the specialized services, medical education, and trauma and disaster care that many safety-net hospitals provide. Today, DSH providers are needed more than ever. The program is broken, but it can and should be fixed.

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Left Atrial Appendage Occlusion — Closure or Just the Beginning?

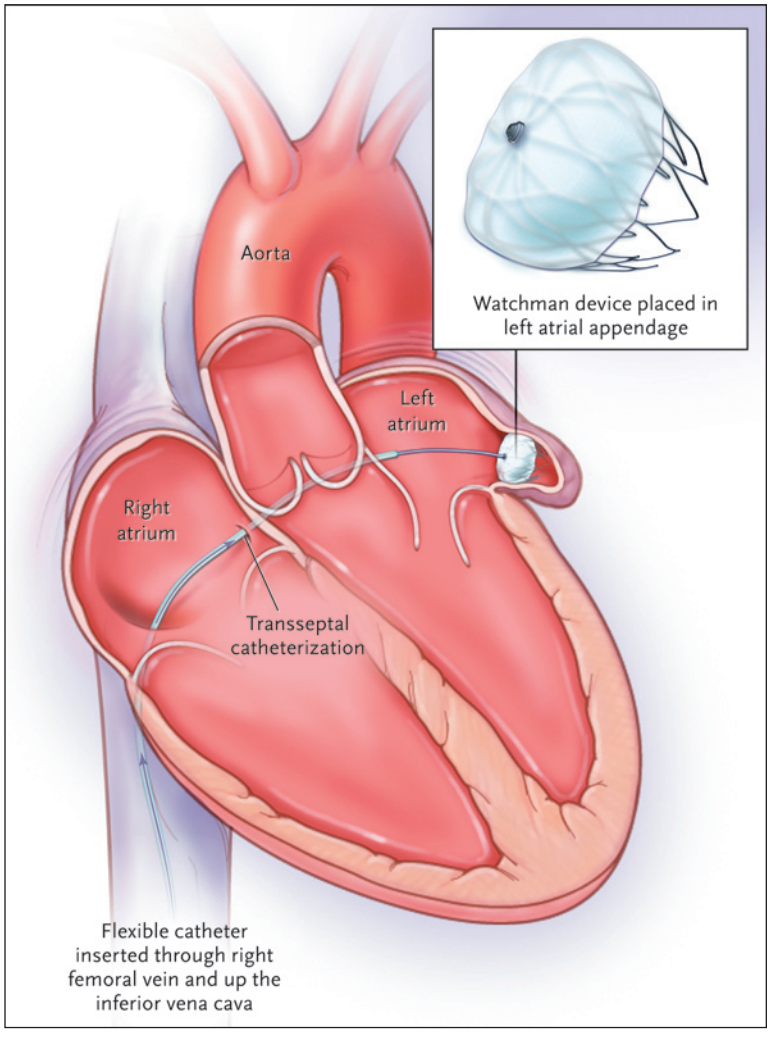
William H. Maisel, M.D., M.P.H.

More than 3 million Americans have atrial fibrillation, which increases their risk of stroke by a factor of 5.[1,2] Patients with atrial fibrillation account for one of every six strokes, and thromboemboli originating from the left atrial appendage are the suspected culprit in the vast majority of these cases.[1,2] Warfarin, a vitamin K antagonist, is the most commonly prescribed treatment for stroke prevention in patients with atrial fibrillation; yet despite warfarin's proven benefit, its effective delivery is challenged by a narrow therapeutic window and an increased risk of bleeding. Efforts have been made to develop alternative treatment strategies — including occlusion of the left atrial appendage. In August 2008, the Food and Drug Administration (FDA) granted expedited-review status to an application submitted by Atritech for the Watchman Left Atrial Appendage Closure Technology, recognizing that the device might represent a breakthrough technology.

Although ischemic stroke and arterial occlusion in atrial fibrillation are generally attributed to dislodgement of thrombi from the left atrial appendage, the pathogenesis of thromboembolism is complex. Up to 25% of strokes in patients with atrial fibrillation may be due to intrinsic cerebrovascular disease or emboli from an atheromatous proximal aorta or other cardiac source.[1] Nevertheless, interest in removing or occluding the left atrial appendage for stroke prevention dates back to the 1930s.[3] Many centers now routinely remove it during valve or arrhythmia surgery, and removal is recommended to reduce the risk of stroke in selected patients undergoing cardiac-valve surgery.[4]

Interest in nonsurgical closure of the left atrial appendage has spawned development of percutaneous devices, but no device has been approved by the FDA for this purpose. The Watchman device is a self-expanding structure made of nitinol (a nickel–titanium alloy) that is delivered percutaneously, with the use of femoral venous access and a transseptal technique, to the left atrial appendage (see diagram).

The pivotal clinical trial evaluating this device was the Embolic Protection in Patients with Atrial Fibrillation (PROTECT-AF) trial (ClinicalTrials.gov number, NCT00129545), a multicenter, prospective, unblinded study of patients with nonvalvular atrial fibrillation who were deemed eligible for warfarin therapy.[2] Patients were randomly assigned to receive conventional warfarin therapy or the Watchman device plus short-term warfarin therapy (45 days). The primary effectiveness end point was a composite of the absence of ischemic and hemorrhagic stroke, cardiovascular and unexplained death, and systemic embolism. After 900 patient-years of observation, the rate of these events was 32% lower in the Watchman group than in the conventional-therapy group — a result that met the prespecified criterion for noninferiority. The interpretation of the data and the device's proper clinical role, how-



The Watchman Left Atrial Appendage Closure Device.

The device is a self-expanding nitinol structure that is delivered percutaneously with femoral venous access and transseptal technique to the left atrial appendage. The device is positioned with the use of angiography and transesophageal echocardiography, and implantation is performed in either a cardiac catheterization or electrophysiology laboratory with the patient under general anesthesia or conscious sedation.

ever, are complicated by several important considerations.

More than one in four patients in the warfarin group either never took the drug or stopped taking it during the study. Previous large studies of atrial fibrillation have shown a doubling of the rate of intracranial hemorrhage when the international normalized ratio (INR) exceeds 3.0 (as 15.4% of INR measurements did in the PROTECT-AF trial) and a 70% increase in the rate of stroke when the INR is less than 2.0 (as 29.6% of INR measurements were in this study).[2] Although the warfarin group underwent INR monitoring every 2 weeks for 6 months and monthly thereafter, INRs remained in the therapeutic range only 55% of the time. This rate is consistent with the rates in other atrial fibrillation trials and with analyses of insurance-claims data, and it underscores the difficulty of maintaining therapeutic INR levels in patients with atrial fibrillation.

Implantation of the Watchman device carries substantial upfront procedural risk. After 449 attempted implantations, the device was successfully placed in 408 patients (90.9%). Overall, 12.3% of patients had serious procedural complications, including pericardial effusion requiring drainage or surgery in approximately 5% and acute ischemic stroke due to air or thromboemboli in 1.1%. Four patients had to have the device removed because of device embolization or postimplantation sepsis. In total, 2.2% of attempted implantations resulted in cardiovascular surgical intervention because of device-related complications; these events were not part of the study's primary effectiveness analysis. In addition, the substantial learning curve associated with device implantation (the rate of serious pericardial effusion was 50% higher at less-experienced centers) has important implications for provider training.

Although discontinuing warfarin therapy is appealing to many patients with atrial fibrillation, anyone who has a Watchman occluder must receive ongoing anticoagulation therapy, antiplatelet therapy, or both. Studies in animals in which antiplatelet therapy was withheld showed acute thrombus formation on the device surface; the use of aspirin and clopidogrel in subsequent studies reduced the quantity of thrombus.

The protocol for the PROTECT-AF trial allowed warfarin therapy to be discontinued if transesophageal echocardiography that was performed 45 days after the implantation of the device showed complete or nearly complete occlusion of the left atrial append-

age. Nearly 90% of patients with the device discontinued warfarin therapy within 60 days after implantation, although approximately 10% subsequently restarted it for clinical reasons; patients who discontinued warfarin therapy were required to take aspirin indefinitely and clopidogrel for 6 months. Despite therapeutic heparinization at implantation, 45 days of warfarin therapy, and aggressive antiplatelet regimens, thrombus was identified on the device in 15 patients (3.7%), including 1 patient in whom it was detected 6 days after an ischemic stroke. The rate of ischemic stroke was 50% higher in the device group than in the warfarin group (3.0% vs. 2.0%), with almost half the events in the device group occurring within 30 days after implantation. Routine brain imaging was not performed, so the true incidence of subclinical cerebral infarcts is not known.

Because of the small sample, the primary efficacy estimate in the PROTECT-AF trial lacks precision, as reflected by the wide 95% credible interval (relative risk, 0.68; 95% credible interval, 0.37 to 1.41). Drug studies comparing alternative therapies to warfarin in patients with atrial fibrillation are typically 5 to 25 times the size of this study, involving at least several thousand patients.[5] The fact that fewer than 100 patients with the device were followed for 2 or more years contributes to the uncertainty regarding efficacy.

Patients in the PROTECT-AF trial were eligible for warfarin therapy and included those with $CHADS_2$ scores ranging from 1 to 6 (reflecting the risk of stroke in patients with atrial fibrillation — 1 point each for congestive heart failure, hypertension, an age of more than 75 years, or diabetes; 2 points for a history of stroke or transient ischemic attack).[1] Nearly 30% of patients receiving devices had a $CHADS_2$ score of 1 and were candidates for aspirin therapy without warfarin even in the absence of the Watchman device.[1] Although percutaneous occlusion of the left atrial appendage may seem to be a reasonable way to avoid warfarin therapy in patients with atrial fibrillation who are at high risk for bleeding, such patients were excluded from the trial. Because of the need for aggressive periprocedural anticoagulation and antiplatelet therapy, the relative clinical risks and benefits of the device for these patients are uncertain.

Providing long-term warfarin therapy safely and effectively to patients with atrial fibrillation is challenging. The Watchman device is designed to reduce the risk of thromboembolic events and to offer an alternative to warfarin therapy. Routine implantation does not appear to be warranted, though the device is promising and may be a reasonable option for selected patients with a particularly high risk of bleeding complications. Nevertheless, we should heed the lessons learned from the well-publicized recent problems with other cardiovascular devices, including drug-eluting stents and implantable defibrillator leads. In those cases, large numbers of patients were rapidly exposed to a new device on which there were limited performance data. The concerns about procedural safety and the need for long-term follow-up should be addressed before this potentially important technology is deployed widely.

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Dr. Maisel was acting chair of the FDA Circulatory System Medical Device Advisory Panel, which met on April 23, 2009, to review data related to the Watchman Left Atrial Appendage Closure Device and voted 7 to 5 in favor of approval with conditions. As acting panel chair, Dr. Maisel did not vote at the meeting. The opinions expressed in this article are those of the author and do not necessarily represent the practices, policies, positions, or opinions of the panel or the FDA.

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