We know that the risk of stroke is increased in patients with atrial fibrillation (AF), presumably because stagnant blood flow within the left atrium leads to thrombus formation. Importantly, 90% of thrombi, when seen by echocardiography in patients with nonrheumatic AF, are located in the left atrial appendage (LAA) (1,2). Standard treatment of patients with AF is anticoagulation with warfarin. If warfarin is not tolerated, aspirin and possibly clopidogrel are used. Despite such therapy, stroke still occurs in patients with AF, and evaluation of alternative strategies to minimize thromboembolic risk makes sense.

The concept of excluding the LAA from the circulation in patients with AF is not new. When surgery is performed for rheumatic mitral valve disease, which is often accompanied by AF, LAA amputation or oversewing of its orifice is routinely done to minimize the risk of future thromboembolism. Minimally invasive transthoracic techniques also have been used to achieve the same result with mixed outcomes—suturing the LAA either from within or without may occlude the orifice of the LAA but persistent flow into and out of the LAA is frequently seen when such patients have echocardiograms at follow-up. In the last 5 years, percutaneous transcatheter devices to exclude the LAA from the circulation have made their debut. The question remains whether such devices can be as effective as standard anticoagulation therapy.

The first transcatheter LAA occlusion device placed via a trans-septal approach (PLAATO System, ev3 Inc., Plymouth, Minnesota) has already been tested in a phase I clinical trial. That study, reported in the Journal in 2005 (3), established that a transcatheter LAA occlusive device could be implanted with acceptable risk, and raised the possibility that patients in AF with contraindications for warfarin therapy might have other treatment options. The PLAATO System Trial included only patients with nonrheumatic AF who were at high risk for ischemic stroke and who were not candidates for long-term anticoagulation with warfarin. To be eligible they were required to have a history of transient ischemic attack (TIA) or stroke and at least 1 (in Europe) or 2 (in North America) of the following risk factors: congestive heart failure, systolic hypertension, diabetes, age >65 years, coronary artery disease, and spontaneous echocardiography contrast or blood flow velocity <20 cm/s within the LAA. The group predicted stroke risk based on the patients’ adjusted CHADS score (4) distribution was 6.3% per year, confirming the treated patients’ high-risk status. We learned from that trial that transcatheter implantation of a device to occlude the LAA was feasible, reasonably safe (9 procedural-related adverse events, of which pericardial effusion [2 patients] and tamponade [2 patients] were the most significant), and raised the possibility that the incidence of stroke after PLAATO implantation was reduced. The actual stroke rate in the study was 4.1%/year. A later report (5) indicated that the actual stroke rate in a larger group of PLAATO patients was reduced to 3.2% (a relative risk reduction of about 50%). No comparison control patients were included in either report, so that the significance of the outcomes can only be surmised. Despite these promising data, no phase II trial of the PLAATO System is currently planned.

In this issue of the Journal (6), we now have information on another LAA occlusion device, the WATCHMAN System developed by Atritech Inc., Plymouth, Minnesota. It too demonstrates that percutaneous LAA occlusion can be performed with reasonable safety and efficacy. The numbers are small, but 54 of 58 patients with devices seen at 45-day follow-up had successful sealing of the LAA. Two patients had TIA at follow-up, but there were no strokes at a mean follow-up of 24 ± 11 months, and 33 patients have been followed for more than 3 years.

What can we take away from these preliminary trials? Most importantly, they demonstrate that percutaneous trans-septal placement of an LAA occlusion device can be done safely and produce a high degree of LAA orifice sealing. However, a comparison of the 2 trials, or combining the results to try and understand outcomes with larger numbers, is not appropriate.

First, the 2 trial designs and the devices themselves are quite different. The PLAATO System is a self-expanding nitinol cage covered with expanded polytetrafluoroethylene that excludes blood from entering the LAA. Post-implantation treatment of patients in that trial consisted of only clopidogrel and aspirin initially and long-term aspirin alone. In contrast, the WATCHMAN System is a nitinol frame structure covered with a permeable polyester fabric that allows blood flow but excludes passage of thrombi out of the LAA. Thus, patients who cannot take warfarin because of bleeding or other problems are not candidates for WATCHMAN implantation because anticoagulation for 45 days to 6 months is necessary by protocol until endothelialization of the device is complete. In the PLAATO trial,
the population of patients potentially treatable with that device was restricted to non-warfarin candidates. Thus, the 2 trial populations are quite disparate. There is, however, nothing specific to the polyester-covered WATCHMAN device that demands warfarin anticoagulation. Instead, what the WATCHMAN phase I trial tested and now promises is that the population of patients potentially treatable with this device is far larger, and might include any patient with AF that would prefer implantation of an LAA occlusion device plus long-term aspirin therapy to long-term warfarin therapy.

Second, the patients treated in the WATCHMAN report are lower risk. Their average CHADS score was 1.8 ± 1.1 compared with the PLAATO group’s 2.5 ± 1.3. Thus, the anticipated stroke rate in the WATCHMAN population would predictably be low, and perhaps the lack of any strokes in this phase I trial is due to this fact as well as the small number of patients enrolled. Third, both the PLAATO and WATCHMAN trials demonstrate that new devices, particularly those placed via trans-septal puncture, are tricky, and a learning curve concerning implantation is inevitable. Pericardial effusion/tamponade occurred in both trials, and device embolization in the first generation of the WATCHMAN device prompted a design change. There is still no free lunch.

Lastly, where do these feasibility trials take us? We can conclude little more than relative safety and feasibility of transcatheter occlusion of the LAA. The temptation to emphasize the reduction in anticipated stroke rate is appealing, but, without a control group of patients, that conclusion is not reliable. What we need is a prospective, randomized trial of either (or both) devices. The WATCHMAN System is now being tested in exactly that manner. The design is straightforward. There is a 2:1 randomization against standard warfarin anticoagulation, and those patients receiving the device will have warfarin for 45 days (or up to 6 months if needed) until endothelialization of the device is complete. Presumably, some patients in the trial will not be able to tolerate warfarin for the required time, and we may learn something about the outcome of reduced warfarin therapy with the device in place. However, I suspect that patient numbers in this subgroup will be small, thereby making difficult or impossible any conclusions about reducing the length of time warfarin is needed after implantation.

To be eligible patients must be 18 years of age or older, have chronic or paroxysmal nonvalvular AF, be eligible for long-term warfarin therapy, be eligible to discontinue warfarin therapy if the LAA is sealed, and have a CHADS score of 1 or greater. The trial is designed to show that the treatment arm is not inferior to the control arm so that if the trial is successful, we may be able to tell our patients that placement of a WATCHMAN device is at least equivalent to standard warfarin therapy. My guess is that since the patients in the trial are relatively low risk, the number of patients reaching end points will be <5% per year. This may make comparisons difficult. The good news is that if the trial shows equivalence, we will have the option of advising our patients that long-term use of warfarin, especially in younger patients with AF or in patients who have problems in maintaining appropriate international normalized ratio levels on warfarin, can be avoided. We all need to watch the WATCHMAN—the strategies available for treatment of patients with AF to prevent thromboembolism may well increase.

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