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STATE OF THE ART REVIEW

Leap or lag: left atrial appendage closure and guidelines

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Abstract

Atrial fibrillation (AF) is associated with life-threatening thromboembolism. Most emboli stem from thrombosis in the left atrial appendage (LAA). The current treatment of choice is oral anticoagulants (OACs), but a small proportion of patients cannot take OACs predominantly because of the so-called unacceptable bleeding risks. However, many who initially accept OACs subsequently stop therapy or reduce the OAC treatment to a potentially non-effective dose leaving them exposed to thromboembolic risk.

A relatively simple alternative therapy involves the catheter-based insertion of a LAA closure (LAAC) device to prevent thromboembolism from the LAA. There is a considerable evidence base for this therapy consisting of clinical trials and observational data which suggests comparable therapeutic efficacy with a possible small excess of ischaemic strokes.

Although LAAC has been very closely examined by regulators and approved for market release, guidelines from most professional societies give only weak recommendations for use of this device which may be the only known effective therapy available to some at-risk AF patients. Guidance materials from the same societies more enthusiastically endorse LAAC.

Clinical practice is running well ahead of the guidelines because equipoise has been lost by physicians faced with patients for whom they have no other effective therapy. Guideline writers are correct in providing recommendations which are less strong for LAAC than for OACs, for those who are able and willing to take OAC treatment, but for those who are not, a stronger recommendation is needed. But, should the guidelines lag behind or leap ahead of the available evidence?

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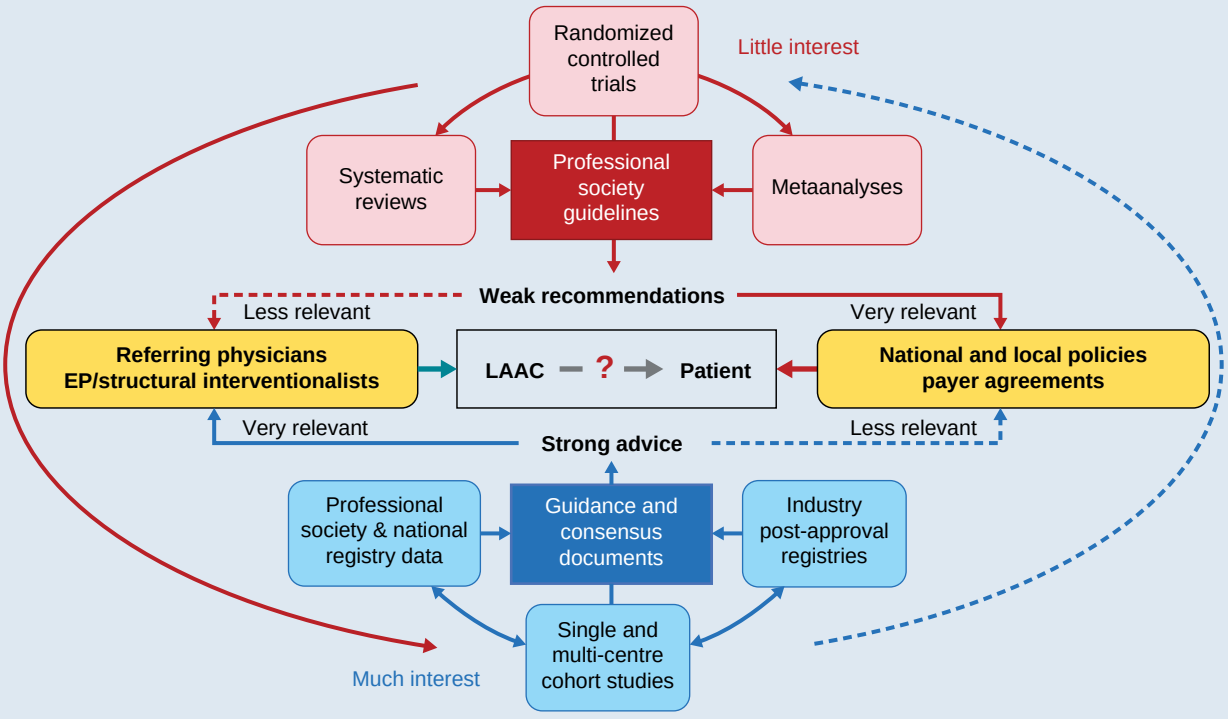
Graphical Abstract



Keywords Atrial fibrillation • Stroke • Oral anticoagulants • Left atrial appendage closure • Guidelines

What's new?

- Medical Practice guidelines and clinical equipoise may be out-of-step with each other. This is the case with the recommendations for LAAC device implantation.
- Therapy approved by regulatory agencies after the submission of some randomised clinical trial and much observational study data is only weakly recommended by professional societies, for an indication for which there is no other treatment which can prevent or reduce life altering complications.
- In such circumstances, guideline writers should consider making a strong recommendation by expert consensus.

Medical guidelines provide great help to the practising clinician, although most clinical decisions for individual patients are not based only on class I guideline recommendations but more often on 'common sense'. Guidelines are difficult to construct and must be prepared by an organization which can ensure a credible writing process and branded endorsement. They have many advantages but also some drawbacks, as summarized and discussed by Rapezzi *et al.*[1] Because the production of guidelines is such a complex and time-consuming process, it is difficult for them to remain up-to-date. The guideline task forces assembled by the European Society of Cardiology (ESC) realistically require a 2-year period for a guideline to be researched, written, reviewed, revised, and published, and the society can at best offer a 4-year cycle between consecutive guidelines on any particular topic. In cardiology arenas which are heavily researched, such as atrial fibrillation, the cycle of 4 years may be too long. One method of dealing with this is to arrange for updates to particular parts of a guideline which have become outdated, and this approach, which is less onerous, has been used occasionally for international atrial fibrillation guidelines such as those produced by the ESC, the American Heart Association, and the American College of Cardiology.[2,3] Unless this is done, the guidelines may rapidly become out-of-date and out-of-step with clinical practice as clinical equipoise is lost.

The iterative process of guideline release by various societies, which is rarely synchronized, does not ameliorate but often worsens the situation because of inconsistencies between guidelines. Altogether, this can result in confused and disorganized clinical practice which is not guideline consistent and this may present peril to both the patients and their doctors. Loss of confidence with older recommendations, often superseded by new recommendations from another body, may not just result from the publication of new randomized clinical trial results but also from good-quality although potentially less reliable sources such as non-randomized but carefully collected and well-adjusted observational data. These considerations apply to current guideline recommendations for left atrial appendage (LAA) occlusion.

Left atrial appendage closure

Left atrial appendage closure (LAAC) with a plug-like device was introduced using a catheter-based interventional technique in the early 2000s.[4] Since then, three relatively large randomized trials, two controlled against dose-adjusted warfarin and one against direct oral anticoagulants (DOACs), together with additional long-term follow-up results have been published.[5–8] Several competent meta-analyses have been undertaken.[9–11] Left atrial appendage closure treatment has generally compared well with oral anticoagulant (OAC), both

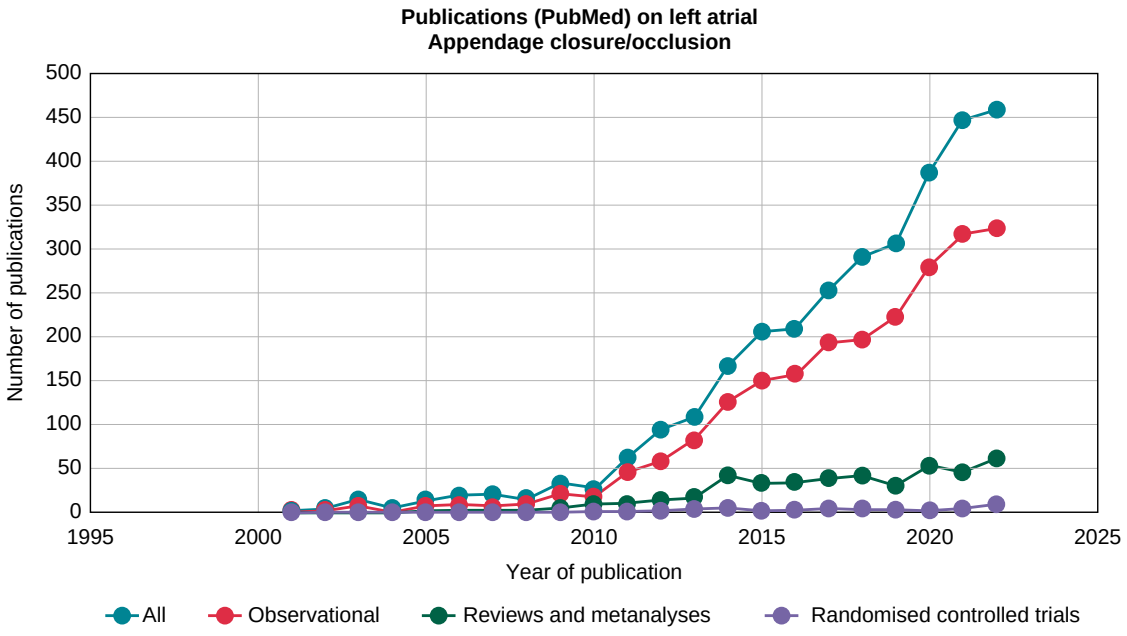


Figure 1 Search on PubMed for publications relating to 'left atrial appendage closure OR left atrial appendage occlusion' from 2001 to 2022. Reviews and metanalyses and RCT (randomized controlled trial) data are obtained using the appropriate NCBI filters and the observational data are derived by adding 'AND observational OR registry' to the search terms.

with warfarin and with DOAC therapy. There appears to be possibly a small excess of ischaemic strokes when using the LAAC device which is offset by a substantial reduction in non-procedure-related bleeding and mortality, and consequently, treatment with the device may result in net clinical benefit.[12]

With all this available evidence, should those responsible for producing evidence-based guidelines provide a strong recommendation for the use of LAAC? There are at least three major concerns that deter such an outcome:

(1) The results of the three randomized trials are not entirely consistent and meta-analyses have not unequivocally shown that stroke prevention with LAAC therapy is as effective as with OAC. Such a result might be expected if not all atrial thrombosis arose in the LAA and if the underlying atrial cardiomyopathy, rather than atrial fibrillation itself, was in part responsible for thrombogenesis.[13]
(2) Only 35% of the oral anticoagulants (OACs) compared with LAAC in the three clinical trials was DOAC therapy, which is now the preferred therapy indicated for stroke prevention in patients with at-risk atrial fibrillation because of their improved safety and efficacy when compared with warfarin in four major pre-approval, controlled randomized trials against dose-adjusted warfarin.[14–17]
(3) No randomized controlled clinical trial has yet reported on LAAC placement vs. standard of care, essentially no treatment, in patients unable to take OAC, despite attempts to conduct such trials. For many investigators, equipoise was lost long ago when the results of LAAC used in other settings suggested that this therapy was at least close to being as effective as OAC for stroke prevention but without substantial non-procedure-related bleeding risks.

Although these three issues present a guideline writing dilemma, there are, in addition to the trial data, a host of registries, established by companies, professional societies, and individual investigators, that have reported and continue to report the clinical value of LAAC therapy for a variety of indications,[18–22] importantly including patients for whom there is no other safe thromboprophylactic alternative.[23,24] This particular group of patients were, of course, excluded in the OAC vs. LAAC clinical trials. The observational data have also allowed the assessment of LAAC treatment against treatment with DOAC therapy.[25] Network metanalysis of observational and trial data suggests that LAAC may be marginally less effective than DOAC therapy at preventing ischaemic stroke but highly effective at reducing major and life-threatening bleeding, an advantage that continues for the whole duration of treatment, suggesting that, as time passes post-implantation, this may become an increasingly important benefit of LAAC when compared to lifelong DOAC therapy.[26,27] The medical literature related to LAAC has burgeoned considerably over the last decade (*Figure 1*).

There are now large-scale ongoing trials comparing LAAC therapy with direct OACs. Other trials are specifically enrolling patients for whom conventional anticoagulation is contraindicated or difficult, such as those with previous intracerebral haemorrhage, advanced chronic kidney disease, or patients for whom previous treatment with anticoagulation has failed to offer protection against ischaemic stroke, etc. Although some of these studies may report in the next 2–3 years, others will take far longer. When these trials are eventually reported, the evidence base for LAAC therapy will be largely complete. Surgical excision or exclusion of the LAA in patients undergoing valve surgery or coronary revascularization has also been undertaken for many years to reduce the likelihood of stroke. Meta-analysis of studies of this therapy shows a significant reduction of stroke risk following surgery.[28] However, the recent LAOOS III trial which evaluated LAA surgical exclusion in a large cohort of patients, the majority of whom were also anticoagulated, showed a similar post-operative stroke risk reduction, implying that the elimination of AF-related stroke might eventually be best achieved with a hybrid approach.[29]

There are clearly two groups of patients for whom LAAC may be a relevant treatment: those for whom OAC is an option and those for whom no currently approved therapy is available. Among those patients who may seem suitable for OAC, there are some who refuse treatment (medication averse) with an OAC[30,31] and many who fail to

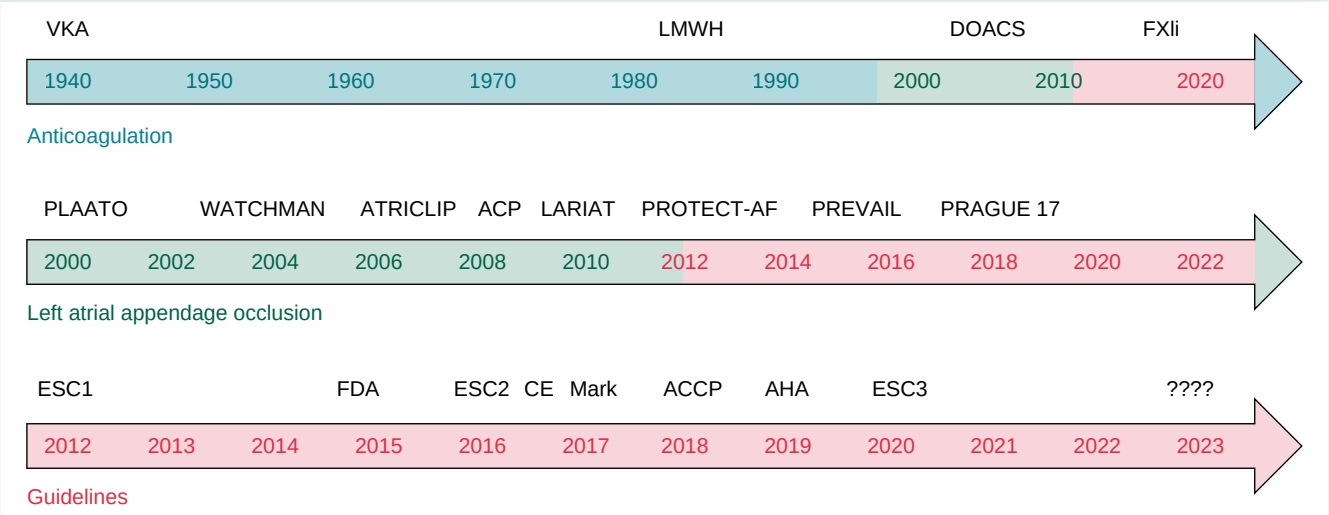


Figure 2 Therapy and guideline development for AF-related stroke thromboprophylaxis. Timelines for the clinical/clinical trial, introduction of anticoagulants, major LAAC therapy trials, and major clinical guidelines and approvals for LAAC therapy. VKA, vitamin K antagonist, LMWH, low-molecular weight heparin, DOACs, direct oral anticoagulants, FXIi, factor XI inhibitors, ESC, first European Society of Cardiology atrial fibrillation guidelines, the numerals following ESC refer to the 2012, 2016 and 2020 guidelines, FDA, Food and Drug Administration, ACCP, American College of Chest Physicians atrial fibrillation guidelines, AHA, American Heart Association/American College of Cardiology/Heart Rhythm Society atrial fibrillation guidelines, CE, conformité européenne (European Conformity). Modified from references.[41,42]

adhere to or persist with OAC therapy, including DOAC treatment,[32] even after a previous ischaemic stroke attributable to atrial fibrillation[33] and despite the best efforts of their physicians. Others include patients unsuitable for anticoagulation only because they are already taking therapy, such as nonsteroidal anti-inflammatory drugs, dual antiplatelet therapy, or powerful *P*-glycoprotein inhibitors, which interact with OAC and potentiate bleeding complications. Essentially, these patients do not receive effective thromboprophylaxis.

Publications stemming from the early days of LAAC rightly emphasized that LAAC was often complicated by serious adverse events.[34] However, recent reports point out that LAAC device placement is now a relatively low-risk procedure.[35–38] Modern, redesigned devices are relatively easy to implant in most patients. The main complications of pericardial effusion, non-occlusion with residual gaps between the device and the atrium, and device-related thrombus and related strokes are now very uncommon.[39] In good and experienced hands, LAAC implantation now has a complication rate which is not significantly different to coronary stenting. It is critically important that both institutions and individual operators have adequate experience of device implantation in order to ensure the safety of the technique.[40] The improved safety of LAAC insertion must improve the benefit–risk of this therapy and lead to a further overall reassessment in comparison to OAC.

The use of the LAAC is becoming relatively commonplace in clinical practice in the USA, but elsewhere, its use is limited. It is estimated that around 200 000 LAAC implants are performed each year in the USA compared with around 16 000 in Europe although the AF population of the USA is roughly half of that in Europe. Almost everywhere, the take-up of this therapy has been patchy and largely in the hands of enthusiasts and pioneers. Therefore, the availability of this treatment is 'postcode-dependent' even for those for whom no other therapy is available. In some regions, the therapy is only available if the patient can join a clinical trial. This unsatisfactory situation is, at least in part, because of the lukewarm recommendations for LAAC use in guidelines from professional societies.

Guidelines

Atrial fibrillation guidelines for the application of LAAC treatment have been offered by the ESC since 2012[2] amid the ongoing development of OACs and LAAC devices (*Figure 2*).[41,42] Many other professional societies have since published their own guidelines, and the ESC guideline was last revised in 2020[43] (*Table 1*).[3,44–47] All are similar in trying to identify high-stroke risk atrial fibrillation patients with sufficient bleeding risks from OAC to warrant using an LAAC device. However, their wording is subtly different, for example, OAC use should be 'absolutely contraindicated', 'clear contraindication', or simply 'contraindicated'; the risk of stroke should be 'very high', 'high', 'increased', or not specified; the quality or level of evidence (LOE) may be 'weak', 'LOE: B', or not graded; and the strength or class of recommendation (COR) goes from 'weak' to 'COR: IIb' to 'strong'. There is also a recommendation from the ESC for the use of the LAAC device 'for patients with atrial fibrillation undergoing PCI if a high stroke risk and contraindication for long-term combined antiplatelet plus OAC therapy is present (COR: IIb, LOE: B)'.[48] Of course, the precise wording of the recommendations and their classifications must be seen as a whole, but suffice it to say that there is a high level of similarity but some inconsistency.

There are other documents which also provide a range of indications for LAAC device implantation. The original FDA regulatory approval for the Watchman device (Boston Scientific) in March 2015 was: 'to reduce the risk of thromboembolism from the LAA in patients with non-valvular atrial fibrillation who are: at increased risk for stroke and systemic embolism based on CHADS2 [cardiac failure, hypertension, age, diabetes, stroke (doubled)] or CHA2DS2-VASc [congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, and sex (female)] scores, are deemed by their physicians to be suitable for warfarin and have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.[49] A range of devices including the Watchman FLX (Boston Scientific) and the Amplatzer Amulet (Abbott) is now also approved.

Table 1 Recent guidelines

	Recommendation
American College of Chest Physicians Lip *et al.*[44]	In patients with AF at **high risk** of ischaemic stroke who have **absolute contraindications** for OAC, we suggest using LAA occlusion (**weak** recommendation, **low** quality evidence)
Asian Pacific Heart Rhythm Society Chao *et al.*[45]	LAA occlusion **may be considered** for stroke prevention in patients with AF and **clear** contraindications for long-term anticoagulant treatment (e.g. intracranial bleeding without a reversible cause)
Cardiac Society of Australia and New Zealand Brieger *et al.*[46]	LAA occlusion **may be considered** for stroke prevention in patients with NVAF at **moderate to high risk** of stroke and with **contraindications** to oral anticoagulation therapy. GRADE quality of evidence, **low**; GRADE strength of recommendation, **strong**
American Heart Association, American College of Cardiology and Heart Rhythm Society January *et al.*[3]	Percutaneous LAA occlusion **may be considered** in patients with AF at **increased risk of stroke** who have **contraindications** to long-term anticoagulation. COR: **IIb** LOE: **B-NR**
Canadian Cardiovascular Society Andrade *et al.*[47]	We suggest that percutaneous LAAO be considered for stroke prevention in patients with NVAF who are at moderate to **high risk** of stroke and have **absolute contraindications** to OAC (w**eak** recommendation; **low**-quality evidence)
European Society of Cardiology Hindricks *et al.*[43]	LAA occlusion **may be considered** for stroke prevention in patients with AF and **contraindications** for long-term anticoagulant treatment (e.g. intracranial bleeding without a reversible cause). COR: **IIb** LOE: **B**

Some current guidelines recommendations illustrating many similarities but some inconsistencies (note bold text).
COR, class of recommendation; LOE, level of evidence.

Table 2 Indication for the LAAC according to the Munich consensus statement

A. Patient not eligible for long-term OAC therapy (absolute or relative contraindications to OAC)	
High risk for bleeding	• Intracranial bleeding • GI bleeding
History of major or minor bleeding (±OAC therapy)	• Symptomatic bleeding in critical organ (i.e. ocular, pericardial, and spinal cord) • Recurrent epistaxis needing medical attention
Increased risk for bleeding due to physical condition and/or co-morbidities	• Recurrent falls with head trauma and significant musculoskeletal injury • Need for additional dual antiplatelet therapy for CAD and stenting • Diffuse intracranial amyloid angiopathy • Bowel angiodysplasia • Severe renal insufficiency/ haemodialysis • Blood cell dyscrasia
Inability to take OACs for reasons other than high risk for bleeding	• Intolerance • Documented poor adherence to medication • Documented variability in the international normalized ratio on warfarin • Higher-risk occupation with increased injury potential • Patient's choice
B. Thromboembolic event/documented presence of thrombus in the LAA despite adequate OAC therapy	
	• Embolic stroke or other systemic thromboembolism on adequate OAC therapy with evidence for thrombus origin from the LAA (malignant LAA) • Documented thrombus formation in the LAA on adequate OAC therapy

Munich Consensus indications for left atrial appendage closure.
OAC, oral anticoagulation; LAA, left atrial appendage (reproduced from reference[53]).

The form of alternative anticoagulation is no longer restricted to warfarin. Some contraindications for device use are also specified.[50]

Several professional society manuscripts which have been published as white papers or consensus documents expand on the detail available in major cardiology society guidelines.[51,52] The writers generally adhere to the principle that when an OAC can be used, it should take precedence over an LAAC implantation. However, relevant bleeding risks have been further explained and the contraindications to OAC use have become more inclusive, not just bleeding risks but also the failure of adequate OAC therapy to prevent ischaemic stroke and the unwillingness or inability of the patient to take medications appropriately. An example, the LAAC indications taken from such a source, the 'Munich Consensus', can be seen in *Table 2*.[53] In this and other papers, an indication labelled as 'patient choice' is included. Whilst this concept is always important, it presently behoves the physician to carefully explain that the

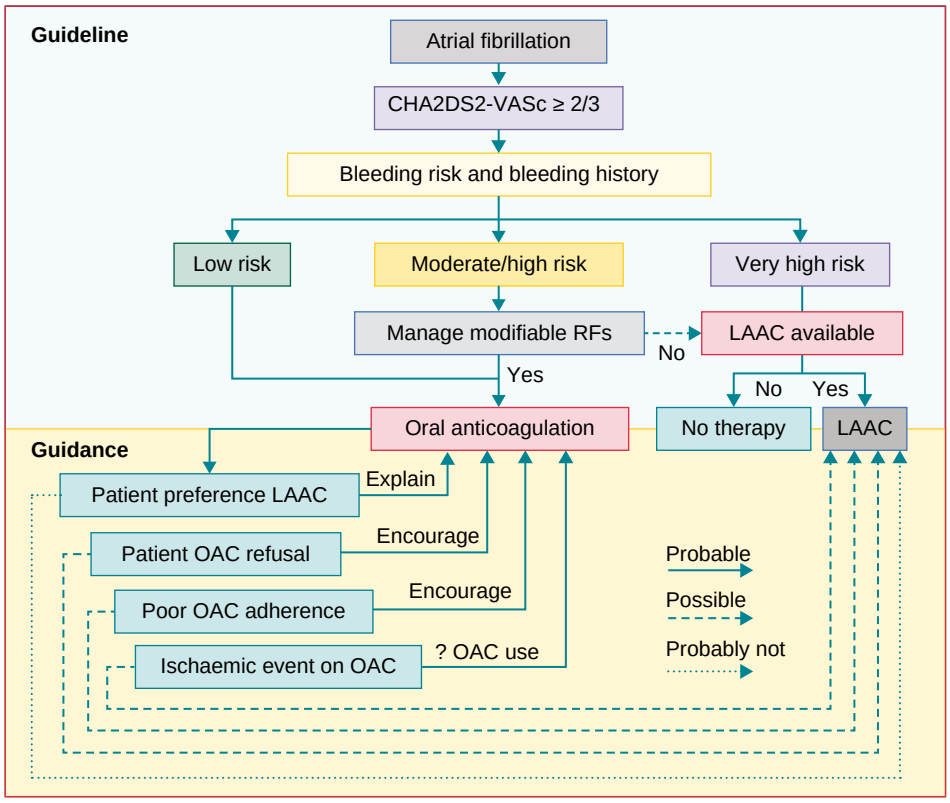


Figure 3 Recommendations for LAAC therapy from guidelines and guidance documents. Both sources are similar but the guidance documents provide more detail. CHA2DS2-VASc = congestive heart failure, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, and sex (female); OAC, oral anticoagulation; LAAC, left atrial appendage closure; RF, risk factors.

encouraging evidence that we have so far does not necessarily extend to patients with little or no risk from anticoagulation. The present advice from the European Heart Rhythm Association fully explains this position.[54]

Guidelines can be interpreted in a very narrow manner, but a plethora of guidance documents have carefully laid out a richer interpretation of the guidelines by explaining the extensive range of bleeding risks (*Table 2*) and extending the concept of patients unsuitable for anticoagulation to include those who cannot take medication reliably or who have sustained an ischaemic stroke despite well evaluated adequate anticoagulation (*Figure 3*).

Finally, numerous local documents relating to national regulations, payers' conditions, hospital policies, and health technology assessments complete the pantheon of material that must be considered by the physician when contemplating resorting to LAAC implantation.[55] Much of this advice is related to the initial cost of device implantation, irrespective of potential long-term savings,[56] and the absence of any strong formal recommendation for the use of the LAAC device from an appropriate professional society such as the ESC.

Resolution

With such a range of major society guidelines, guidance from specialist societies, and national/local regulations, it is easy in the confusion 'not to see the wood for the trees'. What is most important is to encourage and support high-quality research directed towards filling unmet gaps in the evidence base, by encouraging potential device candidates to join randomized trials for which they are eligible. When these trials have been completed, guidelines can be written with full confidence. However, in the meantime, we have patients for whom no guideline applies but the evidence base is not barren. We do have the results from observational studies based on carefully collected and well-adjusted data, together with incomplete but important randomized clinical trial results, that enable us to give cogent advice to our patients. Most conclude that, but for local barriers such as device non-availability, those individuals with the potential to enjoy life despite having atrial fibrillation at high risk of thromboembolic stroke and being unsuitable, for a wide variety of reasons, for guideline-mandated OAC therapy, should be considered for the insertion of an LAAC device. There is, therefore, tension between physicians and the LAAC guidelines and healthcare payers that usually follow guideline recommendations rather than guidance advice (*Figure 4*).

The current ESC recommendation for LAAC (2020) has not changed substantially since it was first included in the 2012 guidelines. It states that 'LAA occlusion may be considered for stroke prevention in patients with AF and contraindications for long-term anticoagulant treatment' and finishes with an example of a contraindication for anticoagulation: 'e.g. intracranial bleeding without a reversible cause'. What should be the class of recommendation for LAAC in a patient like this, for whom there is no alternative thromboprophylaxis? Whilst admitting a shortage of evidence, it may be argued that experts might reach a consensus in favour of a strong class of recommendation, as given by the Australian and New Zealand guideline writers. Other recent ESC guidelines, for example, the 2022 cardio-oncology guidelines, have issued many class I recommendations with only the support of expert

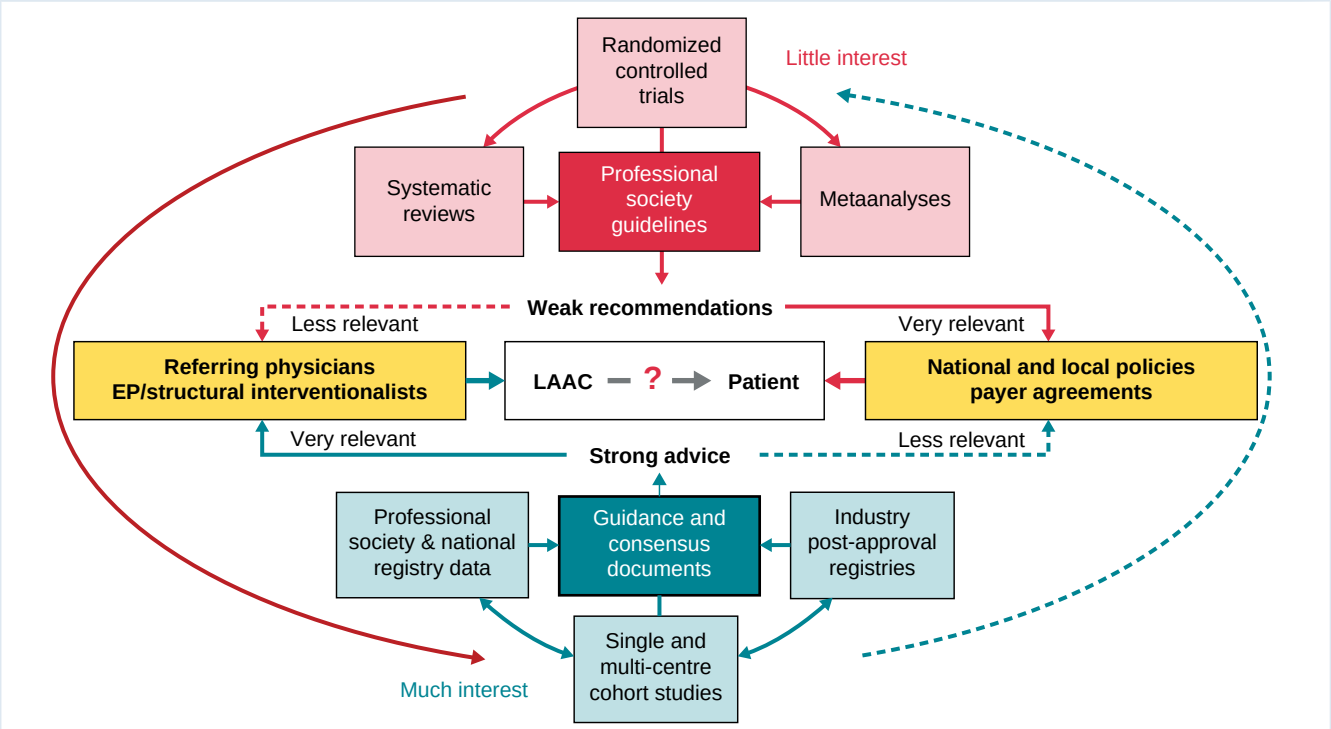


Figure 4 Multiple sources of information are available to the writers of guidelines and guidance material. Guideline writers, who are usually not experts in the specific topic about which they write, pay great attention to randomized controlled trials, systematic reviews, and meta-analyses of this very high-quality data and have relatively little regard for observational data. On the other hand, guidance writers, often experts/enthusiasts, give attention to both types of data. Guidelines strongly influence the development of national/local policies and healthcare-payer agreements whilst physicians are also strongly influenced by guidance material. When there is a conflict between these sources of advice, as it is with left atrial appendage closure (LAAC), the result may be loss of equipoise, clinical confusion, and tension between healthcare professionals and their managers. The patient may be the loser.

The balance between safety and efficacy and timely availability

Regulation of medical devices by the US Food and Drug Administration (FDA) is a *balance between ensuring safety and efficacy and the timely availability of novel (therapies).* The 21st Century Cures Act of 2016 shifted this balance toward expediting approval. The Cures Act stated that **the FDA must "consider the role of post-market information in determining the least burdensome means" for approval** ..... can reduce pre-market data on effectiveness "through reliance on post-market controls *Hidano D, et al. JAMA Intern Med. 2022;183:556-558*

... and the same should be said about guidelines to encourage the appropriate use of drugs or devices and allow post-market studies to flourish and furnish further data

Figure 5 Observation on the 21st Century Cures Act of 2016.[58]

consensus,[57] and in the 2021 ESC AF guidelines, DOAC resumption after ICH was elevated from a class IIb to a class IIa recommendation based on only weak evidence and no randomized controlled trial data.[44] Without a strong recommendation, healthcare systems can dodge their responsibility and essentially offer no therapy to these patients whose care cannot wait for many years for the completion of more clinical trials. However, when considering any recommendation for LAAC as an alternative for OAC, for example, when a patient prefers not to take oral medication, although the evidence available is considerable, it is insufficient to justify a strong class of recommendation.

There are unacceptable delays involved in fully investigating a medical device before it can be approved by regulators for market release. The need for an expedited approach has been fully recognized in the 21st Century Cures Act in the USA (*Figure 5*) because of the long delays

and huge costs involved in bringing novel medical device therapy to market.[58] However, this has not been entirely successful because manufacturers have not been sufficiently active in keeping their side of the bargain—post-approval studies. However, this has not been the case with the LAAC device because numerous clinical trials and observational databases have been initiated by the industry or others and are now ongoing. Regulators have changed their approach so as not to needlessly deprive patients of medical device innovations. In order to support the regulatory changes, a somewhat similar approach may be needed for medical guidelines when considering therapies for patients at high risk of life-changing or life-threatening consequences which can be averted at least in part by a well-documented therapy still awaiting full confirmation from long-duration controlled randomized trials. Cautious and comprehensive monitoring of such treatment must then be implemented in order to halt the runaway application of a therapy which is unsafe.

It is not the function of guidelines to impede the use of therapies which have been deemed worthy of market release because of a sufficient but not yet complete evaluation unless subsequent evidence shows the therapy to be inferior or outperformed by other treatments. In the case of the LAAC, its non-inferiority to vitamin K antagonists is broadly accepted, but when compared against DOACS, a relatively new therapy introduced after the critical phase III studies which led to the approval of the first device, the results are similar but less clear. Therefore, any guideline recommendation for patients able to take an anticoagulant can only be relatively restrained and this may persist for some time with the ongoing development of even newer and possibly safer factor XI/XIa inhibitors[42] although it may by then be the responsibility of the pharma companies to demonstrate that their new drugs outperform the LAAC. However, when no OAC therapy can be effectively prescribed for high-risk patients at risk of stroke, it can be argued that LAAC therapy should qualify now, by expert consensus, for a strong recommendation.

Conclusion

There is an old IBM corporate mantra 'leap before you lag'. The commercial relevance of this is obvious but it should also be considered when guidelines are written. Guideline task forces are conservative and are usually strongly encouraged not to base their recommendations on other than class I evidence. But, because it may take so long to satisfy every requirement to achieve a high level of evidence, valuable therapies, such as LAAC, may become stranded. In consequence, clinical guidelines may lag well behind clinical practice and it is sometimes necessary, especially when patients are left with little or no otherwise effective therapy for their life-threatening illness for guidelines to leap cautiously ahead.

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