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EDITORIAL COMMENT

Transcatheter Left Atrial Appendage Occlusion in the DOAC Era*

Matthew J. Price, MD,[a] Jacqueline Saw, MD[b]

Transcatheter left atrial appendage (LAA) occlusion (LAAO) is a nonpharmacologic alternative to stroke prevention in appropriately selected patients with atrial fibrillation (AF). Because most thromboembolic events in patients with AF are thought to originate from a thrombus formed within the LAA, a targeted approach to exclude this chamber can be beneficial compared with systemic oral anticoagulation (OAC) by preventing AF-driven ischemic stroke while overcoming the challenges of drug therapy (e.g., compliance, drug-drug interactions, and appropriate dosing) and reducing long-term bleeding. In contradistinction, clinically significant procedure-related safety events (e.g., cardiac tamponade) with transcatheter LAAO will diminish or obviate any longer-term advantages over OAC. Therefore, the incorporation of transcatheter LAAO into a stroke prevention strategy for an individual patient relies on the complex interplay of 3 competing hazards: the long-term risks of thromboembolic events without therapy (e.g., CHA_2DS_2-VASc [congestive heart failure, hypertension, 75 years of age and older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, 65 to 74 years of age, female] score), the short-term procedure risk of LAAO, and the longer-term risk of bleeding and noncompliance on indefinite OAC therapy (1). Ongoing data generation is required to inform patient-centered decision making as new LAAO devices are iterated, operator experience grows, and the safety and tolerability profile of OACs improve.

The most robust data for the safety and clinical effectiveness of transcatheter LAAO are derived from 2 U.S. Food and Drug Administration registration trials and their respective continued access registries that were conducted during the warfarin era (2,3). Among patients with AF who were good candidates for OAC, LAAO with the Watchman device (Boston Scientific, Marlborough, Massachusetts) was noninferior to continued warfarin with regard to the composite endpoint of death, all-cause stroke, or systemic embolism and was associated with significantly fewer non-procedure-related major bleeds (2,4). The U.S. Food and Drug Administration approved the device for stroke prophylaxis, but because of concerns about procedure risk and statistical uncertainty surrounding the Bayesian analysis of the ischemic endpoint, the indication was limited to patients who are recommended for OAC (i.e., CHA_2DS_2-VASc $\geq$2), are suitable for warfarin, and have an appropriate rationale for seeking a nonpharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin. The Centers for Medicare and

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From the [a]Division of Cardiovascular Diseases, Scripps Clinic, La Jolla, California; and the [b]Division of Cardiology, Vancouver General Hospital, University of British Columbia, Vancouver, British Columbia, Canada. Dr. Price has received consulting honoraria and speaker bureau fees from Abbott Vascular, AstraZeneca, Boston Scientific, Chiesi USA, and Medtronic; has received consulting honoraria from W.L. Gore and Baylis Medical; has received proctorship honoraria from Abbott Vascular and Boston Scientific; and has received research grants (to institution) from Daiichi- Sankyo. Dr. Saw has received unrestricted research grant support from the Canadian Institutes of Health Research, Heart & Stroke Foundation of Canada, National Institutes of Health, Michael Smith Foundation of Health Research, University of British Columbia Division of Cardiology, AstraZeneca, Abbott Vascular, Boston Scientific, and Servier; has received speaker bureau fees from AstraZeneca, Abbott Vascular, Boston Scientific, and Sunovion; has received consulting and Advisory Board honoraria from AstraZeneca, Boston Scientific, Abbott Vascular, W.L. Gore, Baylis, and FEops; and has received proctorship honoraria from Abbott Vascular and Boston Scientific.

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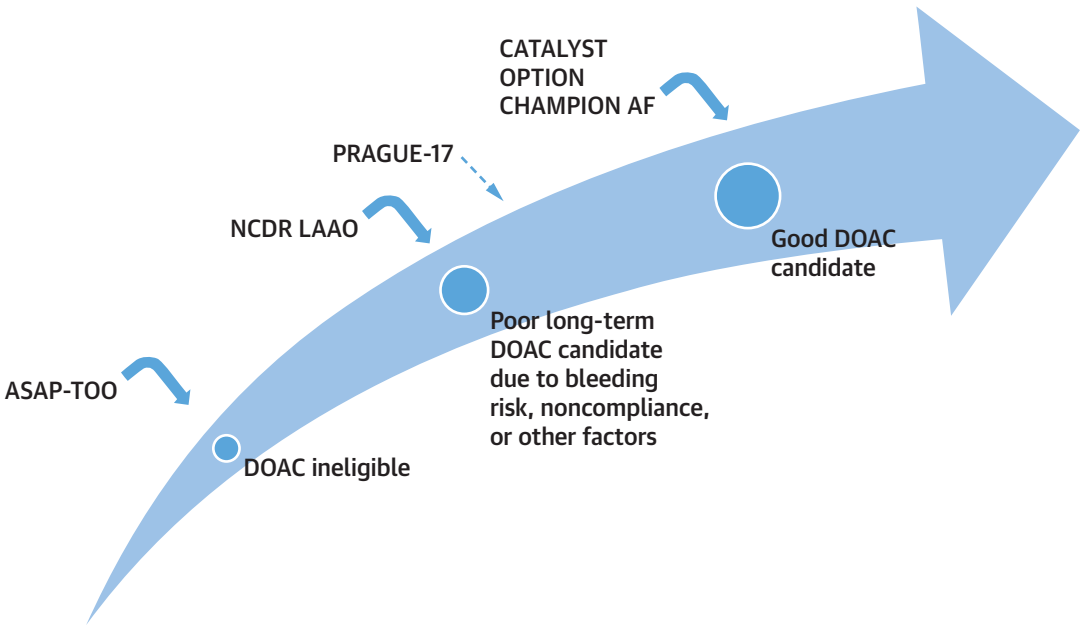
FIGURE 1 Ongoing or Planned Clinical Trials and Registries of Transcatheter LAA Closure



Assessment of the Watchman Device in Patients Unsuitable for Oral Anticoagulation (ASAP-TOO) is evaluating the safety and effectiveness of transcatheter LAAO in approximately 888 participants with AF who are deemed not to be eligible for OAC (NCT02928497). The NCDR LAAO is a large observational registry designed to monitor the utilization, safety, and effectiveness of LAAO devices in real-world clinical practice. PRAGUE-17 is a noninferiority study comparing transcatheter LAAO to DOACs in patients with prior bleeding event, treatment failure, or at a combination of high bleeding and thromboembolic risk. Comparison of Anticoagulation With Left Atrial Appendage Closure After AF Ablation (OPTION) is examining whether transcatheter LAAO with the Watchman FLX (Boston Scientific, Marlborough, Massachusetts) is a reasonable alternative to OAC (including DOACs) following percutaneous catheter ablation in approximately 1,600 patients with AF (NCT03795298); Clinical Trial of Atrial Fibrillation Patients Comparing Left Atrial Appendage Occlusion Therapy to Non-vitamin K Antagonists (CATALYST) will compare Amulet LAAO (Abbott Vascular, Santa Clara, California) to DOACs in >2,650 patients recommended for long-term DOAC therapy (NCT04226547). CHAMPION-AF (WATCHMAN FLX versus NOAC for eMbolic ProtectION in in the management of patients with non-valvular Atrial Fibrillation) will compare the next-generation Watchman FLX to DOACs in patients recommended for long-term DOAC therapy. AF = atrial fibrillation; DOAC = direct oral anticoagulant; LAA = left atrial appendage; LAAO = left atrial appendage occlusion; NCDR = National Cardiovascular Data Registry; OAC = oral anticoagulant.

Medicaid Services further limited reimbursement for LAAO to patients who are at high thromboembolic risk (CHA_2DS_2-VASc ≥3) and can tolerate short-term warfarin but are unable to take long-term therapy. These conditions permitted short-term administration of warfarin for 45 days after Watchman implantation to prevent device-related thrombus (DRT), as was studied in the 2 trials. Transcatheter LAAO appears to be an increasingly accepted treatment option for this patient cohort as more than 38,000 patients have been treated in the United States by approximately 1,300 operators within the first 3 years of commercial availability (5).

The introduction of direct oral anticoagulants (DOACs) has fundamentally changed the pharmacological prevention of AF-related thromboembolism, and any discussion regarding the expansion of transcatheter LAAO beyond its current application must incorporate this shift in clinical practice. The randomized clinical trials of LAAO were initiated before the widespread adoption of DOACs over warfarin for AF-related stroke prevention. How LAAO might stack up against DOAC therapy has remained an open question: compared with warfarin, DOACs are easier to use and are associated with a reduction in mortality, driven by a substantially lower risk of intracranial hemorrhage and fatal bleeding. DOACs are associated with similar rates of ischemic stroke, with the possible exception of dabigatran, and either higher or similar rates of gastrointestinal bleeding. Interestingly, transcatheter LAAO had a DOAC-like effect in the randomized controlled trials versus warfarin, with a significant reduction in intracranial hemorrhage, no statistically significant increase in

ischemic stroke, and a possible reduction in all-cause mortality (2,6). In addition, LAAO reduced the risk of gastrointestinal bleeding (4). These longer-term benefits were mitigated by procedure hazards, although real-world procedure complication rates have dropped dramatically since the clinical trial experience (5).

In this issue of the *Journal,* Osmancik et al. (7) dive into this data vacuum with PRAGUE-17, a dedicated, powered, prospective, randomized, noninferiority trial to compare transcatheter LAAO with DOAC therapy (7). The investigators enrolled 402 patients with either DOAC treatment failure, a significant prior bleed, or a combination of high thromboembolic and high bleeding risk and randomly assigned them to either DOAC therapy (mostly apixaban) or LAAO with

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1 of 3 commonly used devices. The primary endpoint was a composite outcome that included both safety and effectiveness—procedure- or device-related complications, thromboembolic events (cardiovascular death, all-cause stroke, or systemic embolism), and major and nonmajor clinically significant bleeding. According to modified intention-to-treat and as-treated analyses, transcatheter LAAO was noninferior to DOAC therapy at a median follow-up of approximately 20 months, with similar rates of all-cause stroke between groups and numerically lower rates of bleeding with LAAO.

The findings of PRAGUE-17 are provocative given the clinical consensus that DOACs are safer, well tolerated, and generally better than warfarin, which was an easy target for transcatheter LAAO, given warfarin's extensive limitations. Although this trial begins to move the needle toward supporting transcatheter LAAO as an alternative in patients who are DOAC candidates, enthusiasm to expand the target population for LAAO should be tempered by several caveats. First, the patients evaluated in PRAGUE-17 were not optimal candidates for long-term OAC but were selected because they were at high risk for bleeding or because OAC treatment had already failed. Notably, the pivotal trials leading to DOAC approval excluded patients who were deemed to have high bleeding risk, so PRAGUE-17 does not address the relative safety and efficacy of transcatheter LAAO for the populations in which the current DOAC indications are derived. Indeed, the baseline clinical characteristics appear largely similar to those of patients being treated under the current Centers for Medicare and Medicaid Services structure within the United States: nearly one-half of the enrolled patients had a prior bleeding event, and the average CHA_2DS_2-VASc score (4.7 ± 1.5) and HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly) scores (3.0 ± 0.9) are nearly identical to those of patients in the NCDR LAAO registry (4.6 ± 1.5 and 3.0 ± 1.1, respectively) (5). The study findings, therefore, lend support to the current U.S. practice of transcatheter LAAO, even in the DOAC era. Second, the duration of follow-up was relatively short at <2 years, and important differences between the 2 treatment strategies will likely be magnified over time as bleeding events may accrue in the DOAC-treated patients and ischemic events may accrue in the LAAO-treated patients because of DRT or events unrelated to LAA thrombus that DOACs might prevent in patients with high CHA_2DS_2-VASc scores (8). Several large randomized trials are ongoing or planned that will address the role of transcatheter LAAO across the spectrum of patient candidacy for DOAC therapy, with sufficiently large sample sizes to test separately powered ischemic and bleeding endpoints (**Figure 1**). Furthermore, device iterations like those incorporated into the next-generation Watchman FLX may further improve procedure safety, increase anatomic closure rates, and reduce DRT, thereby increasing the likelihood that transcatheter LAAO may provide similar ischemic and possibly better safety outcomes than DOAC therapy.

Despite its imperfections, PRAGUE-17 is an important step forward and reinforces the role of transcatheter LAAO as a stroke-prevention strategy for patients with AF at high risk of bleeding or medical treatment failure, even in the modern era of the DOACs. Going forward, successful enrollment in ongoing and planned clinical trials while avoiding off-label procedures will be critical to define the appropriate use of transcatheter LAAO in expanded patient populations. The heart team model has been adopted for the management of valvular heart disease. The time has come for a similar approach to stroke prevention in AF, in which a multidisciplinary team involving clinical cardiologists, structural heart interventionalists, electrophysiologists, and providers from other disciplines (e.g., gastroenterology, neurology, and neurointervention) provide a

consensus recommendation for systemic anticoagulation, transcatheter intervention, or referral to a clinical trial by weighing patient-specific thromboembolic risk, anticoagulant-associated bleeding risk, anatomic eligibility for LAAO, and patient preferences.

ADDRESS FOR CORRESPONDENCE: Dr. Matthew J. Price, Division of Cardiovascular Diseases, Scripps Clinic, 9898 Genessee Avenue, AMP-200, La Jolla, California 92037. E-mail: price.matthew@scrippshealth.org. Twitter: @matthewjpricemd, @docsaw.

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