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EDITORIAL COMMENT

Left Atrial Appendage Closure

Continuous Progress With Remaining Challenges*

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Randomized trials comparing left atrial appendage closure (LAAC) to vitamin K antagonists (VKA) demonstrated at least equivalency in the prevention of all-cause strokes and superiority with respect to cardiovascular mortality and disabling strokes (1-3). Why then do we need further improvements of available technology? First, in the largest randomized trial to date comparing LAAC to VKA, the PROTECT-AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) trial, it required a mean follow-up of 3.8 years to show equivalency in the rate of safety events (2). Second, and perhaps surprising to many, it must be emphasized that analysis of the PROTECT-AF trial and PREVAIL (Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy), the second randomized trial, did not show a difference in all-cause major bleeding (4). This was related to periprocedural safety events, particularly, pericardial bleeding, that counterbalanced the higher post-procedural bleeding rate in the warfarin group. Fortunately, for those of us who recognize the utility of LACC, the PROTECT-AF trial (after the less convincing results of the PREVAIL trial [3]), at long-term follow-up, did finally show a benefit in all-cause mortality (driven by the lower hemorrhagic stroke rate compared with warfarin) (2). Apart from efficacy, it is the safety events, residual leaks, and thrombus formation that must remain our focus. Experience with the procedure and a number of improvements in the device and delivery system of the Watchman device (Boston Scientific, Natick, Massachusetts) have led to a reduction in safety events compared to those reported in the PROTECT-AF and PREVAIL trials. This was recently demonstrated by the U.S. and European registries (5,6). Likewise, a low number of safety events was reported in the Amplatzer Cardiac Plug (ACP) (St. Jude Medical, St. Paul, Minnesota) multicenter registry (7). The results

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of the prospective, multicenter LAmbre (LifeTech Scientific, Shenzhen, China) clinical study reported in this issue of *JACC: Cardiovascular Interventions* by Huang et al. (8) suggests efficacy when thromboembolic event rates after LAAC were compared with the expected event rate based on $CHA2DS_2$-VASc scores in a historical control group without anticoagulation (8). Though reassuring, regulatory processes in some countries will likely require confirmation in a randomized trial before approval for commercial use. One may argue about ethical concerns regarding randomization of individuals with atrial fibrillation to LAAC or aspirin/no treatment in those who are at prohibitive risk of bleeding from oral anticoagulation, or perhaps, warfarin in those whose bleeding risk is low, because data have now convincingly shown a benefit with LAAC compared with warfarin (1,2). Hence, the next step could be a randomized noninferiority trial comparing the LAmbre device to the Watchman device, or a randomized trial comparing it to direct oral anticoagulation with prothrombin or factor Xa inhibitors. There is an important aspect that stands out. Although peridevice leaks are common with the Watchman device, with incidences ranging between 32% (9) and 64% (10), depending on imaging

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modality, any peridevice leak was demonstrated in only 16% after LAmbre implantation and leaks >3 mm in only 0.7% (8). This may be related to the large diameter of the cover compared with the umbrella and/or the articulating waist allowing favorable alignment of the cover with the appendage ostium. In this context, a peridevice leak was reported in 12% with the ACP (7), a device with similar design features including a larger disc size compared with the anchor accommodating the challenging usually elliptical shape of the appendage ostium. Alternatively, the observed lower leak incidence may be related to the definition of peridevice leak. In devices with a "pacifier" design in which an anchor securing the device is attached to a disc that seals the appendage ostium (i.e., LAmbre or ACP), leaks around the anchor may be rare. However, potentially unaccounted for leaks between the disc and anchor could be more common, and it remains to be determined whether this is less consequential than peridevice leaks described with other devices. Therefore, the low leak rate may be a reflection of the definition rather than device design. Furthermore, leak or thrombus detection and quantification between the disc and anchor is more challenging than surrounding other devices such as the Watchman occluder. It would be important for any future studies to clarify how peridevice leak is defined other than merely by size (i.e., whether or not it includes leaks between the disc and anchor). Though the clinical significance of peridevice leaks remains unclear and some data support the assumption that small leaks are benign (10), the aim should be to achieve as complete an occlusion as possible. The high procedural success rate (99.4%) (8) is similar to that reported in the latest European and U.S. Watchman and ACP multicenter study (98.5%, 95.6%, and 97.3%, respectively) (6,7,11). Likewise, ease of use, measured by number of devices tried at implant and number of times a device required recapturing, an important aspect that impacts procedural safety, appears to be comparable to the Watchman device and ACP. In the ACP multicenter study, in 93%, the first ACP tried was the final implanted device (7); in the EWOLUTION (Registry on Watchman Outcomes in Real-Life Utilization) registry, in 93% of patients, only 1 device was used, and most devices (71%) were implanted at first attempt (5). With the LAmbre device, success was 88% with the first device, and successful implant occurred in 57% at first attempt (8). The incidence of device-associated thrombus formation (1.3%) (8) that may cause the event (stroke) that we are trying to prevent, potentially diminishing efficacy of LAAC, was slightly lower than reported with other devices, 4.2% in the PROTECT-AF trial and the CAP (Continued Access Protocol) registry (12), 3.7% in the EWOLUTION registry using the Watchman device (11), and 3.2% in the ACP multicenter study (7). Lastly, whereas device embolization, a potentially life-threatening event, was reported in 0.6% in the PROTECT-AF trial (13), 0.2% in the EWOLUTION registry (5), and 0.8% in the ACP multicenter registry (7), it did not occur with the LAmbre device (though numbers are too small to draw any final conclusions) (8).

In conclusion, although with LAAC, we have a better alternative to oral anticoagulation with VKA for stroke prevention in patients with atrial fibrillation, challenges remain regarding procedural safety, peridevice leak, thrombus formation, and device embolization. In a procedure with the goal to prevent an event, the annual likelihood of which is relatively low, it is our responsibility to further improve device technology to achieve a procedural risk close to zero. In the prospective multicenter LAmbre device study (8), technical success and ease of use were similar to the 2 other most frequently used LAAC devices, and periprocedural complications were low. Likewise, the incidence of peridevice leak and device-associated thrombus formation were very low. Further, larger studies will be needed to confirm at least equivalency to the Watchman device or direct oral anticoagulants or superiority to VKA.

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