follow-up.

We know that warfarin is well-tolerated compared with other medications. It very rarely will cause a rash or gastrointestinal upset. We also know that INRs may fluctuate in a number of patients and that is associated with its own risks. In the SPAF III trial,[10] 7 of 12 major bleeds occurred in patients with INRs greater than 3.0. Likewise, if the INR is low, the risk of stroke increases. Hylek[11] demonstrated a 3.3 times greater risk of stroke if the INR was 1.5 compared with 2.0.

What do we know about the safety of the Watchman device? In the PROTECT-AF Trial, the procedural success was only 91%. This means that 9% of patients were exposed to the risk of a procedure and did not receive the device. In addition, 4.8% had "serious pericardial effusion," 1.3% had procedural stroke, and 0.6% had device embolization. Over the course of the 45-month follow-up, 4.8% had major bleeding and 0.6% had hemorrhagic stroke compared with 7.4% and 3.7%, respectively, on warfarin. We also know that as physicians gained experience with placement of the device, the procedural complication rates decreased. In the continued access arm of the PROTECT-AF Trial (CAP),[12] the rate of procedure-related or device-related safety events within the first 7 days of the procedure decreased to 3.7% from 7.7% in the initial trial. The rate of serious pericardial effusion within 7 days of the procedure decreased to 2.2% from 5.0%.

What are the known unknowns? These would mainly be with regard to long-term safety and efficacy of the Watchman device. What is the risk of device erosion through the wall of the atrium? What is the risk that leaks into the appendage will develop over time? There are reports[13,14] suggesting that progressive increases in peridevice leakage are associated with an increase in the incidence of stroke. There also are reports of the device itself being a source of thrombus. Will future modifications to the device eliminate that problem?

And as long as we are comparing pharmacologic therapy with device therapy, what would be the long-term comparison of the non–vitamin K antagonist anticoagulant agents with an appendage-occluding device in this patient with fluctuating INRs?

The unknown unknowns? We just don't know….

EFFICACY

The known knowns…. In SPAF, the primary events were ischemic stroke and systemic embolism. During a mean follow-up of 1.3 years, a relatively short time frame, the rate of primary events in patients assigned to placebo was 7.4% versus 2.3% in the warfarin group. In the ACTIVE-W Trial, compared with warfarin therapy, use of clopidogrel/aspirin was associated with a 45% increase in the risk of the primary endpoints of stroke, non–central nervous system (CNS) embolism, myocardial infarction, and vascular death (annual rates for events, 3.93% vs 5.64%, respectively; $P = .0002$). This difference was driven by significantly higher incidences of stroke and non-CNS embolism in the clopidogrel/aspirin arm. The cumulative risk of major bleeding complications was nearly identical in the clopidogrel/aspirin and warfarin groups (2.4% vs 2.2% per year, respectively; $P = .67$).

The Watchman device has been likewise shown to be reasonably effective in prevention of stroke. In the PROTECT-AF Trial, the primary endpoints were stroke, systemic embolization, and cardiovascular (CV) death. Set up as a noninferiority trial, in 1.8 years of follow-up the primary endpoint was met in 3.0% of patients randomized to the Watchman device and 4.9% in the warfarin group (Relative Risk (RR) 0.62). With longer follow-up to 45 months, the primary endpoint was met with 2.3 events per 100 patient-years in the Watchman group and 3.8 events per 100 patient-years for patients randomized to warfarin (RR 0.6).

In the PREVAIL trial, which also compared the Watchman device with warfarin therapy, the procedural success rate had increased to 95.1% with more experience with the device. However, the primary endpoints of stroke, systemic embolism, and CV and unexplained death did not meet noninferiority criteria (RR 1.07) at 18-month follow-up, although there was not a great difference in outcomes between the 2 groups.[15]

The known unknowns would be the same as those mentioned previously. We do not have long-term follow-up of the Watchman device. What are the late complications? What is the long-term efficacy? Is occluding the ostium of a functioning left appendage a good thing to do, or should we just remove it? Where else do clots form?