

# Left atrial appendage occlusion is underutilized



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## Introduction

Stroke prevention is an essential cornerstone in the treatment of patients with atrial fibrillation (AF) and can be achieved medically through oral anticoagulants (OAC) but also mechanically through left atrial appendage occlusion (LAAO). In the past decade, multiple large randomized controlled trials (RCTs) have confirmed the efficacy and safety of both vitamin K antagonists (VKA) and direct oral anticoagulants (DOAC).<sup>1,2</sup> As over 90% of thromboembolic strokes in AF patients appear to be caused by thrombi originating from the left atrial appendage, left atrial appendage occlusion (LAAO) is an alternative treatment option to reduce the risk of thromboembolic events that allows patients to discontinue OAC treatment.<sup>3</sup> The PROTECT AF and the PREVAIL trials compared LAAO to VKA. Together they included 1114 patients, and their combined 5-year results showed noninferiority of LAAO to VKA in the prevention of death and thromboembolic complications and superiority of LAAO for the separate endpoints of mortality as well as major bleeding.<sup>4</sup> Since that time a lot of experience with LAAO has been gained, and currently procedural success rates are almost 100%.<sup>5,6</sup> Furthermore, major complications, of which 50% are major bleeding (of the groin), are nowadays seen in only 2%–4% of patients. Also, improvement of devices has led to a decrease in the occurrence of device-related thrombus.<sup>5,7</sup> Currently, most experience and published data are gained with the Watchman and Amulet device. The recently published AMULET IDE trial showed noninferiority for safety and effectiveness of the Amulet device compared with the Watchman device.<sup>6</sup> In summary, LAAO appears to offer AF patients a safe and effective option to reduce the risk of AF-related thromboembolisms.

**KEYWORDS** Atrial fibrillation; Left atrial appendage occlusion; Stroke; Oral anticoagulation; Prevention (Heart Rhythm 0<sup>2</sup> 2022;3:444–447)

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## Current indication: Patients contraindicated for the use of OAC

Currently, international guidelines recommend to perform LAAO only in patients who are contraindicated for long-term use of OAC, a minority that represents up to 5% of all AF patients.<sup>8–11</sup> The only RCT available in this group of patients to date, the PRAGUE-17 trial, compared LAAO to DOAC (n = 402) in AF patients with both a high stroke and bleeding risk and showed noninferiority on the net clinical benefit endpoint of thromboembolic complications and bleeding.<sup>12</sup> In the absence of enough adequately powered RCT data in this patient category, the recommendation for LAAO has remained a class IIB, level of evidence B since it first appeared in the ESC guidelines in 2012. However, on top of the RCT data, a large amount of registry data has been published in thousands of patients in everyday clinical practice, confirming the improved safety of the procedure and the low rate of stroke during follow-up.<sup>4,7,13</sup> Based on the abovementioned data and while awaiting further RCT data, in our opinion LAAO should be offered to all patients with a strong contraindication for the use of OAC, and guideline recommendations should take into consideration to upgrade the indication to a class IIA, level of evidence B recommendation, as many such patients are currently undertreated for AF-related thromboembolism.

A cost-effectiveness analysis of LAAO from the pooled 5-year follow-up data of the PROTECT AF and PREVAIL trials showed that, relative to warfarin and DOACs, LAAO was cost-effective after, respectively, 7 and 5 years and even cost-saving after, respectively, 10 and 5 years.<sup>14</sup> Therefore, it appears to be evident that LAAO would be cost-saving in patients with a high stroke risk and a contraindication for OAC. Cost-effectiveness analyses from observational data support this, but randomized data are desired.<sup>15</sup> At present, LAAO is underutilized for a variety of reasons. Firstly, in many countries LAAO is neither available nor reimbursed, as it has not obtained approval from healthcare authorities. This has led to large geographic differences in the availability of LAAO. In countries without reimbursement, neurologists, gastroenterologists, and pulmonologists are frequently not even aware or are skeptical about LAAO, so that suitable patients are often not identified and referred. As a result, in everyday clinical practice many patients are undertreated with inferior low-dose DOAC, single or dual antiplatelet

## KEY FINDINGS

- Left atrial appendage occlusion (LAAO) is a safe and effective treatment option for stroke prevention in atrial fibrillation (AF) patients and is currently mainly performed in patients with a contraindication for oral anticoagulants (OAC), who represent a minority of up to 5% of all AF patients.
- The use of LAAO is underutilized owing to various reasons: despite the overwhelming amount of observational data, the guidelines recommendation still remains class IIB, level of evidence B. Therefore, there is lack of availability and/or reimbursement in many countries, which leads to nescience or skepticism in referring specialists (eg, neurologists, gastroenterologists).
- LAAO has great potential in other patient populations: in patients with stroke under OAC, combined with other structural heart procedures, and ultimately as an alternative treatment option for all AF patients. Several randomized controlled trials are currently pending to provide the required evidence.

therapy (APT), or no stroke prevention at all. Aside from the availability of LAAO treatment options, there is also no unifying widely accepted definition for an absolute contraindication to OAC. Following the ESC 2020 guidelines on AF and stroke prevention, a neurologist is more likely to restart OAC after an intracranial hemorrhage (ICH) than to refer a patient for LAAO, even if the downsides of restarting OAC seem to be larger than to perform LAAO.<sup>16,17</sup> Lastly, there are upfront costs associated with the LAAO procedure, and although there is a favorable cost-effectiveness of LAAO compared to DOAC already after a few years, healthcare authorities and insurance companies might be reluctant to favor LAAO.<sup>15</sup>

To provide evidence for a stronger guideline recommendation, the Dutch COMPARE-LAAO RCT (NCT04676880) intends to prove that LAAO is superior to optimal medical therapy (which often means APT or no therapy at all) for patients contraindicated to the use of OAC. The COMPARE-LAAO trial was funded by a governmental grant in 2020 to gather evidence for reimbursement purposes in the Netherlands and should be completed in 2026. The ASAP TOO trial (NCT02928497), which was aiming to obtain a similar proof of concept, terminated prematurely owing to low enrollment in countries that already have reimbursement for LAAO. The STROKECLOSE trial (NCT02830152) is randomizing patients with a previous ICH to LAAO or optimal medical therapy according to the treating physician (OAC, APT, or no therapy), but is also facing slow enrollment for similar reasons.

## Potential patient population that may benefit from LAAO

LAAO may also be performed in other patient populations that are currently not mentioned in the AF guidelines and therefore not widely considered.<sup>8,9</sup>

### Combined procedures

Fear of complications may be one of the arguments to not perform LAAO. However, the access technique of an endovascular LAAO procedure is very similar to procedures such as AF ablation and MitraClip placement. AF ablation is mainly performed for symptom reduction and does not obviate OAC in patients at high risk for stroke. Therefore, if LAAO is performed directly after ablation in the same procedure, it is appealing to offer AF patients a combined procedure, especially if they have strong reasons to stop using OAC. Several observational registry studies<sup>18,19</sup> as well as a meta-analysis of observational and small randomized studies have demonstrated good safety and efficacy of these procedures.<sup>20</sup> Conclusive evidence from the OPTION RCT (NCT03795298), in which patients scheduled for AF ablation were randomized to LAAO or OAC, is expected in the near future. Also, in other structural heart procedures patients might benefit from the 1-stop-shop principle. Initial experiences of concomitant LAAO with transcatheter aortic valve implantation, MitraClip, or percutaneous coronary intervention have already been reported,<sup>21–23</sup> and RCTs are pending (Table 1). Furthermore, the randomized LAAOS III trial showed lower stroke rates after surgical LAAO compared to standard of care in patients undergoing cardiac surgery.<sup>24</sup> As ischemic strokes still regularly occur in patients while they are being prescribed OAC,<sup>25,26</sup> a combined approach of (surgical) LAAO and OAC for stroke prevention might be appropriate.

### Stroke in anticoagulated patients

A recently published study in pooled individual patient data of 5413 subjects by Seiffge and colleagues<sup>25</sup> demonstrated a higher risk of stroke recurrence in patients with a history of embolic strokes despite adequate OAC, compared to patients with a similar CHA<sub>2</sub>DS<sub>2</sub>VASc score. Switching to another type of OAC after stroke was not associated with a decreased stroke risk. Therefore, these patients might benefit from (adding) LAAO therapy. In the EWOLUTION trial, LAAO was equally effective for stroke reduction in patients after prior stroke as for other indications.<sup>13</sup> Other small observational studies also suggest the effectiveness of LAAO in this population; however, adequately powered controlled trials are needed to further investigate the use of LAAO in patients with previous stroke despite OAC.<sup>27,28</sup>

### LAAO for a broader population

As LAAO is a 1-time procedure that offers patients an alternative to the stringent lifelong use of OAC, the ultimate utilization would be to offer it to potentially all AF patients with

**Table 1** Ongoing trials that investigate various left atrial appendage occlusion indications

| Trial name   | Design                     | Allocation ratio | Intervention                               | Device                               | Study population                           | Estimated sample size | Estimated primary completion date (mo-y) |
|--|----------------------------|------------------|--|--------------------------------------|--|-----------------------|--|
| <i>LAAO for AF patients with a contraindication to OAC</i> |                            |                  |  |                                      |  |                       |  |
| COMPARE-LAAO (NCT04676880)                                 | PROBE                      | 2:1              | LAAO vs APT/none                           | CE mark-approved LAA closure devices | AF & absolute contraindication to OAC      | 609                   | 05-2026                                  |
| STROKECLOSE (NCT02830152)                                  | PROBE                      | 2:1              | LAAO vs medical therapy                    | Amplatzer Amulet                     | AF & ICH                                   | 750                   | 05-2022                                  |
| CLOSURE-AF (NCT03463317)                                   | Open label                 | 1:1              | LAAO vs best medical care                  | CE mark-approved LAA closure devices | AF & high bleeding risk                    | 1512                  | 09-2023                                  |
| A3ICH (NCT03243175)  | PROBE                      | 1:1:1            | LAAO vs apixaban vs APT/none               | Chosen by local teams                | AF & ICH                                   | 300                   | 12-2023                                  |
| <i>Combined procedures</i>                                 |                            |                  |  |                                      |  |                       |  |
| OPTION (NCT03795298)                                       | Open label                 | 1:1              | Ablation+LAAO vs ablation+OAC              | Watchman FLX                         | AF patients scheduled for ablation therapy | 1600                  | 11-2024                                  |
| WATCH-TAVR (NCT03173534)                                   | Open label                 | 1:1              | TAVR+OAC vs TAVR+LAAO                      | Watchman                             | AF patients scheduled for TAVR             | 350                   | 11-2022                                  |
| TAVI/LAAO (NCT03088098)                                    | Open label                 | 1:1              | TAVI+LAAO vs TAVI+standard medical therapy | Amplatzer Amulet                     | AF patients scheduled for TAVI             | 80                    | 05-2023                                  |
| WATCH-TMVR (NCT04494347)                                   | Open label                 | N/A              | TMVr+LAAO                                  | MitraClip / Watchman FLX             | AF patients scheduled for TMVr             | 25                    | 09-2022                                  |
| <i>Broad population</i>                                    |                            |                  |  |                                      |  |                       |  |
| CHAMPION-AF (NCT04394546)                                  | Single (Outcomes Assessor) | 1:1              | LAAO vs OAC                                | Watchman FLX                         | AF + indicated for OAC                     | 3000                  | 12-2025                                  |
| CATALYST (NCT04226547)                                     | Single (Outcomes Assessor) | 1:1              | LAAO vs OAC                                | Amplatzer Amulet                     | AF + indicated for OAC                     | 2650                  | 12-2024                                  |

AF = atrial fibrillation; APT = antiplatelet therapy; ICH = intracranial hemorrhage; LAA = left atrial appendage; LAAO = left atrial appendage occlusion; N/A = not available; OAC = oral anticoagulants; TAVI = transcatheter aortic valve implantation; TAVR = transcatheter aortic valve replacement; TMVr = transcatheter mitral valve repair.

a need for stroke prevention. Worldwide, the prevalence of AF is increasing and so is the number of patients who require stroke prevention by OAC.<sup>9</sup> At the same time, conditions with an enlarged risk of bleeding, such as cerebral amyloid angiopathy, are also increasing and owing to the rising life expectancy more patients will develop bleeding and comorbidity overall.<sup>29,30</sup> As the risk factors that govern both are very similar, 79% of patients with a high risk for stroke also have an intermediate bleeding risk and 11% even a high bleeding risk.<sup>31</sup> Although DOACs are now preferred over VKA because of lower risk of ICH, their overall bleeding rate is not negligible.<sup>1</sup> And although ease of use seems attractive, a fundamental disadvantage of DOAC compared to VKA is the inability to monitor patient compliance, while LAAO is a continuous therapy that does not need monitoring. In daily practice, 30% of DOAC patients and 50% of VKA patients discontinue their medication within 2 years, while 30% of patients using OAC are nonadherent and/or noncompliant.<sup>32</sup> The international CHAMPION-AF (NCT04394546) and CATALYST (NCT04226547) RCTs, which both compare LAAO to DOAC in AF patients without

a contraindication for OAC and aim to include around 3000 patients each, are currently recruiting. These trials aim to show noninferiority for stroke prevention but superiority for bleeding, which would make LAAO an attractive therapy over lifelong need for OAC.

## Conclusion

In conclusion, LAAO should be offered and be available to all AF patients contraindicated for the use of OAC, since these patients have no acceptable alternative. Based on the overwhelming amount of observational data, an upgrade of the guideline recommendation from class IIB to IIA appears to be likely. Furthermore, recommendations for other LAAO indications, such as in patients with “stroke under OAC” and combined interventions for patients scheduled for ablation may deserve a IIB recommendation in the AF guidelines, and RCT data are underway to provide evidence. Offering LAAO to all AF patients would be the ultimate utilization but will require compelling evidence by RCTs comparing LAAO to DOAC.

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## References

- Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;383:955–962.
- Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;146:857–867.
- Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg* 1996;61:755–759.
- Reddy VY, Doshi SK, Kar S, et al. 5-Year outcomes after left atrial appendage closure: from the PREVALE and PROTECT AF trials. *J Am Coll Cardiol* 2017;70:2964–2975.
- Kar S, Doshi SK, Sadhu A, et al. Primary outcome evaluation of a next-generation left atrial appendage closure device: results from the PINNACLE FLX trial. *Circulation* 2021;143:1754–1762.
- Lakkireddy D. Amplatzer™ Amulet™ left atrial appendage occluder versus Watchman™ device for stroke prophylaxis (AMULET IDE): a randomized controlled trial. *Circulation* 2021;144:1543–1552.
- Hildick-Smith D, Landmesser U, John Camm A, et al. Left atrial appendage occlusion with the Amplatzer™ Amulet™ device: full results of the prospective global observational study. *Eur Heart J* 2020;41:2894–2901.
- January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS Guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2019;74:104–132.
- Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2021;42:373–498.
- Gorczyca I, Jelonek O, Michalska A, Chrapek M, Walek P, Wożakowska-Kapton B. Stroke prevention and guideline adherent antithrombotic treatment in elderly patients with atrial fibrillation: a real-world experience. *Medicine (Baltimore)* 2020;99:e21209.
- Steinberg BA, Greiner MA, Hammill BG, et al. Contraindications to anticoagulation therapy and eligibility for novel anticoagulants in older patients with atrial fibrillation. *Cardiovasc Ther* 2015;33:177–183.
- Osmancik P, Herman D, Neuzil P, et al. Left atrial appendage closure versus direct oral anticoagulants in high-risk patients with atrial fibrillation. *J Am Coll Cardiol* 2020;75:3122–3135.
- Boersma LV, Ince H, Kische S, et al. Evaluating real-world clinical outcomes in atrial fibrillation patients receiving the WATCHMAN left atrial appendage closure technology: final 2-year outcome data of the EWOLUTION trial focusing on history of stroke and hemorrhage. *Circ Arrhythm Electrophysiol* 2019;12:1–13.
- Reddy VY, Akehurst RL, Gavaghan MB, Amorosi SL, Holmes DR. Cost-effectiveness of left atrial appendage closure for stroke reduction in atrial fibrillation: analysis of pooled, 5-year, long-term data. *J Am Heart Assoc* 2019;8:e011577.
- Labori F, Persson J, Bonander C, Jood K, Svensson M. Cost-effectiveness analysis of left atrial appendage occlusion in patients with atrial fibrillation and contraindication to oral anticoagulation. *Eur Heart J* 2022;43:1348–1356.
- Schreuder FHBM, van Nieuwenhuizen KM, Hofmeijer J, et al. Apixaban versus no anticoagulation after anticoagulation-associated intracerebral haemorrhage in patients with atrial fibrillation in the Netherlands (APACHE-AF): a randomised, open-label, phase 2 trial. *Lancet Neurol* 2021;20:907–916.
- Al-Shahi Salman R. Effects of long-term oral anticoagulation for atrial fibrillation after spontaneous intracranial haemorrhage: the start or stop anticoagulants randomised trial (SoSTART). *Eur Stroke J* 2021;6:10.
- Wintgens L, Romanov A, Phillips K, et al. Combined atrial fibrillation ablation and left atrial appendage closure: long-term follow-up from a large multicentre registry. *Europace* 2018;20:1783–1789.
- Phillips KP, Romanov A, Artemenko S, et al. Combining left atrial appendage closure and catheter ablation for atrial fibrillation: 2-year outcomes from a multinational registry. *Europace* 2020;22:225–231.
- Jiang Y, Li F, Li D, et al. Efficacy and safety of catheter ablation combined with left atrial appendage occlusion for nonvalvular atrial fibrillation: a systematic review and meta-analysis. *Pacing Clin Electrophysiol* 2020;43:123–132.
- Kuwata S, Taramasso M, Zuber M, et al. Feasibility of concomitant MitraClip and left atrial appendage occlusion. *EuroIntervention* 2017;12:1940–1945.
- Ghenzi RA, Obeid S, Maisano F, et al. The evolving role of left atrial appendage occlusion: a high-volume single-centre experience. *Cardiovasc Med* 2016;19:288–295.
- Kook H, Kim HD, Shim J, et al. Comparison of clinical outcomes between multiple antithrombotic therapy versus left atrial appendage occlusion with dual antiplatelet therapy in patients with atrial fibrillation undergoing drug-eluting stent implantation. *PLoS One* 2021;16:1–15.
- Whitlock RP, Belley-Cote EP, Paparella D, et al. Left atrial appendage occlusion during cardiac surgery to prevent stroke. *N Engl J Med* 2021;384:2081–2091.
- Seiffge DJ, De Marchis GM, Koga M, et al. Ischemic stroke despite oral anticoagulant therapy in patients with atrial fibrillation. *Ann Neurol* 2020;87:677–687.
- Stretz C, Wu TY, Wilson D, et al. Ischaemic stroke in anticoagulated patients with atrial fibrillation. *J Neurol Neurosurg Psychiatr* 2021;92:1164–1172.
- Galloo X, Carmeliet T, Prihadi EA, et al. Left atrial appendage occlusion in recurrent ischaemic stroke, a multicentre experience. *Acta Clin Belg* 2020;00:1–6.
- Cruz-González I, González-Ferreiro R, Freixa X, et al. Left atrial appendage occlusion for stroke despite oral anticoagulation (resistant stroke). Results from the Amplatzer Cardiac Plug registry. *Rev Esp Cardiol (Engl Ed)* 2020;73:28–34.
- Kelly J. New horizons: managing antithrombotic dilemmas in patients with cerebral amyloid angiopathy. *Age Ageing* 2021;50:347–355.
- Goodman SG, Wojdyla DM, Piccini JP, et al. Factors associated with major bleeding events: insights from the ROCKET AF trial (rivaroxaban once-daily oral direct factor XA inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation). *J Am Coll Cardiol* 2014;63:891–900.
- Marcucci M, Lip GYH, Nieuwlaar R, Pisters R, Crijns HJGM, Iorio A. Stroke and bleeding risk co-distribution in real-world patients with atrial fibrillation: the Euro heart survey. *Am J Med* 2014;127:979–986.e2.
- Salmasi S, Loewen PS, Tandun R, Andrade JG, De Vera MA. Adherence to oral anticoagulants among patients with atrial fibrillation: a systematic review and meta-analysis of observational studies. *BMJ Open* 2020;10:1–14.