



SCAI/HRS technical review on transcatheter left atrial appendage occlusion

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ABSTRACT

BACKGROUND Nonvalvular atrial fibrillation (NVAf) is associated with an increased risk of stroke due to thrombus formation in the left atrial appendage, where over 90% of thrombi originate. While oral anticoagulation (OAC) is the standard therapy for stroke prevention, many patients cannot tolerate long-term OAC due to bleeding risks. Percutaneous left atrial appendage occlusion (LAAO) has emerged as an alternative strategy. Despite its rapid adoption, substantial variability exists in clinical practice regarding patient selection, imaging techniques, procedural guidance, and postprocedural management. This systematic review aims to collect and synthesize evidence to inform the development of new Society for Cardiovascular Angiography & Interventions and the Heart Rhythm Society guidelines on LAAO.

METHODS We searched PubMed, Embase, and Cochrane Library from inception through January 5, 2024, for studies of the percutaneous LAAO procedure. Eligible studies were conducted in adults with NVAf undergoing LAAO, or with peridevice leak or device-related thrombus after an occlusion procedure. Studies of surgical LAAO, double device or combined procedures, and devices that are not currently marketed in the United States were excluded. Data were extracted from studies in duplicate and summarized using meta-analysis and narrative synthesis. Risk of bias (RoB) was assessed using the RoB in nonrandomized studies of interventions tool, and version 2 of the Cochrane RoB tool for randomized trials (RoB 2.0). Overall certainty of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation approach.

RESULTS Our search identified 3769 titles and abstracts, of which 27 studies met eligibility criteria and contributed data to the analysis. Data were abstracted to address outcomes of LAAO for stroke prevention in patients with NVAf, in comparison to OAC, no therapy, and across various approaches including preprocedure imaging, intraprocedure guidance, and postprocedure antithrombotic regimens.

CONCLUSIONS Left atrial appendage occlusion is an effective alternative to OAC for stroke prevention in NVAf patients with bleeding risks, but uncertainties remain regarding imaging strategies and postprocedural management.

KEYWORDS Antiplatelet therapy; atrial fibrillation; device-related thrombus; left atrial appendage occlusion; peri-device leak; stroke

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<https://doi.org/10.1016/j.hrthm.2025.05.049>

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ABBREVIATIONS CoE = certainty of evidence; DAPT = dual antiplatelet therapy; DRT = device-related thrombus; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; NRS = non-randomized study; OAC

= oral anticoagulation; PDL = peridevice leak; PICO = patient, intervention, comparator, outcomes; RoB = risk of bias; SAPT = single antiplatelet therapy

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Introduction

The left atrial appendage, an anatomically complex structure arising from the lateral aspect of the left atrium, is the location of >90% of left atrial thrombi in patients with nonvalvular atrial fibrillation (NVAF).¹ Patients with NVAF have an elevated risk for stroke compared with the general population, primarily related to the increased risk for left atrial appendage thrombus.² Although long-term oral anticoagulation (OAC) is currently indicated as the first-line therapy for the prevention of stroke and systemic embolism among patients with NVAF,^{3–5} alternative options for the prevention of stroke and systemic embolism are needed among patients who cannot tolerate long-term OAC due to prior bleeding complications or high bleeding risk. Percutaneous left atrial appendage occlusion (LAAO) is now an established option to prevent stroke and systemic embolism in patients with NVAF, based on multiple randomized trials demonstrating comparable long-term outcomes of LAAO and OAC.^{6–8}

Despite the brisk adoption of LAAO as an alternative form of stroke prevention in patients with nonvalvular AF at high bleeding risk,⁹ there remain multiple areas of variability and uncertainty in the management of patients undergoing LAAO. There are now 2 commercially approved percutaneous LAAO devices, with several additional devices being tested in randomized clinical trials.^{10–12} The use of computed tomography angiography imaging to plan LAAO procedures and evaluate LAAO devices after implantation

has grown.¹³ The use of intracardiac echocardiography (ICE) to guide LAAO procedures has been an area of rapid development in recent years.¹⁴ Additionally, postprocedure antithrombotic therapy is highly variable with multiple drug regimens approved by the US Food and Drug Administration and numerous off-label regimens being used in clinical practice.^{15–17} The long-term issues of diagnosing and managing peridevice leak (PDL) and device-related thrombus (DRT) also remain areas of considerable uncertainty.^{18,19}

In 2023, Society for Cardiovascular Angiography & Interventions (SCAI) and Heart Rhythm Society (HRS) published a joint expert consensus statement on LAAO, while the American College of Cardiology and American Heart Association released a multisociety guideline on the diagnosis and management of atrial fibrillation.^{20,21} In the latter document, percutaneous LAAO is given a class 2a indication for patients contraindicated for OAC and a class 2b indication for patients at high risk of major bleeding while on OAC. Given the rapid adoption of LAAO, the increasing scientific evidence in this area, and the variability in practice patterns, there is a need for a guideline document focused specifically on LAAO to provide better clinical guidance for patients and physicians.

SCAI and HRS conducted this systematic review to answer prioritized clinical questions regarding the utilization of LAAO in adult patients with NVAF. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

approach was used to assess the certainty of evidence (CoE) and guide decision-making. In areas where insufficient evidence exists, directions for further research are suggested. The findings from this review inform the SCAI/HRS clinical guideline panel's recommendations on the use of LAAO to guide interventional cardiologists, cardiac electrophysiologists, and patients to maximize the benefits of LAAO. This review focuses on indications for LAAO, pre- and intraprocedural imaging, and postprocedural management; however, topics such as device selection, procedural techniques, and timing of imaging studies are beyond the scope of this review.

Scope and clinical questions

This technical review assessed the evidence for use of LAAO to address 8 clinical questions formulated in the patient, intervention, comparator, and outcomes (PICO) format:²²

1. In adults with NVAF, should LAAO be performed rather than no OAC?
2. In adults with NVAF, should LAAO be performed rather than OAC?
3. In adults with NVAF who are undergoing LAAO, should CT or transesophageal echocardiography (TEE) be performed prior to the procedure compared to no imaging prior to the procedure?
4. In adults with NVAF who are undergoing LAAO, should ICE guidance be used rather than TEE during the procedure?
5. In adults with NVAF who have undergone LAAO, should OAC be preferred over antiplatelet therapy?
6. In adults with NVAF who have undergone LAAO, should TEE or CT imaging be preferred over no follow-up TEE or CT?
7. In adults with NVAF who have a PDL after undergoing LAAO, should OAC be preferred over no OAC?
8. In adults with NVAF who have DRT after undergoing LAAO, should indefinite OAC be preferred over no OAC?

Patient-important outcomes were prespecified by the guideline panel for all clinical questions as follows: mortality, stroke, bleeding, procedure-related adverse events, PDL, and DRT.

Materials and methods

The Technical Review Panel was composed of clinical interventional cardiologists, electrophysiologists, and methodological experts. The panel collected and synthesized evidence on different options for the management of patients undergoing percutaneous LAAO, including common post-procedure complications. This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards.²³ A protocol for the review was developed and registered in PROSPERO (registration number: CRD42024509047) prior to data collection.

The systematic review process included the following steps:

1. Systematic search of the published literature to identify primary studies and relevant high-quality systematic reviews.

2. Screening of titles, abstracts, and full texts to identify eligible studies to inform the research questions.
3. Risk of bias (RoB) assessment of individual studies.
4. Synthesis of the evidence using meta-analysis or narrative synthesis.
5. Assessment of the overall CoE using GRADE.

The GRADE approach provided the basis and methodology for systematically reviewing and rating the CoE for each outcome and rating the overall CoE for each research question.

Formulation of clinical questions and determining outcomes of interest

The panel formulated and prioritized the questions to be addressed by this guideline using the PICO format.²² The SCAI/HRS Guideline Panel approved the final set of questions and outcomes. Members of the Guideline Panel selected patient-important outcomes for each question a priori. Only critical or important outcomes for decision-making were included in the final list of PICO questions (Supplemental Table S1).

Literature search strategy and study selection

Database search strategies were developed in consultation with an information specialist. The published literature was searched in the following databases: PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials. The search strategies used controlled vocabulary, including the National Library of Medicine's Medical Subject Headings (MeSH) and keywords without any restrictions on the publication date or language (Supplemental Table S2). The strategies were calibrated for sensitivity and specificity using key articles identified by subject matter experts.

Abstracts and full-text reports were uploaded to Covidence (Covidence systematic review software, Veritas Health Innovation. Available at: www.covidence.org) for screening. Retrieved references were screened for eligibility by the Technical Review Panel. Titles, abstracts, and full texts were independently screened by 2 researchers in duplicate. Conflicts were managed and resolved through discussion or with input from a third researcher to reach a consensus. Studies were eligible for inclusion if they met the following criteria: published in English or German languages and reporting on a source population of adults with NVAF undergoing LAAO. Randomized controlled trials (RCTs) and comparative non-randomized studies (NRSs) were considered the preferred source of evidence for each PICO question. However, in the absence of RCTs and comparative NRSs, single-arm, noncomparative studies were included to reflect the extent of literature for each PICO question. Systematic reviews were assessed for applicability to the prioritized PICO questions. We excluded studies published in any language other than English or German, narrative reviews, commentaries and letters, conference abstracts, and research protocols without full results available, individual case reports, and studies without adult human participants. Studies of surgical LAAO,

combined or double device procedures, and devices that are not currently marketed for use in the United States were also excluded.

Data extraction and RoB assessment

Data from the included studies were extracted by 1 Technical Review Panel member and reviewed by a second using a standardized Google sheet developed and piloted by the researchers. Discrepancies were resolved through discussion to reach consensus. Researchers extracted the study design, year of publication, country of origin, funding source, study abbreviation (eg, PROTECT), study duration, population information, description of the procedure performed (intervention), comparator (if applicable), and outcome measures, including adverse events.

One Technical Review Panel member assessed the RoB for eligible studies, which was then reviewed by a second member. The RoB in Non-randomized Studies of Interventions (ROBINS-I) tool was used to assess NRS and version 2 of the Cochrane RoB tool for randomized trials (RoB 2.0) was used to assess RCTs.^{24,25} Disagreements between assessors were discussed and resolved in consultation with a methodologist.

Analytic approach

Data and study characteristics extracted from the studies were synthesized into tables. When appropriate, study findings were quantitatively pooled in a random effects meta-analysis. These quantitative analyses were expressed as a relative risk (RR) or hazard ratio (HR). The Der Simonian and Laird method for random effects or fixed-effects models was used to determine the overall effect size with 95% CI. Fixed-effects models were planned when only 2 trials were pooled for the overall effect size.²⁶ Heterogeneity was assessed using the I^2 or X^2 metric, and visual inspection of the forest plots was conducted. When pooling was not possible, the results were summarized narratively. All analyses and resulting figures such as forest plots were developed in Review Manager (RevMan) version 5.3 (The Cochrane Collaboration).

CoE

The GRADE approach was used to assess the overall CoE.²⁷ The CoE was rated as "High," "Moderate," "Low," or "Very Low." Evidence for each outcome could be rated down due to concerns in the following domains: RoB (ie, study limitations), inconsistency (ie, unexplained heterogeneity), indirectness (ie, applicability to population, intervention, or outcome of interest), imprecision (ie, the fragility of the estimate), and/or publication bias. CoE for NRS could be strengthened on the basis of a large magnitude of effect, a dose-response gradient, or opposing residual confounding.²⁸

CoE was first ascertained for each outcome and then assessed across all outcomes. Using the GRADEpro Guideline Development Tool,²⁹ an evidence profile and summary of findings for each PICO question was prepared.

Results

Question 1

In adults with NVAF, should LAAO be performed rather than no OAC?

The initial literature search yielded 3769 studies, from which the Technical Review Panel identified 4 eligible studies to evaluate PICO 1 (Supplemental Table S3A).^{6-8,30} Outcomes of interest for PICO 1 included mortality and systemic thromboembolism, including stroke, major bleeding, procedure-related adverse events, and cardiovascular events. One NRS described the outcomes of patients treated with LAAO or no OAC, specifically those with end-stage renal disease on hemodialysis.³⁰ This study had a very serious RoB due to concerns about uncontrolled confounding, selection bias, and missing outcome data (Supplemental Table S4B). Three RCTs were pooled to evaluate procedural adverse events in a noncomparative manner, as patients in the no OAC group would not be exposed to the LAAO procedure. These 3 RCTs were assessed to have a low RoB (Supplemental Table S4A).⁶⁻⁸

The 1 NRS was used to generate evidence profiles for the outcomes of mortality and systemic thromboembolism including stroke, major bleeding, and cardiovascular events over a median follow-up of 5 years (Supplemental Appendix S1). CoE was graded as very low for each of these outcomes due to the very serious RoB as well as serious indirectness and serious imprecision. LAAO may result in lower risks of mortality compared with no OAC (HR, 0.52; 95% CI, 0.34-0.78; very low certainty), systemic thromboembolism including stroke (HR, 0.16; 95% CI, 0.04-0.66; very low certainty), major bleeding (defined as a hemoglobin drop of ≥ 2 g/dL, documented transfusion of at least 2 units, or involvement of a critical anatomical site, HR, 0.51; 95% CI, 0.23-1.12; very low certainty), and cardiovascular events, which were not further defined (HR, 0.45; 95% CI, 0.29-0.70), but these effects are very uncertain.

Procedural adverse events were summarized by pooling data from 3 RCTs, as these adverse events would be the same regardless of whether the comparator is OAC or no OAC. Procedural risks of LAAO may include pericardial effusion (observed in 2.7% of people undergoing LAAO), device embolization (0.6%), and procedure-related stroke (0.6%). Overall procedure-related complications (pericardial effusion, device embolization, stroke, vascular complications, and major bleeding) were observed in 6.9% of patients. The overall certainty in the evidence is moderate due to serious concerns with imprecision.

Discussion

In summary, there was a serious paucity of evidence to compare outcomes of patients with NVAF and a contraindication to OAC who were treated with LAAO or no OAC. A single NRS among patients with end-stage renal disease on dialysis with a very serious RoB and a very low CoE suggested that LAAO may possibly result in a lower risk of mortality, systemic thromboembolism including stroke, and cardiovascular

events compared with no OAC. Future studies addressing this question may help guide clinical decision-making.

Question 2

In adults with NVAf, should LAAO be performed rather than OAC?

The initial literature search yielded 3769 studies, from which the Technical Review Panel identified 3 RCTs—the PROTECT-AF, PREVAIL, and PRAGUE-17 trials—to evaluate PICO 2 (Supplemental Table S3A).^{6–8} PROTECT-AF and PREVAIL included patients randomized to LAAO using a WATCHMAN device or OAC with warfarin while PRAGUE-17 included multiple different LAAO devices and various OAC medications including both direct oral anticoagulants and warfarin. The Technical Review Panel characterized the RoB in each study as not serious, with the concerns including lack of blinding among participants and study personnel, unclear blinding for outcome assessment, and a loss to follow-up rate of 12%–30%, which did not differ between treatment arms (Supplemental Table S4A).

Outcomes of interest for PICO 2 included mortality, stroke, major bleeding, procedure-related adverse events, cardiac mortality, major nonprocedural bleeding, and ischemic stroke. The follow-up range for all outcomes except procedure-related adverse events was 40 to 60 months. For each outcome, there was moderate CoE, with the only concern being imprecision (Supplemental Appendix S2).

The pooled estimates from these 3 RCTs showed a likely reduction in the risk for mortality (HR, 0.76; 95% CI, 0.59–0.96; moderate certainty), cardiac mortality (defined as cardiovascular or unexplained death) (HR, 0.64; 95% CI, 0.43–0.95; moderate CoE), and major nonprocedural bleeding (HR, 0.52; 95% CI, 0.37–0.74; moderate certainty) with LAAO compared with OAC. LAAO may result in trivially higher rates of ischemic stroke (HR, 1.52; 95% CI, 0.93–2.50; moderate CoE). This translates to an absolute effect of 21 additional ischemic strokes per 1000 patients (95% CI, 3 fewer to 59 more) in patients who underwent LAAO compared with OAC. LAAO likely results in little or no difference in the risk for any stroke (HR, 1.05; 95% CI, 0.62–1.77; moderate CoE) and major bleeding (defined using ISTH criteria or an event requiring at least 2 units of blood transfusion or surgery) (HR, 0.88; 95% CI, 0.65–1.20; moderate CoE) compared with OAC.

Procedure-related adverse events were summarized only for patients in the LAAO group because those treated with OAC were not exposed to LAAO. The same data from the discussion on PICO 1 apply to PICO 2, as well.

Discussion

Among patients with NVAf, pooled data from 3 RCTs with low RoB provided moderate certainty evidence that patients treated with LAAO likely have lower risk of mortality, cardiovascular mortality, and nonprocedural bleeding compared with OAC but may have a possible increase in ischemic stroke. No clinically concerning differences were observed between

LAAO and OAC in terms of the risk of major bleeding or any stroke. However, there were concerns about imprecision with each of the outcomes.

Question 3

In adults with NVAf who are undergoing LAAO, should CT or TEE be performed prior to the procedure compared with no imaging prior to the procedure?

The Technical Review Panel found 2 eligible studies comparing preprocedure imaging with TEE or CT, or no preprocedural imaging, in patients undergoing LAAO (Supplemental Table S3B).^{31,32} Both studies were observational. RoB was very serious in both due to the concern for unknown, uncontrolled confounding, and residual confounding (Supplemental Table S4B). The panel also noted serious concerns with indirectness due to multiple cointerventions and imprecision (Supplemental Appendix S3).³¹

The primary outcomes of interest for PICO question 3 were the rates of PDL and procedural success. Mortality, stroke, bleeding, procedure time, contrast dose, and radiation dose associated with each strategy were considered important but not critical for decision-making. Both studies offered information about PDL, defined in 1 NRS as any leak assessed via TEE within 45 days of the procedure³² or a leak of greater than 5 mm.³¹ Absence of preprocedure imaging may have a limited effect on PDL compared with imaging with CT or TEE, although this effect is very uncertain (RR, 1.17; 95% CI, 0.65–2.13; very low CoE). One study provided data on short-term procedural success, defined as the lack of any residual PDL by TEE and/or fluoroscopy at the end of the procedure without major procedure-related complications. The lack of preprocedural imaging may lead to decreased procedural success (RR, 0.87; 95% CI, 0.79–0.96; very low CoE), resulting in an estimated absolute difference of 122 fewer successful cases per 1000 (95% CI, 196 fewer to 37 fewer), but again, the effect is very uncertain.

Very few deaths and strokes occurred in the 2 studies, and there may be no difference in these outcomes between patients who did not receive imaging vs those who did (mortality RR 1.24; 95% CI, 0.19–7.98; very low CoE), or 1 more death per 1000 (95% CI, 5 fewer to 43 more) and 10 more strokes per 1000 (from 4 more to 24 more, very low certainty). Both studies provided information on bleeding, defined as Bleeding Academic Research Consortium type³³ 3 and assessed at 45 days. The effect of no preprocedural imaging on major bleeding is very uncertain (RR, 1.85; 95% CI, 0.54–6.26; very low CoE). One NRS indicated a possible lower procedure time without preprocedural imaging, although cointerventions likely also affected the outcome (MD, 30.1 minutes fewer; 95% CI, 37.83 fewer to 22.37 fewer; very low CoE).³¹ One study indicated that forgoing preprocedural imaging may increase contrast dose (MD, 14.4 mL higher; 95% CI, 3.5 higher to 25.3 higher; very low CoE) and radiation dose (median, 3306 cGy.cm²; IQR, 1465.5–6545 vs median 2237 cGy.cm², IQR 450–4748, very low CoE), but these effects

are very uncertain. It should be noted that these figures do not include the radiation dose from the CT.³²

Discussion

The available evidence for preprocedural imaging in patients undergoing LAAO is limited. The 2 studies included were not randomized, which raised concerns about confounding and the RoB. The available evidence is very uncertain about the effect of no preprocedural imaging. Skipping imaging may reduce procedural success, increase contrast dose, and increase radiation dose, but decrease procedural times. There may be little impact on clinical outcomes such as mortality, stroke, and bleeding. These findings are plausible and desirable from an efficiency and cost standpoint. However, the certainty of these findings was very low due to the limitations of the studies included.

Question 4

In adults with NVAF who are undergoing LAAO, should ICE guidance be used rather than TEE during the procedure?

The Technical Review Panel found 6 eligible studies that addressed intraprocedural imaging guidance with ICE vs TEE during LAAO (Supplemental Table S3B).^{34–39} All studies were NRS of data collected from device registries. The RoB in these studies was generally judged to be very serious due to concerns about unknown and uncontrolled confounding and residual confounding due to selection of patients with contraindications to TEE and operator experience. The largest National Cardiovascular Data Registry study primarily influenced the judgment of RoB, despite some smaller studies being at potentially higher risk (Supplemental Table S4B).³⁴ Sensitivity analysis showed that removing the registry studies at high RoB from the pooled estimate did not meaningfully change the effect estimate.

The primary outcomes of interest for PICO question 4 were rates of mortality, stroke, bleeding, PDL, and procedural success associated with each imaging strategy (Supplemental Appendix S4). Three studies provided information about mortality,^{34–36} which was measured at 45 days and defined as death from any cause. The risk of mortality may be slightly higher with ICE-supported procedures than with TEE (RR, 1.65; 95% CI, 1.02–2.08; low CoE), potentially leading to an estimated 5 additional deaths per 1000 patients (95% CI, 0–9 more). The evidence was downgraded due to concerns about confounding from patient selection and operator experience, and the estimate of absolute effects fell below the a priori threshold for clinical significance of 10 deaths per 1000 patients. In particular, the publication by Ferro et al.³⁴ included operators who were much less experienced with ICE than TEE, with many in the study performing LAAO guided by ICE for only the first or second time. Three studies reported on stroke with follow-up ranging from 45 days to 2 years. The evidence suggests no difference in stroke rates between patients undergoing ICE-guided vs TEE-guided procedures (RR, 0.96; 95% CI, 0.55–1.68; low CoE). Four studies provided information about major bleeding, and the rates were similar between

the 2 imaging strategies (RR, 1.06; 95% CI, 0.87–1.29; low CoE). Three studies reported on PDL, defined as a leak greater than 5 mm during follow-up, and there is likely no difference in PDL regarding ICE-guided LAAO compared with TEE-guided LAAO (RR, 1.10; 95% CI, 0.63–1.92; low CoE).

Finally, 4 studies provided information regarding procedural success as defined as complete LAAO. Rates of procedural success were similar between ICE-supported LAAO and TEE-supported LAAO, with ICE potentially leading to an estimated 10 more successful occlusions per 1000 patients (95% CI, 0 fewer to 10 more) than TEE (RR, 1.01; 95% CI, 1.00–1.01; low CoE). Again, the CoE was rated down due to very serious concerns of RoB and concerns about unknown and uncontrolled confounding.

Discussion

The available evidence supporting 1 particular imaging strategy for LAAO is limited, and there are no randomized studies. Furthermore, the available NRSs raise concerns about confounding due to patient selection and operator experience. However, the available data suggest there may be similar outcomes with respect to mortality, stroke, bleeding, PDL, and procedural success with either imaging technique could be used for the LAAO procedure.

Question 5

For adults with NVAF who have undergone LAAO, should clinicians prescribe postprocedural OAC vs antiplatelet therapy?

The Technical Review Panel identified 5 NRSs comparing OAC with dual antiplatelet therapy (DAPT) comprised of several large analyses from the National Cardiovascular Data Registry including over 34,000 patients (Supplemental Table S3C). Outcomes of interest were DRT, major bleeding events, stroke, and mortality (Supplemental Appendix S5). The studies were rated as having a serious RoB due to the potential for unknown, unmeasured, and residual confounding (Supplemental Table S4B).

Device-related thrombus was reported in 4 of the 5 NRSs. The rate of DRT is likely slightly higher in the DAPT group (RR, 1.40; 95% CI, 1.00–1.96; moderate CoE), but an absolute effect estimate of 1 additional DRT per 1000 patients (95% CI, 0–3 more) falls below the prespecified threshold for clinical significance. Major bleeding (RR, 1.07; 95% CI, 0.93–1.23; moderate CoE) and stroke (RR, 1.33; 95% CI, 0.97–1.81, moderate CoE) were likewise similar between groups using data from 4 NRSs and 3 NRSs, respectively. Mortality may be increased in patients receiving DAPT (RR, 1.31; 95% CI, 1.13–1.53, low CoE), although the absolute effect estimate of 8 more deaths per 1000 patients (95% CI, 3 more to 14 more) is less than the a priori threshold for clinical significance of 10 per 1000. This outcome was pooled from 3 of the 5 NRSs and rated down for imprecision.

Three NRSs compared the use of single antiplatelet therapy (SAPT) to OAC, reporting on the rates of DRT, ischemic stroke, major bleeding, and mortality (Supplemental Appendix S5). RoB was rated as extremely serious due to

the potential for unmeasured, uncontrolled, and residual confounding, as well as selection bias. There were also serious concerns with indirectness due to many patients receiving no postprocedure treatment. The overall level of certainty was low to very low.

The effect of SAPT vs OAC on the rate of DRT taken from 3 NRSs at up to 6 months of follow-up is very uncertain (RR, 0.68; 95% CI, 0.11-4.06; very low level of certainty). One study reported on ischemic stroke, and due to 0 events in the OAC group, an RR was not estimable, and the effect is very uncertain. In absolute terms, SAPT led to 8 more strokes per 1000 patients than OAC (95% CI, 7 fewer to 23 more; very low level of certainty). The rate of major bleeding at up to 12 months was reported in 2 NRSs and suffered from very serious issues with imprecision, making the effect very uncertain (RR, 0.56; 95% CI, 0.01-37.10; very low level of certainty). No deaths occurred in the SAPT group, and the absolute difference was 36 fewer deaths compared with OAC (95% CI, 36 fewer to 4 more; very low level of certainty).

The Technical Review Panel identified 4 eligible studies comparing SAPT with DAPT for adults undergoing LAEO (Supplemental Appendix S5).⁴⁰⁻⁴³ All studies were nonrandomized and conducted in Italy, with 2 studies being single-centered^{40,42} and 2 multicentered.^{41,43} One study was restricted to patients with previous intracranial hemorrhage.⁴³ The RoB was judged to be extremely serious due to unmeasured/uncontrolled confounding, residual confounding, and selection bias. There were serious concerns for indirectness as study populations combined patients who had received either SAPT or nothing postprocedure. There were serious concerns about imprecision. Overall certainty was very low.

Three of the 4 studies investigated the outcome of DRT in patients treated with SAPT vs DAPT.⁴⁰⁻⁴² Follow-up ranged from 45 days to 6 months and assessed with TEE. The rate of DRT may be higher in the SAPT group (RR, 1.47; 95% CI, 0.43-5.01; very low level of certainty), with an absolute effect of 5 more DRT events per 1000 patients (95% CI, 6 fewer to 41 more), but serious risk of imprecision makes the effect very uncertain.

From 4 included NRSs, the rate of ischemic stroke at 6 months may not differ for SAPT vs DAPT, but the effect is again very uncertain (RR, 1.12; 95% CI, 0.49-2.55, very low level of certainty).⁴⁰⁻⁴³ All 4 studies included an outcome of major bleeding, with a follow-up of 6 to 12 months.⁴⁰⁻⁴³ SAPT may increase major bleeding, but the effect is very uncertain (RR, 1.52; 95% CI, 0.33-7.03, very low level of certainty).

Three of the 4 studies included an outcome of all-cause mortality, with a range of follow-up of 6 to 12 months.⁴⁰⁻⁴² There may be no difference in mortality between groups (RR, 1.17; 95% CI, 0.6-2.09, very low level of certainty).

Discussion

PICO Question 5 comprised 3 comparisons: DAPT vs OAC, SAPT vs OAC, and SAPT vs DAPT following LAEO. Available evidence did not clearly favor either DAPT or OAC. Extremely high RoB leading to very low certainty limited any conclusions

regarding the use of SAPT vs OAC. Although SAPT may have had greater relative risks for DRT, ischemic stroke, major bleeding, and all-cause mortality in comparison to DAPT, there were serious concerns with imprecision, and certainty was again very low.

Question 6

In adults with NVAF who have undergone LAEO, should follow-up TEE or CT imaging be performed vs no follow-up TEE or CT?

The Technical Review Panel found 5 NRSs that addressed surveillance imaging after LAEO (Supplemental Table S3B).^{9,44-47} None of the 5 NRSs compared postprocedure imaging vs no imaging, so these studies were used to provide information about background rates of adverse events that may be detected with postprocedural imaging.

The primary outcomes of interest were rates of DRT assessed with TEE, risk of PDL assessed with TEE, and procedural success, which was defined as PDL of ≤ 5 mm and no other major complications. RoB was assessed as very serious due to concerns with residual and uncontrolled confounding, as well as concerns with selection bias (Supplemental Table S4B). Combined with serious indirectness, the panel rated the overall CoE for each outcome as very low (Supplemental Appendix S6).

In a registry analysis of 835 patients by Sedaghat et al, the DRT rate was found to be 4.1% for the WATCHMAN device at a median 54-day follow-up, whereas an analysis of 1088 patients by Aminian et al⁴⁴ found a DRT rate of 1.6% at 1 year for the Amulet device.

Baseline rates of PDL >5 mm with the WATCHMAN device ranged from 0.2% in a large registry analysis by Freeman et al⁹ to 3.2% as reported by Lakkireddy et al,⁴⁷ both at 45 days.¹³

Boersma et al⁴⁶ reported a complete seal in 91.4% WATCHMAN patients at 30 days, with 7.9% of patients having a PDL of ≤ 5 mm, and >5 mm leak in 0.7% of patients. Lakkireddy et al⁴⁷ also reported a PDL of >5 mm rate of 1.1% in patients receiving the Amulet device.

In Freeman's large registry analysis, the procedural success rate was 98.3%. As with the above studies, the RoB assessment was rated as very serious, and the CoE was judged to be low due to concerns about the RoB and the indirectness of the data.

Discussion

After reviewing 5 relevant NRSs, the rates of DRT and significant PDL appear low, whereas procedural success following LAEO seems high. However, the panel found no data comparing the outcomes of patients who underwent imaging vs those who did not follow LAEO, preventing them from comparing different postprocedure imaging strategies. The information from this review may help provide insights into background rates of events. Randomized controlled studies examining the outcomes of those who receive imaging compared with those who do not would be valuable. Additionally, comparative effectiveness studies between various

types of surveillance imaging modalities (ie, CT vs TEE) may also guide future practice.

Question 7

In adults with NVAf who have a PDL after undergoing LAAO, should OAC be prescribed over no OAC?

The Technical Review Panel found 1 eligible study that compared OAC to no OAC in patients with a PDL (Supplemental Table S3D).⁴⁸ This study was a retrospective analysis of patients enrolled in the PROTECT-AF trial.⁴⁹ RoB was rated as very serious due to unknown/uncontrolled and residual confounding and concerns about selection bias (Supplemental Table S4B). The panel also identified serious concerns with indirectness, as the outcomes included flows below the generally adopted threshold for a significant flow of at least 3 mm.

Additionally, there were serious concerns about imprecision due to the low number of outcome events, leading to very low CoE (Supplemental Appendix S7). In this study,⁴⁸ 449 patients underwent TEE imaging at 45 days, 6 months, and 12 months. Warfarin was discontinued at 45 days if TEE showed no longer than a 5 mm peridevice flow width, and clopidogrel was prescribed from 45 days to 6 months in addition to life-long aspirin.

Peridevice leak was categorized as minor (<1 mm), moderate (1-3 mm), or major (>3 mm). However, outcome events comparing OAC with no OAC were reported grouping together all peridevice flows of any size. Continued OAC may not result in a reduced ischemic or hemorrhagic stroke rate compared with discontinued OAC (HR, 0.85; 95% CI, 0.45-1.51; very low CoE). This translates to an absolute effect estimate of 3 fewer events per 1000 patients (95% CI, 11 fewer to 10 more) if treated with OAC.

Discussion

A single NRS was identified that investigated the impact of OAC on outcomes in patients with a residual peridevice flow following implant of a WATCHMAN device. This study finds no statistically or clinically significant impact of OAC on the outcome of stroke with any degree of peridevice flow. The certainty of the evidence from this study is judged to be very low due to issues related to bias, indirectness, and imprecision.

Question 8

In adults with NVAf who have DRT after undergoing LAAO, should indefinite OAC be prescribed over no OAC?

The Technical Review Panel found 5 eligible studies comparing OAC with no OAC for patients with DRT (Supplemental Table S3D).⁵⁰⁻⁵⁴ All 5 studies were NRSs with follow-up imaging using TEE or cardiac CT.⁵² Due to the lack of standardized diagnostic criteria, most studies define DRT as an echogenic density in contact with the device. The follow-up period ranged from 35 days to 21 months. Reported outcomes include DRT resolution assessed with TEE or cardiac CT and major bleeding. The RoB was assessed as very

serious due to both unknown/uncontrolled confounding and residual confounding, along with concerns about selection bias (Supplemental Table S4B). The CoE for each outcome was very low (Supplemental Appendix S8).

Device-related thrombus resolution was reported in 5 of the 5 selected NRSs. OAC may result in no clinically meaningful reduction in DRT resolution compared with no OAC (RR, 1.13; 95% CI, 0.90-1.41; very low level of certainty). The absolute effect was estimated at 92 more patients with DRT resolution per 1000 (95% CI, 71 fewer to 289 more), and the effect is very uncertain. The panel assessed the concern of indirectness as serious, as DRT will not necessarily cause a stroke. Furthermore, the panel had serious concerns with imprecision due to the small sample size not resulting in the optimal information size for events and 95% CI including the possibility of both important benefit and important harm.

Major bleeding was reported in 2 of the 5 studies with use of OAC therapy vs no OAC therapy for DRT. Patients who were on OAC may be at higher risk of major bleeding (RR, 1.73; 95% CI, 0.32-9.27; very low level of certainty) with 25 more bleeds per 1000 persons (95% CI, 23 fewer to 285 more bleeds). The panel rated the imprecision of this study as serious as well due to the same concerns that studies did not achieve optimal information size, and the 95% CI including the possibility of both important benefit and important harm.

Discussion

Although the point estimates suggest that treatment with OAC compared with no OAC may result in a higher rate of DRT resolution at the expense of a higher rate of bleeding, there is very low certainty regarding this finding. Since the included studies did not report on stroke rates between the 2 treatments, this represents a significant knowledge gap in our evidence review.

Several studies have reported the incidence, predictors, and outcomes associated with DRT.^{55,56} Although the link between DRT and long-term adverse events remains uncertain, there is evidence suggesting that DRT may be associated with a higher rate of stroke or transient ischemic attacks in the short-term. However, since most strokes occur in patients without DRT, the significance of DRT in this context is not yet fully understood. DRT management can be challenging because it occurs in patients hoping to avoid long-term anticoagulation. The 2023 SCAI/HRS Consensus Statement recommends that DRT be treated with OAC and continued until resolution can be documented by follow-up imaging.²⁰ However, the optimal duration of OAC therapy remains unknown.

Conclusion

Using the GRADE approach, this systematic review identified and evaluated the literature regarding the use of LAAO in adult patients with NVAf. Pooled data from multiple RCTs with low RoB provided moderate CoE that LAAO likely reduces the risk of mortality, cardiovascular mortality, and

nonprocedural bleeding compared with OAC and no difference in terms of major bleeding, any stroke, or ischemic stroke compared with OAC. However, the remaining 7 clinical questions were addressed by NRS with a multitude of concerns such as the RoB and indirectness. This review highlights the need for further studies evaluating key questions pertaining to LAAO such as the need for preprocedural imaging, use of TEE vs ICE for intraprocedural guidance, and a variety of postprocedure management issues, including imaging requirements, antithrombotic regimens, and management of PDL and DRT. Given the current evidence base and its limitations, these questions could not be addressed with a high degree of certainty. Data from this technical review informed the SCAI/HRS Guidelines for Transcatheter Left Atrial Appendage Closure.

Strengths and limitations

This technical review rigorously and transparently assesses the evidence regarding indications for LAAO, preprocedural imaging, intraprocedural imaging, and postprocedure management after LAAO (including postprocedure imaging, medical therapy, and management of PDL and DRT). Strengths of this review include a comprehensive literature search, rigorous RoB assessments, and the application of the GRADE approach to determine the certainty of the body of evidence for each outcome, considering the evidence from both randomized and NRSs.

Despite the strengths of this methodology, we would like to highlight a few limitations. First, we limited our search strategy to English or German-only peer-reviewed publications. Second, the field of LAAO is rapidly evolving, and pertinent studies have been published between the completion of this technical review and its publication. However, this is the nature of summarizing a field with technological advances, and future updates will be necessary to incorporate additional data in the coming years. Third, although numerous RCTs were available to evaluate LAAO vs OAC, the remaining clinical questions brought to the Technical Review Panel were limited by a lack of RCT evidence. Using GRADE methodology, these questions were evaluated using NRS within the limitations of the available evidence.

Areas for future research

One of the primary findings from this technical review was the lack of high-quality evidence focusing on several key questions pertinent to LAAO. While RCT evidence exists to guide the use of LAAO vs OAC for long-term prevention of stroke and systemic embolism, other issues surrounding LAAO procedures have primarily been addressed with NRSs. Prior RCTs in this space have evaluated LAAO vs OAC, and therefore, patients had to be eligible for randomization to long-term OAC to be included in those RCTs.^{6–8} However, in practice, LAAO is approved only among patients either contraindicated for long-term OAC or deemed to be at high bleeding risk on OAC. Many of these patients cannot take long-term OAC, but there is a paucity of evidence comparing LAAO to no

OAC for stroke prevention, although this clinical circumstance arises frequently. Future studies evaluating LAAO vs no OAC would be useful to confirm whether LAAO offers long-term reduction in the risk of stroke and systemic embolism among OAC-contraindicated patients.

One area of significant variability among providers and hospitals is the use of preprocedure imaging for planning LAAO procedures. Preprocedure imaging provides several advantages, including anatomic assessment of the left atrial appendage and determining its suitability for closure, exclusion of a baseline left atrial appendage thrombus, and assistance in procedural planning to select equipment and techniques that can enhance success rates and reduce procedure times. However, preprocedure imaging also leads to increased use of health care services and associated costs. Moreover, computed tomography angiography prescreening exposes patients to radiation and contrast agents, whereas TEE prescreening is an invasive procedure with a minor risk of procedural or anesthesia-related complications. Whether preprocedure imaging is advantageous for patients remains uncertain based on current evidence, emphasizing the need for prospective randomized studies on this subject.

Similarly, the optimal timing, modality, and frequency of postprocedure imaging after LAAO remains unclear. While this technical review found no RCTs comparing the use of postprocedure imaging to no postprocedure imaging after LAAO, multiple other questions remain. In prior LAAO RCTs, postprocedure imaging was routinely performed at 45 days postimplant and again at 1 year.^{6,7,10} However, recent trials and off-label protocols have used differing imaging schedules, which may forego 45-day imaging in favor of a delayed first imaging study and no imaging requirement for 1 year.⁵⁷ It is unknown whether routine 1-year imaging improves patient outcomes. Additionally, it is unclear whether imaging beyond 1 year should be considered in certain patients. Future studies evaluating these issues would be valuable to guide care of the increasing number of patients living with LAAO devices.

Postprocedure medical therapy is an area of growing interest, given the complexity of balancing bleeding and ischemic risk in a population at high risk for both bleeding and ischemic events. In real-world practice, numerous drug regimens have been used with varying success.¹⁵ Ongoing RCTs will evaluate this question in greater detail and should provide better data to guide future recommendations. However, current literature is limited.

Finally, the long-term issues of PDL and DRT warrant further investigation. Strategies that have been suggested to manage PDL vary widely and include no intervention, continued long-term OAC, and transcatheter PDL closure with various devices such as plugs or coils. There is no RCT evidence in this space, and further research is needed to understand what intervention, if any, may improve outcomes among patients with PDL after LAAO. Similarly, DRT is a potentially hazardous complication of LAAO, but there is no RCT evidence to guide management of this problem. Given

the low number of DRT events, designing RCTs for this population has obvious challenges. However, future studies, both RCTs and NRSs, should focus on the optimal intensity and duration of medical therapy to treat DRT, and the optimal timing and frequency of surveillance imaging after DRT has been identified. These questions arise commonly in practice and additional data to guide clinical decision-making are needed.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.hrthm.2025.05.049>.

Declaration of competing interest: Michael E. Field discloses being the recipient of research funding from Boston Scientific. Chetan Huded discloses serving as a consultant for Boston Scientific. All other authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding sources: This work was not supported by funding agencies in the public, commercial, or not-for-profit sectors.

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