Journal Pre-proof

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PII: S0735-1097(21)07894-3
DOI: https://doi.org/10.1016/j.jacc.2021.10.022
Reference: JAC 28998

To appear in: Journal of the American College of Cardiology

Received Date: 12 October 2021
Accepted Date: 13 October 2021

Please cite this article as: Merchant FM, Does Percutaneous Left Atrial Appendage Closure Stand the Test of Time?, Journal of the American College of Cardiology (2021), doi: https://doi.org/10.1016/j.jacc.2021.10.022.

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Does Percutaneous Left Atrial Appendage Closure Stand the Test of Time?

Brief/Cover Title: Long-term evaluation of LAAC

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Conflicts/disclosure: none

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In this week’s issue of JACC, Osmancik and colleagues present the pre-specified four year follow-up of PRAGUE-17 (1), a randomized, non-inferiority comparison of percutaneous left atrial appendage closure (LAAC) versus non-vitamin K oral anticoagulants (NOAC). The initial results of PRAGUE-17, reported at a median follow-up of 19.9 months, demonstrated that LAAC was non-inferior to NOAC for the primary composite endpoint of stroke, transient ischemic attack, systemic embolism, cardiovascular death, major or non-major clinically relevant bleeding and procedure-/device-related complications. Although the study was not powered to evaluate individual components of the composite endpoint, the rate of bleeding events was similar between groups. Nearly one-third of the bleeding events in the LAAC group were procedure-related, whereas non-procedure related bleeding was more common in the NOAC group (26 vs. 13 hazard ratio [HR] 0.53, 95% confidence interval [CI] 0.26-1.06)(2). The results of the longer-term follow-up presented in this issue, at a median of 3.5 years, are generally similar to the original report. LAAC remains non-inferior to NOAC for the composite endpoint (1). As might be expected, non-procedural bleeding events continued to diverge over time and by four year follow-up, non-procedural clinically-relevant bleeding was significantly more common in the NOAC group (40 vs. 23, HR 0.55, 95% CI 0.31-0.97), with the curves for non-procedural bleeding starting to diverge about 6 months after randomization.

So, what additional clinical insights do we gain from the longer follow-up of PRAGUE-17? The goals of LAAC and anticoagulation are the same – to minimize risk of stroke/systemic embolism (SSE) due to atrial fibrillation in the safest manner possible. However, the short- and long-term benefits and risks of these therapies are obviously very different. Short-term procedural risks associated with LAAC have been well-described (3,4) and in PRAGUE-17, nine patients (4.5%) in the LAAC group experienced significant procedural complications, including
2 procedure-associated deaths (2). However, longer-term device associated adverse events are less well-characterized. Device-related thrombus (DRT), an Achilles’ heel of LAAC, occurs with a reported incidence of ~3-4%, can present well over a year after implant, and is associated with significantly increased risk of SSE (5,6). Most patients diagnosed with DRT resume anticoagulation, even if transiently, which may offset some of the long-term benefit associated with LAAC. Another longer-term device-related risk is peri-device leak (PDL). Following LAAC, large leaks around the device may increase risk of SSE and preclude discontinuation of anticoagulation. Although most PDLs are identified at device implant, it has recently been reported that new PDL measuring > 3 mm is identified in about 3% of patients at 45 - 90 day follow-up and is also associated with increased risk of SSE (7). However, the true incidences of late DRT and PDL, and the associated risks of SSE, are not well-defined.

Unfortunately, with regard to understanding late device-associated risks, PRAGUE-17 is a real missed opportunity. To their credit, the investigators had planned to perform transesophageal echocardiograms (TEE) in the LAAC group 6 to 18 months after randomization (1). But due to Covid-19, the vast majority of these follow-up TEEs were canceled. So although the incidence of late DRT and PDL isn’t known, the longer-term PRAGUE-17 data are helpful in demonstrating that rates of SSE remain similar in the LAAC and NOAC groups over time, without any obvious signal of late ischemic events in the LAAC group. Admittedly the number of ischemic events in PRAGUE-17, even during longer follow-up, is small, but these data are consistent with large, real-world registries which demonstrate similar long-term rates of SSE following LAAC compared to propensity score matched patients treated with NOAC (8). Clearly more detailed assessment of late DRT and PDL is needed, but until such data are
available, the longer-term PRAGUE-17 results provide some reassurance that the originally-reported results appear stable over time.

PRAGUE-17 also provides important context for longer-term risks associated with anticoagulation. At the four-year follow-up, 26 patients (13%) in the NOAC group permanently stopped anticoagulation, of whom 15 had experienced clinically-relevant bleeding (1). The reasons for stopping anticoagulation in the other 11 patients are not specified. But given the observed trend of significantly increased non-procedural clinically-relevant bleeding in the NOAC arm, it is likely that late bleeding events will increasingly favor LAAC over time. Conversely, 17 patients (8.5%) in the LAAC group were treated with anticoagulation at some point during longer follow-up: 3 for DRT and 3 for PDL. The indications in the other patients are not specified but NOACs obviously have important indications beyond prevention of left atrial appendage thrombi, including prevention of non-LAA sources of SSE and treatment of venous thromboembolism. If significant numbers of patients treated with LAAC end up on anticoagulation in the long run, the benefits of LAAC are likely to be attenuated. Although the number of events in PRAGUE-17 is too small to say anything meaningful about quantifying these anticoagulation-associated risks, the data do provide some insight into the longer-term indications for resuming NOAC in patients previously treated with LAAC.

An additional, often overlooked, aspect of long-term medical therapy is adherence to aspirin. Patients undergoing LAAC are typically treated with a more intensified antiplatelet and/or anticoagulation regimen for the first few months after device implant and then remain on low-dose aspirin indefinitely. However, the percentage of LAAC-treated patients who discontinue long-term aspirin is not well-described, and is not reported in PRAGUE-17 (1). In the Apixaban versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients
Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) study, aspirin was permanently discontinued in 20.5% of patients at 2 years, compared to a discontinuation rate of only 17.9% in the apixaban group (9). It is plausible that discontinuation of aspirin may contribute to late ischemic events in patients treated with LAAC, potentially by increasing the risk of late DRT or through other mechanisms. Adherence to, and the impact of, long-term antiplatelet therapy should be a focus of future LAAC studies.

When placing the longer-term results of PRAGUE-17 in clinical context, it is also important to bear in mind the challenges in interpreting a composite endpoint which includes both efficacy and safety events (10). In this study design, widely disparate endpoints carry the same weight: for instance, preventing a 2.0 g/dL drop in hemoglobin is as important as preventing a stroke. But are these endpoints equally meaningful for patients? When engaging in shared decision-making interactions with patients, it is crucial to be able to communicate the severity of the endpoints prevented and to understand whether LAAC and NOAC are truly similarly efficacious. Unfortunately, the severity of ischemic and bleeding events in PRAGUE-17 is not reported (1). And as the authors point out, much larger studies are needed to rigorously compare the efficacy of LAAC and NOAC for preventing SSE.

Fortunately, larger studies are underway. Two large, randomized trials are comparing LAAC to NOAC and will provide more data on individual components of efficacy and safety endpoints (11). Given the large number of patients with atrial fibrillation who merit stroke prevention therapy, it is incumbent upon us to really understand which therapies are most effective at preventing the endpoints which are most important to patients. But until such data are available, the longer-term results from PRAGUE-17 provide an important perspective on the
challenges of evaluating late risks associated with SSE and bleeding in patients with atrial fibrillation.
References


