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EDITORIAL

Watchman FLX's Sophomore Year Report Card

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Oral anticoagulation is a highly effective and generally well-tolerated therapy for the prevention of atrial fibrillation (AF)-associated stroke. Select patients, however, do not or cannot receive this treatment, either because of prior bleeding events or comorbidities that confer an unacceptably high bleeding risk. The familiarity of this clinical scenario, coupled with the observation that the left atrial appendage (LAA) frequently serves as the anatomic source of AF-associated thrombus, resulted in the development of mechanical devices capable of closing the LAA via a percutaneous approach. The Watchman LAA closure device (Boston Scientific, Marlborough, MA) is now an approved therapy for AF-associated stroke prevention among individuals who are poor candidates for long-term anticoagulant therapy.

See Article by Doshi et al.

Fortunately, the yearly risk of AF-associated stroke is low for most individuals. Because the aim of LAA occlusion is to prevent these relatively uncommon thromboembolic events, an occlusion device must have an excellent performance profile, with minimal device-related complications; for the device to result in net clinical benefit, acute complications must be offset by a reduction in stroke and bleeding events during follow-up. The invasive nature of LAA occlusion unfortunately guarantees at least some individuals will experience an implant-related complication. Concerns have been raised regarding the risk of periprocedural complications observed with the first-generation Watchman device,[1] especially in the hands of less experienced physicians and centers.[2] After successful LAA occlusion, patients are vulnerable to device-related thrombus, presumably until an endothelial layer has formed over the exposed face of the implant. Protection from device-related thrombus typically involves treatment with antiplatelet and/or anticoagulant medications for 6 months, then antiplatelet monotherapy thereafter. Exposing a patient with an elevated bleeding risk to this antithrombotic regimen can be problematic for obvious reasons, and successfully navigating these competing risks of thrombus and hemorrhage is a frequent source of concern for both patients and physicians.

In 2018, a second-generation Watchman device (Watchman FLX) was introduced. Several design changes were implemented, with the goal of reducing procedural complications, peridevice leaks, and device-related thrombus. The 1-year performance of this second-generation device, evaluated in the context of a United States Investigational Device Exemption study, has been previously reported (PINNACLE FLX [Protection Against Embolism for Nonvalvular AF Patients: Investigational Device Evaluation of the Watchman FLX LAA Closure Technology]).[3] This single-armed study of 400 patients demonstrated the second-generation Watchman FLX device could be successfully

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implanted in most individuals (98.8%), with a low risk of acute procedural complication (0.5%). At 1 year of follow-up, the risks of ischemic stroke/systemic embolism and major bleeding were 3.1% and 7.9%, respectively.[3,4]

In the present study by Doshi et al in this issue of *Journal of the American Heart Association* (*JAHA*),[4] the authors report the 2-year safety and effectiveness outcomes from the PINNACLE FLX study. From an effectiveness perspective, the combined risk of ischemic stroke or systemic embolism at 2 years was 3.4%. It is worth highlighting that the majority of these thromboembolic events (>90%) occurred during the first year of follow-up. In the second year after implant, only 1 ischemic stroke event was observed. Importantly, a nonnegligible proportion of individuals in this study cohort were treated with off-protocol antiplatelet or anticoagulant medications at 2 years of follow-up (6.2% dual antiplatelet therapy, 7% oral anticoagulation), which may have contributed to the low risk of ischemic stroke observed during the second study year. Between 1 and 2 years of follow-up, the risk of significant bleeding complication was 1.9%; none of these bleeding events were fatal. However, 1 patient who resumed oral anticoagulation and antiplatelet therapy for a device-related thrombus suffered a hemorrhagic stroke. No pericardial effusions or device embolization events were noted during the second study year.

How should we interpret these new results? The authors provide a statistical comparison between the presently observed 2-year risk of ischemic stroke/systemic embolism and a historically defined performance goal. Interpretation of this analysis is not completely straightforward, as this performance metric was determined by taking the risk of ischemic stroke/systemic embolism from first-generation Watchman studies (4.7%) and adding an additional 4 percentage points. Although it is encouraging that the FLX device cleared this arbitrary and arguably low statistical hurdle, the necessity of a historical benchmark underscores the central limitation of this study; the absence of an active comparator group makes it difficult to fully contextualize the results. The risk of bleeding in the present analysis is similarly subject to this limitation. As above, the previously reported risk of bleeding in PINNACLE FLX at 12 months was 7.9%,[3] whereas the presently described risk of bleeding in the second year fell to 1.9%. The authors note that 70% of major bleeding events occurred during the first 6 months after implant, presumably attributable to the requisite postimplant use of dual antiplatelet and/or oral anticoagulation. To provide some perspective for comparison, the yearly risk of major bleeding in the landmark direct oral anticoagulant trials was 2.1% with apixaban[5] and 3.6% with rivaroxaban.[6] However, differences in bleeding definitions and baseline bleeding risk again limit comparison between the PINNACLE FLX study and prior oral anticoagulation trials. When specifically focusing on the low second-year risks of thromboembolism and bleeding in this study, it is not clear to what degree survivorship bias may have contributed to the findings. Finally, it should be noted that although participants enrolled in PINNACLE FLX were required to have a "rationale for a nonpharmacological approach to stroke prevention," the protocol did not explicitly specify enrollment of individuals who were poor candidates for long-term anticoagulation. It is therefore conceivable that patients with clinical AF who receive a Watchman FLX out of concern for hemorrhagic complication with oral anticoagulation may differ with regard to bleeding risk from those individuals enrolled in the PINNACLE FLX study.

Despite these issues, the current investigation adds to the literature by demonstrating an overall low rate of adverse events 2 years after Watchman FLX implantation. The comparatively higher rate of thromboembolism and bleeding in the first year raises the possibility that the risks of LAA occlusion are generally front loaded and could be mitigated with alternative procedural or postprocedural strategies. Although continued improvements in device and delivery-system design are likely, a more complete understanding of how we should pharmacologically treat individuals after implantation is critically needed. Recent observational data, for instance, hint that regimens favoring anticoagulant therapy may provide superior device-related thrombus protection and minimize bleeding complications relative to antiplatelet agents.[7] Finally, the true importance of indefinite aspirin monotherapy after LAA occlusion requires clarification, especially because several lines of evidence suggest that the long-term bleeding risk on aspirin approximates that of anticoagulation therapy.[8,9]

These data from the PINNACLE FLX study suggest that second-generation LAA occlusion devices can be implanted with low procedural risk, high appendage closure rates, and reasonable midterm stroke and bleeding outcomes. Ongoing randomized clinical trials, including comparison of Watchman FLX with contemporary oral anticoagulation therapies (CHAMPION-AF [WATCHMAN FLX Versus NOAC for Embolic ProtectION in the Management of Patients with Non-Valvular Atrial Fibrillation], NCT04394546) and comparison of various postimplant antithrombotic regimens (FADE-DRT [Efficacy of Different Anti-Thrombotic Strategies on Device-Related Thrombosis Prevention After Percutaneous Left Atrial Appendage Occlusion], NCT04502017), will build upon this evidence base and help advance the standard of care for AF-associated stroke prevention.

ARTICLE INFORMATION

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Disclosures

None.

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