

# Diagnostic and therapeutic pathways for the malignant left atrial appendage: European Heart Rhythm Association physician survey

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## Aims

Patients with atrial fibrillation who despite taking oral anti-coagulant therapy (OAT) suffer a stroke or systemic embolism (SSE) without vascular cause or who develop left atrial appendage (LAA) thrombus (LAAT) should be considered as having malignant LAA. The optimal treatment strategy to reduce SSE risk in such patients is unknown. The aim of the study is to investigate the diagnostic and therapeutic pathways for malignant LAA practiced in European cardiac centres.

## Methods and results

An 18-item online questionnaire on malignant LAA was disseminated by the European Heart Rhythm Association (EHRA) Scientific Initiatives Committee. A total of 196 physicians participated in the survey. There seems to be high confidence in transoesophageal echocardiography (TEE) imaging, considering LAAT diagnosis. Switching to another direct oral anti-coagulant (DOAC) is the preferred initial step for the treatment of malignant LAA followed by a switch to vitamin K antagonist (VKA), low-molecular-weight heparin, or continued/optimized DOAC dosage, whereas LAA closure is the last option. Left atrial appendage closure is a viable option in patients with embolic stroke despite OAT and no evidence of thrombus at TEE (empty LAA) after comprehensive diagnostic measures to exclude other sources of embolism.

## Conclusion

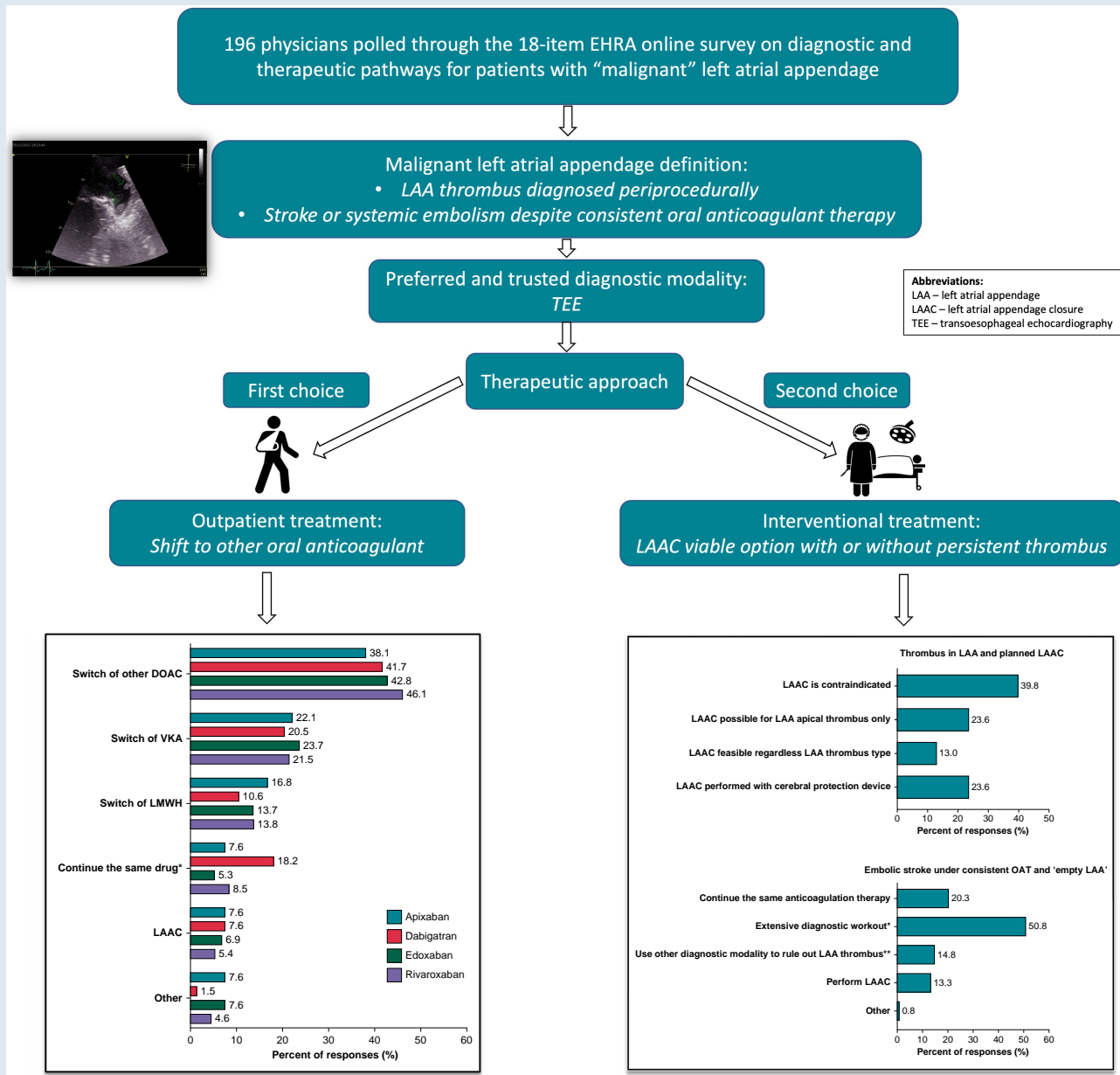
This EHRA survey provides a snapshot of the contemporary management of patients diagnosed with malignant LAA. Currently, the majority of patients are treated on an outpatient basis with either shifting from VKA to DOAC or from one DOAC to another. Left atrial appendage closure in this population seems to be reserved for patients with higher bleeding risk or complications of malignant LAA, such as stroke.

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## Graphical Abstract



## Keywords

Left atrial appendage thrombus • Stroke • Oral anti-coagulant therapy • Left atrial appendage closure • Malignant left atrial appendage • EHRA survey

## What's new?

- We report on the contemporary management of patients with atrial fibrillation diagnosed with malignant left atrial appendage (LAA; thrombus formation despite consistent anti-coagulation).
- Patients in whom LAA thrombus is diagnosed during a pre-procedural diagnostic workout or those who suffer a stroke or systemic embolism while adequately dosed with oral anti-coagulant therapy continue to be treated on an outpatient basis.
- Changing an oral anti-coagulant, vitamin K antagonist to direct oral anti-coagulant (DOAC) or changing from one DOAC to another is the preferred therapeutic strategy for malignant LAA.
- Left atrial appendage closure is reserved for patients with higher bleeding risk or complications from malignant LAA, such as stroke.

## Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia, and its incidence is increasing. Cardioembolic stroke remains the most devastating consequence of AF.<sup>1</sup> Despite a pleasing safety profile of contemporary ablation procedures that has led to a widespread adoption of this treatment, it is unlikely that ablation itself will obviate the need for anti-coagulant therapy in the foreseeable future.<sup>2</sup> Left atrial appendage (LAA) is the predominant source of thrombus formation in patients with AF. Patients who develop stroke and systemic embolism (SSE) despite taking oral anti-coagulant therapy (OAT) or who are diagnosed with LAA thrombus (LAAT) formation using standard imaging techniques and develop LAAT despite consistent OAT may be diagnosed as having malignant LAA.

This term should not be used in a population that has been inconsistent with OAT (incompliant or treated with a lower intensity of OAT, not according to recommended dosage). Therefore, consistent OAT, assuming that the patient is following the recommendations of the Summary of Product Characteristics (SmPC), is a prerequisite for the diagnosis of malignant LAA.<sup>3–6</sup> According to the literature, LAAT developed in up to 3.6% of patients on direct oral anti-coagulant (DOAC), and the prevalence was up to 7.7% in patients receiving vitamin K antagonist (VKA).<sup>7–9</sup>

The optimal treatment/prevention strategy to reduce the risk of SSE in such patients is unknown. The results of the 2019 European Heart Rhythm Association (EHRA) survey of patients diagnosed with LAAT indicate that the most commonly used strategy was switching to another OAT.<sup>10</sup> More recent data do not support this strategy, showing that the overall effectiveness of dissolution seems to be ~50%.<sup>11–14</sup>

Therefore, the aim of this physician survey is to evaluate the diagnostic and therapeutic pathways currently practiced in this underreported scenario.

## Methods

The EHRA Scientific Initiatives Committee disseminated an 18-item online questionnaire on malignant LAA aimed at a group of clinical and interventional cardiologists. The questionnaire was distributed through official EHRA channels (EHRA newsletters, Scientific Research Network members, and national electrophysiology working groups) and social media platforms. It was active between 12 July and 30 August 2022.

The survey was structured to capture both diagnostic and therapeutic strategies in the malignant LAA population. The questions on therapeutic strategies were drug specific to understand whether there was a difference in the decision-making process depending on which specific OAT malignant under which LAA occurred.

The full questionnaire is included in [Supplementary material](#).

## Statistical analysis

All variables collected were categorical and therefore presented as absolute numbers and percentages. The authors were aware of the ICMJE authorship criteria, had full access to the data, and took full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as presented.

## Results

A total of 196 physicians participated in the survey. The number of responses received for the part of the survey that was specific (non-general) dropped from 196 to 134 on average. The average completion time was 8 min. One hundred forty-nine responses were collected via the dedicated EHRA bulletin, and 47 via social media.

Two-thirds of the responses (118 out of 180) were from academic hospitals, 80% of which perform LAA closure (LAAC) procedures (142 out of 178). Seventy per cent (125 out of 178) have on-site cardiac surgery and 65% have 24/7 access to urgent neurovascular procedures (116 out of 178). Sixty per cent (108 out of 180) of physicians surveyed are invasive electrophysiologists, with the remainder evenly split between general and interventional cardiologists.

The predominant practice in patients diagnosed with LAAT while receiving consistent OAT is outpatient care (65%, i.e. 87 out of 134), but inpatient care is considered in 30% of cases (40 out of 134). Only 6% (eight respondents) reported hospitalizing these patients at the time of diagnosis.

## Diagnostic pathways

Transoesophageal echocardiography (TEE) represents the preferred modality to detect LAAT. Only 3% ( $n = 4$ ) of respondents routinely

request that LAAT be detected by another imaging modality [multislice computer tomography (MSCT) angiography] before making therapeutic decisions. Magnetic resonance imaging for thrombus detection is rarely performed (3 out of 134, 2%, respectively). However, 48% of respondents (64 out of 134) are willing to use another imaging modality if the TEE finding is inconclusive.

In patients diagnosed with LAA 'sludge' without obvious/solid thrombus on TEE imaging before direct-current cardioversion (DCCV) or AF ablation, 57 out of 133 (43%) would proceed with the procedure, while 24% ( $n = 32$ ) would postpone it and change OAT. Provocative testing, such as an inotropic infusion (dobutamine, isoproterenol) to confirm that the LAA is free of sludge, is performed in only a minority of cases (8 out of 133, 6%).

## Therapeutic pathways

When LAAT is diagnosed in patients apparently inadequately treated with OAT (labile or low INR, inadequate DOAC dose), most (89 out of 131, 68%) would replace the medication with another with a more favourable clinical profile, i.e. considerations based on a renal function or for improved adherence. Only 22% (29 out of 131) would adjust the same therapy and seek to improve INR control or prescribe DOAC dose according to SmPC. Usage of low-molecular-weight heparin/unfractionated heparin would be an option for 10% of the respondents (13 out of 131).

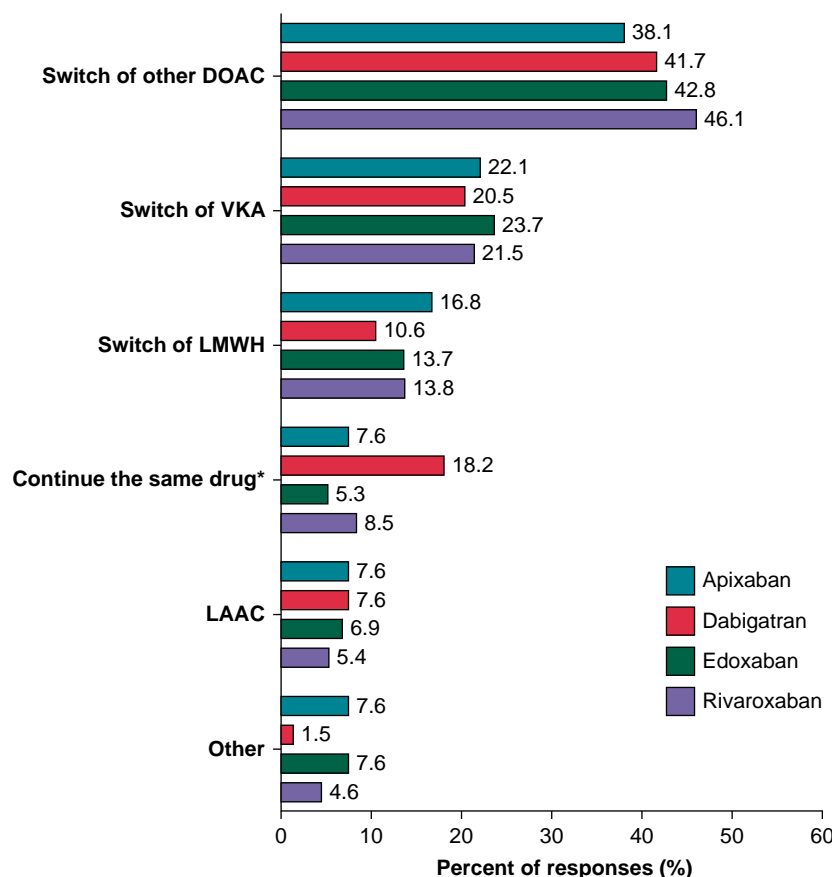
Approaches to LAAT management despite SmPC-recommended anti-coagulation with various DOACs are summarized in [Figure 1](#).

In patients treated with VKA (otherwise no contraindications to DOAC) who are diagnosed with LAAT on routine TEE/MSCT angiography before DCCV or AF ablation, 63% of respondents (83 out of 132) would switch to DOAC, and 18 out of 132 or 14% would continue with VKA if their INR is below their target INR. Low-molecular-weight heparin is an option for only 11 (i.e. 8%) respondents, while only 3% (4 out of 132) would go directly to LAAC if the INR is in the therapeutic range.

Performing LAAC as soon as possible is an increasingly common option in patients diagnosed with LAAT on routine TEE/MSCT angiography before DCCV or AF ablation while receiving the SmPC-recommended dose of dabigatran (assuming compliance; 8 vs. 3% on VKA). Nevertheless, most would switch to another DOAC (55 out of 132, 42%). Switching to VKA is practiced in 21% of cases (i.e. 28 respondents).

In the event of LAAT on routine TEE/MSCT angiography before DCCV or AF ablation in rivaroxaban-treated patients (at SmPC-recommended dose of 20 mg OD and assuming good compliance), most respondents (55 out of 130, 42%) would switch therapy to a DOAC with the BID dosing regimen. Twenty-two per cent (29 out of 130) of respondents would switch to VKA, while the LAAC option would have been chosen by 5% of respondents (7 out of 130). Similarly, in patients treated with edoxaban (at the SmPC-recommended dose of 60 mg OD with good compliance) who are diagnosed with LAAT on routine angiography TEE/MSCT before DCCV or AF ablation, most respondents (52 out of 131, 40%) would switch to DOAC with the BID dosing regimen. Switching to VKA was also considered a good option by 24% (i.e. 31) of respondents. Left atrial appendage closure performed as soon as possible would be favoured by 7% of respondents ( $n = 9$ ).

Performing LAAC as soon as possible in patients diagnosed with LAAT on routine TEE/MSCT angiography before DCCV or AF ablation while taking the SmPC-recommended apixaban dose (assuming compliance) would be considered a viable option, according to 8% of respondents (11 out of 131). However, a large percentage of respondents (22%, i.e. 29 out of 131) would switch to VKA, and the majority of them (31%) would switch from apixaban to dabigatran ( $n = 41$ ).



**Figure 1** Approach to diagnosed LAAT despite SmPC-recommended anti-coagulation by different DOACs (number of respondents for each question was between 130 and 132). \*For apixaban and rivaroxaban, options were continuation of the same dosage for an additional 3 weeks or dose escalation to 10 or 15 mg BID, respectively; for dabigatran options involved increasing dose to 150 mg BID if the prior dosing regimen was 110 mg BID or intentional addition of verapamil in the therapy; for edoxaban, options were continuation of the same dose for an additional 3 weeks. DOAC, direct oral anti-coagulant; LAA, left atrial appendage; LAAC, left atrial appendage closure; LAAT, left atrial appendage thrombus; LMWH, low-molecular-weight heparin; SmPC, Summary of Product Characteristics; VKA, vitamin K antagonist.

If LAAT is diagnosed in a patient treated with the recommended low dose of any DOAC (adjusted to renal function), the majority (46 out of 130, 35%) would switch to VKA. Nevertheless, in this scenario, a significant number (16 out of 130, 12%) of respondents would proceed to LAAC as soon as possible.

## Left atrial appendage closure

### Indication and devices

Left atrial appendage closure is often considered a contraindication for all types of LAAT (40% or 49 out of 123) but may be considered in selected cases with apical thrombus (24%,  $n = 32$ ) or with cerebral protection device (CPD) use regardless of LAAT location (24%,  $n = 32$ ). The preferred method of LAAC in patients with persistent LAAT despite intensified anti-coagulation therapy was percutaneous LAA occluder (LAAO) implantation (69%, 90 out of 130). There was no significant difference in device preference [Amplatzer Amulet vs. Watchman FLX device, 38 vs. 32% (49 vs. 42)]. No one suggested a different LAAO device. Less than 20% (26 out of 130) of respondents opted for surgical LAA excision. Of note, LAAC is not the preferred treatment for electrically isolated LAA. Most respondents would continue anti-coagulant therapy after LAA isolation (41 out of 127).

Left atrial appendage closure is performed in the majority of patients (65 out of 128 responses) with an embolic stroke under OAT and no evidence of thrombus at TEE after comprehensive diagnostic measures to exclude other sources of embolism, though 14% of respondents ( $n = 18$ ) weigh in the decision to proceed with LAAC based on low LAA emptying velocities.

### Post-implantation management

Among patients with persistent LAAT despite intensified anti-coagulant treatment who underwent LAAC, there is a significant divergence in post-procedural anti-thrombotic therapy (Table 1). Dual therapy [acetylsalicylic acid (ASA) + DOAC] was prescribed in one-third of patients (41 out of 131, 31%). The second most common option (22% or 29 responses) included dual anti-platelet therapy, followed by anti-coagulant-only monotherapy (16% or 21 responses). In most cases, the duration of treatment is between 3 and 6 months (47 and 21%, respectively, total  $n = 130$ ).

The most common long-term anti-thrombotic strategy in these patients is the administration of ASA alone (30%, 39 out of 131, respectively). The second most common option was a long-term continuation of monotherapy with anti-coagulants (VKA or DOAC) in 24% of cases (31 out of 131).

**Table 1** Prescribed post-procedural and long-term therapy after LAAC

	Post-procedural (%)	Long-term (%)
ASA	1.5	29.8
DAPT	22.1	9.9
ASA + DOAC	31.3	6.1
ASA + VKA	4.6	0
Triple therapy (VKA + DAPT)	3.1	0.8
Triple therapy (DOAC + DAPT)	8.4	3.1
Anti-coagulant monotherapy (VKA or DOAC)	16	24.4
Same as post-procedural	N/A	14.5
Other	13	11.5

Values represent the percentage of answers (N = 131).

ASA, acetylsalicylic acid; DAPT, dual anti-platelet therapy; DOAC, direct oral anti-coagulant; LAAC, left atrial appendage closure; N/A, not applicable; VKA, vitamin K antagonist.

The majority of respondents (69 out of 128) believe that TEE should be performed before DCCV in LAAC patients to rule out device-related thrombosis and significant leaks.

Figure 2 summarizes the setting for LAAC depending on the presence of LAAT and therapeutic strategy in patients with an embolic stroke under consistent OAT and no evidence of thrombus on TEE (empty LAA).

## Discussion

This survey provides insight into current clinical management related to the diagnosis and therapeutic pathways of malignant LAA in European centres. The main findings are:

- (1) Transoesophageal echocardiography is widely considered to be the best imaging modality.
- (2) Left atrial appendage thrombus is predominantly treated on an out-patient basis.
- (3) Left atrial appendage sludge does not automatically trigger intensified anti-thrombotic treatment.
- (4) Left atrial appendage thrombus is typically treated by switching from one OAT to another.
- (5) Left atrial appendage closure is considered an option in selected patients with LAAT despite optimal OAT.
- (6) Left atrial appendage closure is considered in selected cases with LAAT (apical thrombus or with the use of CPD), but often LAAT is considered to be a contraindication to LAAC.
- (7) Both Amulet and Watchman FLX may be used.
- (8) Left atrial appendage closure is not necessarily considered after LAA isolation.

Currently, there are no guidelines for the management of patients with persistent LAAT despite adequate OAT. It is unknown how the morphological LAA features influence the decision-making process in the malignant LAA population since certain anatomical variants are considered more thrombogenic and might be driving specific therapeutic options. While higher risk morphological LAA features are expected to be more often found in the malignant LAA population, we believe the malignant LAA term should be reserved for the clinical scenarios as they were described in our paper, LAAT detected by imaging

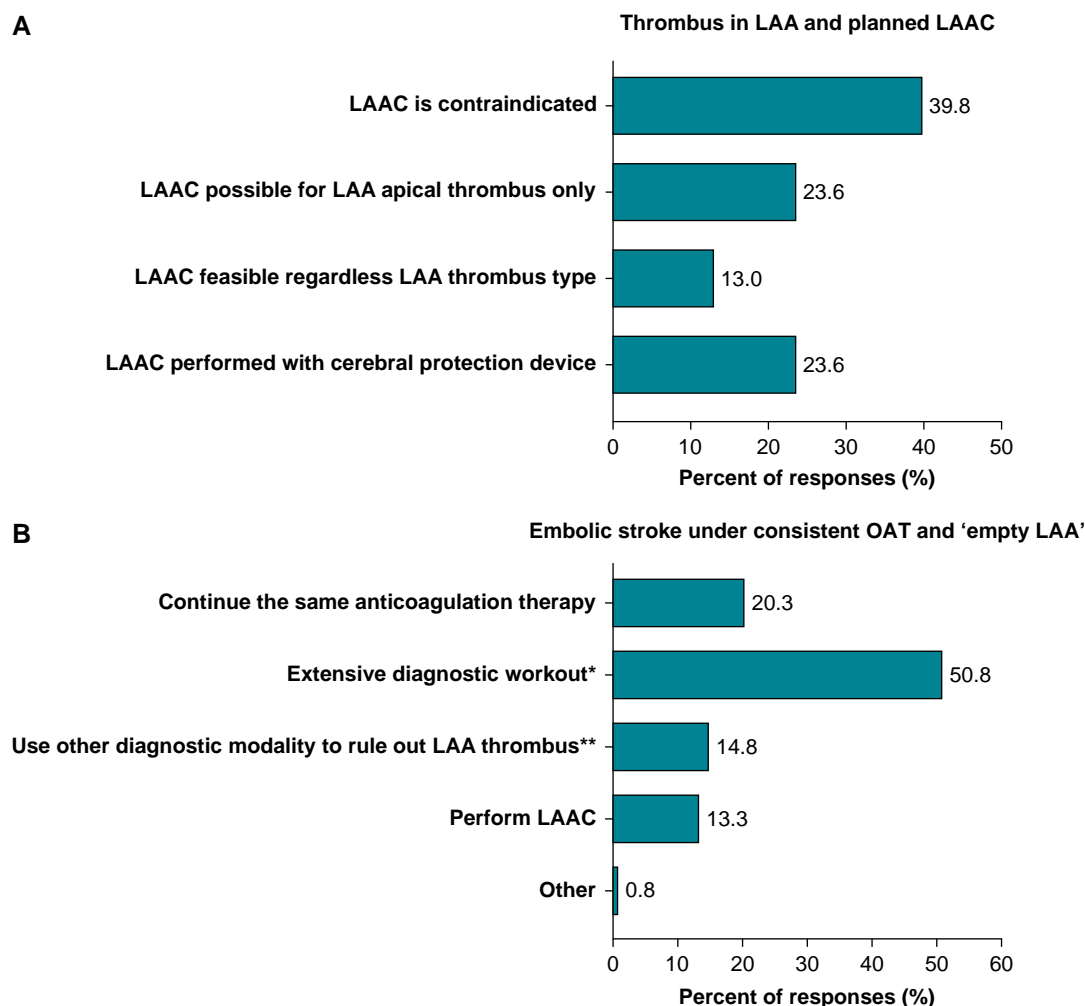
modalities or SSE in adequately anti-coagulated patients since the prevalence of higher risk LAA morphology in general population fairly exceeds the incidence of its clinical expression. In a survey conducted by the EHRA, the predominant strategy for treating malignant LAA was the intensification of OAT or switching the current OAC to another with a different mechanism of action.<sup>10</sup> When DOAC substitution was considered, apixaban or dabigatran were the most commonly chosen substitutes. European Heart Rhythm Association practical guide on the use of non-VKAs states that treatment of resistant LAA thrombi should be selected on an individual basis: both switching between different DOACs and switching to VKA are allowed.<sup>15</sup> Because >90% of thromboembolic strokes in patients with AF appear to be caused by thrombi originating from the LAA, LAAC is an alternative treatment option to reduce the risk of thromboembolic events. Transcatheter LAAC has undergone significant improvements in recent years with pleasing procedural success and safety profile.<sup>16,17</sup> It has emerged as a non-pharmacologic alternative to OAC, particularly in patients at high risk for major bleeding.<sup>1,18</sup> The PRAGUE-17 trial compared LAAC with DOAC in 402 patients with AF at high risk of stroke and bleeding and showed no inferiority in terms of the net clinical endpoint of thromboembolic complications and bleeding in follow-up for up to 4 years.<sup>19,20</sup>

Commonly, LAAT is considered a contraindication to percutaneous LAAC because of the risk of dislodgement of thrombus material and distal embolism.<sup>21</sup>

Accordingly, patients with LAAT were excluded from the large LAAC studies but data from case reports and small case series suggest the feasibility of LAAC in this context.<sup>22–24</sup> An increased risk of bleeding and incomplete resolution of the thrombus despite OAC could suggest a role for off-label LAAC, even when a thrombus is present. However, there is no specific data comparing any strategy of the OAC to the LAAC in this scenario. Marroquin *et al.*<sup>25</sup> reported the results of a multicentre observational registry of 126 consecutive patients referred to LAAC with LAAT detected at pre-procedural imaging. Comparing OAT and LAAC, their results also support the feasibility and safety of direct LAAC with high procedural success and the absence of periprocedural embolic complications. The risk of distal contact and embolization may be higher with umbrella-shaped devices.<sup>26</sup> The flap and disc devices may be better suited for LAAC in this subset of patients. However, the new Watchman FLX presents some key features (e.g. an atraumatic distal end, 10–20% reduced length) that contribute to better control during deployment and improved appendage sealing.<sup>16,17</sup> The minimum appendage depth required for the FLX is just half of the LAA ostial diameter, thereby allowing a more ostial deployment with potentially less risk of embolic complications, if a LAAT is present.<sup>27,28</sup> Nonetheless, the data are not yet sufficient to make specific recommendations. Overall, the LAAC can be performed effectively and safely in patients with a LAAT in high-volume centres and with a non-touch technique under precise guidance.<sup>29</sup> Despite these facts, about a quarter of respondents prefer the LAAC with a CPD. Although there are few systematic studies on the role of CPD in LAAC with LAAT, a CPD device may mechanistically play a protective role in preventing stroke in patients with LAAT undergoing LAAC.<sup>30</sup>

The other significant proportion of patients with malignant LAA are those with SSE under OAT but in whom LAAT is not confirmed by initial imaging studies. Regardless of the efficacy of OAT, they continue to have a high residual risk as they already suffered a stroke during treatment with OAT. These patients are at high risk for recurrent ischaemic stroke. It is necessary to investigate the cause of the stroke, and a simple change in the type of anti-coagulation was not associated with a reduced risk of ischaemic stroke.<sup>11–14</sup> Approximately, half of our respondents favoured comprehensive diagnostic testing to exclude other stroke mechanisms. According to a retrospective study, the safety and efficacy of LAAC in patients with AF who suffered stroke despite OAT is similar to that in patients without stroke.<sup>31</sup>





**Figure 2** (A) Attitude towards LAAC depending on the presence of LAAT (based on 123 responses). (B) Therapeutic strategy in a patient with embolic stroke under consistent OAT and no sign of thrombus at TEE (empty LAA) based on 128 responses. \*If no other probable embolic source is found, treat as cardioembolic event under consistent OAT. \*\*By MSCT or MRI. If ruled out, treat it as a cardioembolic event if LAA emptying velocity is low. LAA, left atrial appendage; LAAC, left atrial appendage closure; LAAT, left atrial appendage thrombus; MSCT, multislice computer tomography; MRI, magnetic resonance imaging; OAT, oral anti-coagulant therapy; TEE, transoesophageal echocardiography.

While 15% of respondents designate this scenario to be a cardioembolic event only if LAA emptying velocities are low, 13% would perform the LAAC procedure regardless of these parameters.

Post-procedural anti-thrombotic therapy is another unanswered question in patients undergoing LAAC, especially those with LAAT. Early and long-term post-implantation anti-coagulation strategies in patients with and without device thrombosis were very heterogeneous between centres with most strategies not being supported by randomized trials.<sup>32</sup> Consequently, there are mixed results in our survey regarding the choice and duration of therapy. Due to the constraint of survey size, stratification of post-procedural anti-thrombotic therapy according to the device type was not investigated.

Retrospective data indicate an increased risk of thrombus formation and embolic events despite OAT for patients in whom LAA isolation occurred (intentional or inadvertent) at ablation procedure.<sup>33</sup> Despite this, LAAC is regularly performed in this scenario only by 24% of respondents, with an additional 16% performing the LAAC if durable LAA isolation is proven at invasive remap 3 months post-ablation procedure.

## Limitations

Participation in this EHRA survey was voluntary. The conclusions that were drawn from the survey represent how respondents approach this clinical scenario and do not necessarily represent how the majority of patients are treated. Participants were allowed to skip questions at their discretion, so a decline in the number of responses received for the specific part of the survey resulted in a sample size reduction. The data were self-reported with no independent confirmation of their congruency with real clinical practice. Selection bias might have occurred as two-thirds of the answers received came from the academic centres with 80% having access to the LAAC procedures. On the other side, this specific scenario is expected to be treated at specialized centres with capabilities of comprehensive stroke prevention diagnostic and therapeutic options. Another limitation is the unknown annual LAAC procedure volume for the responding physicians. It is likely that multiyear experience and the high annual volume of LAAC procedures could change physicians' preferences towards LAAC as an option in the malignant LAA population. This EHRA survey was not comprehensive enough to collect data on the morphological types of LAA

encountered in the malignant LAA population and its subsequent effect on therapeutic actions. Finally, the lack of information on geographic distribution is a significant limitation, as not all treatment options are readily available in all parts of Europe.

## Conclusions

This EHRA survey demonstrated a lack of consensus in the treatment of LAAT formation in adequately anti-coagulated patients with AF. Outpatient adjustment of anti-thrombotic medication represents the preferred initial treatment. The role of LAAC is currently unclear but it appears to be a viable option for a selected patient population.

## Supplementary material

Supplementary material is available at *Europace* online.

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## Data availability

The data underlying this article and its online [Supplementary material](#) will be shared on reasonable request to the corresponding author with permission of EHRA Scientific Initiatives Committee.

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