

The left atrial appendage arrhythmogenic and thrombogenic substrate

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The left atrial appendage (LAA) is a significant source of strokes in patients with atrial fibrillation (AF). Helena Dominguez from the Department of Cardiology at the University of Copenhagen discusses the LAACS studies, which investigate the effects of LAA exclusion during heart surgery

The left atrial appendage (LAA) is known as a feared cardioembolic source of strokes in patients with atrial fibrillation (AF). This has been attributed to a so-called atrial myopathy, where structural and functional changes in the LAA may render the LAA prone to form blood clots (Blume et al., 2011; Goette et al., 2016) and also prone to developing AF (Ma et al., 2017; Zhao et al., 2017). In this regard, considerable attention is focused on the development of fibrosis in the LAA, as it occurs more frequently in patients with AF compared to those without (Bertelsen et al., 2020; Marrouche et al., 2014; Miyauchi et al., 2022; Vasan et al., 2003). Additionally, thrombi have been found to be associated with fibrosis in the left atrial appendage (LAA) (Akoum et al., 2013; Miyauchi et al., 2022).

Therefore, the LAA has been excluded during heart surgery for many years.

The LAACS study

The Left Atrial Appendage Closure by Surgery (LAACS) study was the first randomized clinical trial (NCT02378116) to demonstrate significant protection of the brain against ischemic lesions by excluding the left atrial appendage (LAA) during surgery (Park-Hansen et al., 2018). The effectiveness of the LAA exclusion on patients with AF was later firmly established by the LAAOS-3 trial (Whitlock et al., 2021).

As the aim of the LAACS study was to provide permanent protection in the event of future atrial fibrillation (AF) after surgery, patients were included regardless of their history of AF. The LAACS study showed a significant effect on the primary endpoint, which was a combination of strokes and silent infarctions. However, due to the relatively small number of patients randomized (N = 189), it lacked sufficient power to demonstrate a significant protection against stroke. For this purpose, the LAACS-2 study was subsequently initiated in 2019 with stroke as the primary endpoint in this population (NCT03724318) (Madsen et al., 2023). In this multicenter international study, involving two sites in Denmark, one in Spain, and one in Sweden, 1,500 patients were randomized to undergo LAA closure or have the procedure left open as a control. The study is projected to be resumed in October 2025, when the last randomized patient will complete two years of follow-up after surgery.

It is remarkable that closure of the LAA in the first LAACS study, with a moderate number of participants (N187), could demonstrate significant cerebral ischemia protection with closure of the LAA, since most patients had no history of AF (86,2%) and less than 4% of patients of these patients got diagnosed AF in the ten years follow-up, beyond the first three months after surgery (Madsen et al., 2022). This suggests that patients may form blood clots in the LAA without having atrial fibrillation (AF).

Findings on patients with paroxysmal AF bearing implanted cardiac devices seem to support this notion, as patients suffered strokes while having sinus rhythm, not preceded by AF (Cotter et al., 2013; Diederichsen et al., 2022; Svendsen et al., 2021). Furthermore, prominent fibrosis has been identified with magnetic resonance heart scans with late gadolinium enhancement, a marker of fibrosis, among patients with stroke of undetermined source (Fonseca et al., 2018), also on those without AF (Larsen et al., 2023).

Finally, although fibrosis is a prominent feature of atrial myopathy, it may not be the sole structural and functional transformation of the left atrial appendage (LAA). Indeed, studies using tissue collected from the left atrial appendage (LAA) during heart surgery have revealed increased inflammatory markers (Fakih et al., 2023; Shaihov-Teper et al., 2021) that can precede fibrosis (Smolgovsky et al., 2024) and promote thrombogenesis (Berezin & Berezin, 2022).

In summary, a thrombogenic substrate of the LAA that can be present before atrial fibrillation is recognized, or even before AF ever occurs, can explain the benefit of closure of the LAA. LAA and blood samples collected in the LAACS-2 study and the recently initiated Left Atrial Appendage Thrombogenic and Arrhythmogenic substrate (LAATAS, NCT06405750) aim to explore the extent of inflammation, regulation of thrombogenic factors, and fibrosis associated with the occurrence of strokes.

The LAACS-2 trial, in which only 5% of patients have been diagnosed with AF before surgery, can help establish whether a LAACS procedure should be added to all patients undergoing planned open-heart surgery.

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