



## Percutaneous Left Atrial Appendage Occlusion: Putting the Most Lethal Human Attachment Behind Bars

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Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting millions of people worldwide. Since AF mainly affects the elderly, its prevalence is expected to increase with the aging of the population. In the United States alone, over 15 million people will have AF by the year 2050<sup>1</sup>. Among its many consequences, the one that carries the greatest burden with regard to morbidity is embolic stroke. The rate of ischemic stroke among patients with nonvalvular AF averages 5% per year, a fivefold increase compared with that of people without AF<sup>2</sup>. The risk of stroke increases with age. The annual risk of stroke attributed to AF is 1.5% in subjects aged 50 to 59 years and 23% in those aged 80 to 89 years. Importantly, the left atrial appendage (LAA) is the primary site of thrombus formation as a precursor to embolic stroke in nonvalvular AF patients<sup>1</sup>. In these patients, anticoagulation with warfarin has become standard medical therapy, reducing the risk of stroke by ~60%. Nonetheless, the long-term use of warfarin carries several drawbacks and complications, including non-tolerance, non-adherence, interactions with food and other medications, a very narrow therapeutic range, and an increased risk of bleeding<sup>3</sup>. In addition, oral anticoagulation is contraindicated in up to 40% of patients with AF who are at risk for stroke. Accordingly, several surgical and percutaneous techniques have been explored to occlude the LAA for stroke prevention. As an alternative to surgical closure, percutaneous transcatheter LAA closure (LAAC) represents a novel approach to prevent strokes in high-risk patients with nonvalvular AF and contraindications to long-term oral anticoagulant therapy. In selected patients, dedicated LAAC devices such as Watchman (Atritech Inc, Plymouth, Minn) and the Amplatzer cardiac plug (ACP; AGA Medical Corp., Minneapolis, MN, USA) have shown encouraging initial results. For instance, The Watchman Left Atrial Appendage System for Embolic Protection in

Patients With AF (PROTECT AF) trial — the only randomized study to address this issue — has shown the therapeutic noninferiority of LAAC when used as an alternative to long-term warfarin in preventing stroke (with less intracranial hemorrhages) in patients with a CHADS<sub>2</sub> score  $\geq 1$ <sup>4</sup>. The events in the Watchman group occurred early and were related to the procedure, predominantly pericardial effusion and procedural stroke related to air embolism.

Besides the aforementioned clinical criteria for percutaneous LAAC and the assessment of stroke risk by CHADS<sub>2</sub> and the CHA<sub>2</sub>DS<sub>2</sub>-VASc scores, anatomical characteristics of the LAA should be taken into account when selecting candidates for this procedure. The left atrial appendage is a long, tubular and hooked structure which has a narrow junction with the venous component of the atrium. In adults, the mean volume of the LAA is approximately 5.2 ml, with orifice diameters ranging from 5 to 40 mm. There is considerable inter-individual variability in the size and shape of the LAA. Functions of the LAA include modulation of sympathetic and parasympathetic tone, decompression of the left atrium in the setting of elevated atrial pressure and volume overload, production of natriuretic peptides (atrial natriuretic peptide, brain natriuretic peptide) and contribution to the diastolic filling of the left ventricle<sup>5</sup>. In general, the inclusion criteria for LAAC consist of: 1) absence of intracardiac thrombus or dense spontaneous echo contrast by transesophageal echocardiogram; 2) any adverse anatomy such as multiple LAA lobes; and 3) LAA ostium diameter > 17 mm and < 28 mm (32 mm for Watchman device) and LAA length > 20 mm; dimensions suitable to accommodate the prosthesis. Multilobular LAA and ostium geometric variability may result in an incomplete seal of the appendage.

In the largest single center observational study of the subject by Gu  rios et al.<sup>6</sup>, the authors report the short- and mid-term results of LAAC using the Amplatzer cardiac plug. The study, which included 86 patients with a high predicted risk score of 2.6% by CHADS<sub>2</sub>, demonstrated high procedural success (99%) with a low rate of acute or subacute complications, including 2 cerebrovascular events. Of note, there was a high 97% rate of complete LAAC by echocardiogram 3 to 6 months after the procedure with no strokes or late device embolization. The overall rate of complications in this report was lower than in previous smaller registries as well as in the PROTECT-AF trial or the Multicentric European Experience<sup>4,7</sup>. It is noteworthy that most patients in the study by Gu  rios et al<sup>7</sup> (55.8%) underwent concomitant procedures along

### Keywords

Atrial Appendage / physiopathology; Atrial Fibrillation / complications; Anticoagulants / therapeutic use; Heart Catheterization.

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with LAAC (e.g., transcatheter aortic valve implantation, percutaneous coronary intervention, patent foramen ovale or atrial septal defect closure) — that were once considered exclusion criteria in the PROTECT AF trial. The authors also report the feasibility and safety of the elegant practice of performing the procedure guided by angiography alone. Most importantly, although it is an observational study and there is no direct comparison with oral anticoagulation, no events in this cohort were observed during follow-up against an estimated rate of 5.2% embolic events/year by CHADS<sub>2</sub> score.

The challenge of selecting patients for percutaneous LAAC relies on 4 main factors: 1) there is a lack of equipoise when comparing LAAC vs. medical therapy in patients with contraindications to oral anticoagulation. For ethical reasons, such a head-to-head comparison cannot be conducted. Thus, since there is no alternative option to prevent embolic strokes, patients who are contraindicated for anticoagulants seem to be the ideal candidates for LAAC; 2) conversely, in patients eligible for oral anticoagulation, there is a paucity of data comparing the 2 strategies; as mentioned before, PROTECT AF<sup>4</sup> is the only randomized trial thus far comparing LAAC vs. oral anticoagulation. The trial demonstrated noninferiority with regard to the primary endpoint, although a higher risk of procedural complications was shown, a finding most likely biased by the initial learning curve. As with all new interventional procedures, however, there has been a significant improvement in the safety of LAAC with increased operator experience<sup>8</sup> and device development, a phenomenon previously demonstrated and corroborated by Guérios et al<sup>6</sup>. Further randomized controlled trials with longer follow-up comparing novel LAAC procedures (such as with the Amplatzer Cardiac Plug) with oral anticoagulation are

required to investigate the impact of LAAC on these lower risk patients (i.e., patients eligible for oral anticoagulant). Furthermore, the role of these devices in lower risk patients in the era of novel anticoagulants, including the use of oral factor Xa inhibitors apixaban and rivaroxaban, and the direct thrombin inhibitor dabigatran, should also be determined in further randomized controlled trials. Although compliance may improve with these novel anticoagulants and the risk of bleeding complications can be somewhat reduced compared with warfarin, there is still an increased risk of bleeding over time<sup>9</sup>. Guidelines for non-pharmacological approaches to prevention of thromboembolism such as percutaneous LAAC are pending the results of additional ongoing trials. At present, the indication for the procedure must be individualized after a thorough evaluation of the patient's global risk, which includes balancing the risk of stroke and bleeding; 3) LAAC may contribute to a reduction in the risk of thromboembolism, but this may result in undesirable physiological sequelae such as reduced atrial compliance and a decreased capacity for atrial natriuretic factor secretion in response to pressure and volume overload. Nonetheless, these physiological consequences are still unknown; and, finally 4) the cost-effectiveness of the procedure must be explored in future studies, weighing the initial substantial cost of the device against the total cost of long-term oral anticoagulation therapy.

In conclusion, LAAC is an acceptable therapeutic option in selected high-risk patients with non-valvular AF who are suboptimal candidates — or not candidates at all — for oral anticoagulant therapy. Once deemed “our most lethal human attachment” in AF patients<sup>10</sup>, the LAA can now be safely and efficaciously excluded, isolated, and imprisoned percutaneously with a life sentence for causing embolic strokes.

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