Anticoagulation for atrial fibrillation after cardiac surgery: Do guidelines reflect the evidence?

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Postoperative atrial fibrillation (POAF) is common after cardiac surgery, affecting approximately 30% (range, 20%-40%) of patients.1 Typically, POAF develops between postoperative days 2 and 4; with pharmacological intervention, POAF usually resolves within 24 hours, such that approximately 90% of patients have regained sinus rhythm at discharge.2,3

Medical management of atrial fibrillation (AF) rests on 2 foundations: (1) rate versus rhythm control and (2) oral anticoagulation (OAC) to reduce the risk for stroke and thromboembolism.4,5 Our assumption has been to treat POAF similarly; nonetheless, balancing stroke and thromboembolism risks with early perioperative bleeding risk remains problematic.

CURRENT RECOMMENDATIONS

Current recommendations (Figure 1) have little consensus on OAC for POAF. The 2014 American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines recommended a Class IIA indication (level of evidence B) for anticoagulation in POAF “as advised for nonsurgical patients.”6 This recommendation was derived from the PREVENT-IV randomized trial, which evaluated prevention of saphenous vein graft failure.7 Subgroup analysis found that 25% of patients who underwent coronary artery bypass grafting (CABG) and developed POAF were discharged with OAC. However, that subanalysis was not stratified by OAC versus non-OAC, so those outcomes could not be compared.7 The significance of these findings is uncertain given the lack of POAF-focused randomized trials. The 2019 update to the 2014 guidelines did not change POAF recommendations but added a Class IC indication for patients with AF to achieve “shared decision-making” and “individualized” anticoagulation.4

The Society of Cardiovascular Anesthesiologists/European Association of Cardiothoracic Anaesthetists 2019 practice advisory issued a IIA recommendation (level of evidence B/C) for POAF OAC.8 The European Society of Cardiology/European Association for Cardio-Thoracic Surgery/European Heart Rhythm Association downgraded their 2020 recommendation from IIA-B (its 2016 level) to IIB-B,9 stating that evidence supporting OAC in patients with perioperative AF “is not very robust.” The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society guidelines issued a weak recommendation (low quality of evidence) against early anticoagulation, recommending that it be held during the first 72 hours postoperatively.10

See Commentary on page XXX.
WHAT IS THE POSTOPERATIVE ATRIAL FIBRILLATION–RELATED RISK FOR STROKE?

Understanding stroke risk in POAF requires knowing the number needed to treat (NNT) or number needed to harm (NNH) for a given therapy. Many risk factors associated with postoperative stroke (increasing age, renal insufficiency, hypertension, cerebrovascular disease, valvular heart surgery) are also associated with POAF.

Early stroke occurs in-hospital or within 30 days of surgery; among early strokes, *intraoperative* strokes are already apparent as the patient awakens from anesthesia, whereas early stroke that develops later in the index admission is termed *postoperative* stroke, implicating POAF. Late stroke develops 30 days or more postdischarge.

In a systematic review and meta-analysis of 55 studies aggregating 540,209 patients who underwent cardiac surgery, POAF incidence was 28.1%. The estimated risk for early stroke was 4.5% in the POAF group versus 2.5% in the no POAF group (absolute risk [AR] difference 2.0%, 95% confidence interval [CI], 1.28-2.89, NNH 50). Stratified by procedure, POAF incidence in 134,216 patients who underwent CABG was 25.2%; the estimated early stroke difference was 2.7% in the POAF group versus 1.3% in the no POAF group (AR difference 1.4%, 95% CI, 1.11-1.83, NNH 69). In 131,652 patients who underwent valve surgery, POAF incidence was 49.0%; the estimated early stroke incidence was 8.0% in the POAF group versus 5.3% in the no POAF group (AR difference 2.7%, 95% CI, 0.79-5.37, NNH 36).

DOES ANTICOAGULATION REDUCE POSTOPERATIVE ATRIAL FIBRILLATION–RELATED STROKE RISK?

Evidence From Systematic Reviews and Meta-Analyses

Post hoc analyses of randomized trials indicate that 20% to 45% of patients who develop POAF are discharged on OAC. Effects of OAC were investigated in 3 systematic reviews and meta-analyses that came to slightly different
conclusions (Table 1). In an analysis of 5 retrospective studies comprising 203,946 patients who underwent cardiac surgery, Neves and colleagues found that OAC was associated with lower risk for thromboembolism compared with no OAC (odds ratio [OR], 0.68; 95% CI, 0.47-0.96); treatment effect was estimated to be 6 fewer per 1000. Conversely, risk for bleeding events was higher with OAC (OR, 4.30; 95% CI, 3.69-5.02); treatment effect was estimated to be 6 more per 1000. No difference in all-cause mortality was observed. Fragno-Marques and colleagues analyzed 8 cohort studies totaling 15,335 patients and found that although OAC was not associated with lower risk for thromboembolism (hazard ratio [HR], 0.68; 95% CI, 0.40-1.15; \( P = .15 \)), it may be associated with lower all-cause mortality (OR, 0.85; 95% CI, 0.72-1.01; \( P = .07 \)). Wang and colleagues analyzed 9 observational studies of 254,200 patients with an overall 27.3% use of OAC for POAF. Thromboembolism risk was lower in patients taking OACs (relative risk [RR], 0.83; 95% CI, 0.61-0.91; \( P = .04 \)); AR reduction was 0.8%, or 2 events per 1000 patient years. Bleeding risk was higher (RR, 3.22, 95% CI, 2.82-3.68); AR increase was 0.5%, or 42 events per 1000 patient years. No difference in mortality was found (RR, 1.02; 95% CI, 0.91-1.08).

Thus, 2 analyses found a lower thromboembolism rate with OAC versus no OAC, a higher bleeding complication tradeoff, and no difference in mortality, whereas the third study showed a nonsignificant trend toward lower mortality for the OAC group but no difference in thromboembolic events. As is typical in systematic reviews of population studies, the quality of the evidence varied due to differences in clinical management patterns, timing of initiation and discontinuation of OAC, and baseline risks (eg, age, sex, type of surgery, previous stroke). For that reason, systematic reviews do not offer a clear answer as to the benefits of OAC in POAF.

Evidence From Registry Data

Large registries from Scandinavia and North America provide data on real-world use of OAC for POAF. An 8-year study of data from the Swedish SWEDHEART registry, an observational, population-based longitudinal database, found a 30% incidence of POAF (median follow-up, 4.5 years) in 24,523 patients who underwent CABG; 24% were discharged on OAC. Compared with patients who did not develop POAF, patients with POAF were at higher risk for stroke, thromboembolic events, hospitalization for heart failure, and especially recurrent AF (adjusted HR, 4.16; 95% CI, 3.76-4.50), but no difference in all-cause mortality was detected. OAC was associated with greater risk for major bleeding (adjusted HR, 1.40, 95% CI, 1.08-1.82). Follow-up analysis of this cohort stratified by CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 [doubled], diabetes, stroke [doubled], vascular disease, age 65 to 74, and sex category [female]) score revealed a low risk for ischemic stroke when the CHA2DS2-VASc score was 3 or less (0.3% for a score of 1, 0.7% for a score of 2, 1.5% for a score of 3), such that the authors recommended OAC only when the CHA2DS2-VASc score was 4 or greater (stroke risk ≥2.3%).

A direct comparison of POAF with nonvalvular AF comes from an analysis of 10,540 patients (2108 with POAF after CABG, 8432 with nonvalvular AF) from the Danish National Patient Registry. Among the POAF cohort, the OAC rate was 8.4% throughout the study; among the nonvalvular AF cohort, the initial OAC rate of 42.9% increased to more than 60% by the end of the study. Risk for thromboembolism was lower in the POAF group than in the nonvalvular AF group (18.3 vs 29.7 events per 1000 person-years; adjusted HR, 0.67, 95% CI, 0.55-0.81; \( P < .001 \)). Thus, despite significantly less OAC use in POAF, the lower thromboembolism risk suggests POAF may differ from nonvalvular AF.

An analysis of data from the Society of Thoracic Surgeons Adult Cardiac Surgery Database (STS ACSD) found that 25.7% of 166,747 patients who developed POAF after isolated CABG were discharged with OAC. The use of OAC ranged from 17% in patients with a CHA2DS2-VASc score of 0 up to 30% in those with a CHA2DS2-VASc score 5 or greater. In comparisons of the OAC and no OAC groups, the 30-day stroke readmission rate did not differ between groups (adjusted OR, 0.87, 95% CI, 0.65-1.16; \( P = .35 \)), whereas 30-day mortality (adjusted OR, 1.20, 95% CI, 1.02-1.40; \( P = .02 \)) and 30-day readmission for bleeding (adjusted OR, 4.30, 95% CI, 3.69-5.03; \( P < .001 \)) rates were higher in the OAC group.

Interestingly, more than three-fourths of the 74.3% of the no OAC group (62.8% overall) in the STS ACSD analysis were prescribed amiodarone alone at discharge, which is not a specific guideline recommendation. Prescribing patterns for amiodarone without anticoagulation at discharge varied widely across centers, ranging from 8% to 92%. Of note, amiodarone without OAC was not associated with higher risk for readmission for stroke, major bleeding, or greater 30-day mortality.

One other STS ACSD study further investigated the role of OAC for POAF. Riad and colleagues analyzed 38,936 patients who underwent CABG who developed POAF after isolated CABG were discharged with OAC. Of note, amiodarone without OAC was not associated with higher risk for readmission for stroke, major bleeding, or greater 30-day mortality.
than 5, no interaction was found among CHA2DS2-VASc score, OAC, and mortality.

These large STS ACSD studies reflecting real-world use of OAC for POAF after CABG do not show a clear clinical benefit and appear to indicate harm. Matos and colleagues18 concluded by advocating for a randomized controlled trial to help establish the optimal strategy for OAC in the POAF setting. Despite guidelines calling for shared decision-making and individualized care, the widespread heterogeneity in these studies reflects the lack of consensus within the cardiothoracic surgical community on how to apply the guidelines in clinical practice.

### TABLE 1. Observational studies included in 3 cited systematic review/meta-analyses evaluating anticoagulation and postoperative atrial fibrillation outcomes after cardiac surgery

<table>
<thead>
<tr>
<th>First author, publication date</th>
<th>Location(s)</th>
<th>Study design (study period)</th>
<th>No. of patients</th>
<th>Patient cohort</th>
<th>POAF rate</th>
<th>OAC rate</th>
<th>Systematic reviews/meta-analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butt, 201815 Denmark</td>
<td></td>
<td>Prospective cohort of a national registry (2000-2015)</td>
<td>n = 10,540</td>
<td>Isolated CABG</td>
<td>20.0%</td>
<td>8.4%</td>
<td>X X X</td>
</tr>
<tr>
<td>Butt, 201916 Denmark</td>
<td></td>
<td>Prospective cohort of a national registry (2000-2015)</td>
<td>n = 1587</td>
<td>Isolated valve surgery</td>
<td>46.7%</td>
<td>62.9%</td>
<td>X X X</td>
</tr>
<tr>
<td>Lamy, 201217 International</td>
<td></td>
<td>CORONARY Trial (2006-2011)</td>
<td>n = 4752</td>
<td>Isolated CABG</td>
<td>14.0%</td>
<td>10.0%</td>
<td>X</td>
</tr>
<tr>
<td>Matos, 202118 United States, Canada</td>
<td>Society of Thoracic Surgeons Adult Cardiac Surgery Database national registry (2011-2018)</td>
<td>n = 1,075,433</td>
<td>Isolated CABG</td>
<td>16.0%</td>
<td>25.7%</td>
<td>X X</td>
<td></td>
</tr>
<tr>
<td>El-Chami, 201019 United States</td>
<td></td>
<td>Retrospective analysis of a prospective cohort (1996-2007)</td>
<td>n = 16,169</td>
<td>Isolated CABG</td>
<td>18.0%</td>
<td>20.5%</td>
<td>X X X</td>
</tr>
<tr>
<td>Hata, 201320 Japan</td>
<td></td>
<td>Retrospective cohort (2008-2011)</td>
<td>n = 447</td>
<td>Isolated CABG</td>
<td>31.5%</td>
<td>38.4%</td>
<td>X</td>
</tr>
<tr>
<td>Marazzato, 202121 Italy</td>
<td></td>
<td>Prospective cohort (2005-2009)</td>
<td>N = 1386</td>
<td>CABG and valve (31%)</td>
<td>31.0%</td>
<td>62.0%</td>
<td>X</td>
</tr>
<tr>
<td>Nauffal, 202122 United States</td>
<td></td>
<td>Society of Thoracic Surgeons Adult Cardiac Surgery Database national registry (2017-2018)</td>
<td>Total N not reported; POAF = 73,072</td>
<td>CABG, valve, combined</td>
<td>X</td>
<td>36.3%</td>
<td>X</td>
</tr>
<tr>
<td>Taha, 202123 Sweden</td>
<td></td>
<td>Prospective cohort of a national registry (2007-2015)</td>
<td>n = 24,523</td>
<td>Isolated CABG</td>
<td>30.0%</td>
<td>24.0%</td>
<td>X</td>
</tr>
<tr>
<td>*Ahlsson, 201024 Sweden</td>
<td></td>
<td>Retrospective cohort (1991-2000)</td>
<td>n = 13,556</td>
<td>TAVR registry Isolated CABG</td>
<td>28.9%</td>
<td>3.6%</td>
<td>X</td>
</tr>
<tr>
<td>Vora, 201825 United States</td>
<td></td>
<td>Prospective cohort (2010-2017)</td>
<td>n = 13,556</td>
<td>TAVR patients</td>
<td>8.4%</td>
<td>28.9%</td>
<td>X X</td>
</tr>
<tr>
<td>Yoon, 201926 South Korea</td>
<td></td>
<td>Prospective cohort (2010-2017)</td>
<td>n = 347</td>
<td>TAVR patients</td>
<td>10.4%</td>
<td>18%</td>
<td>X</td>
</tr>
<tr>
<td>Benedetto, 202027 International</td>
<td></td>
<td>Post hoc analysis of randomized multicenter Arterial Revascularization Trial (2004-2007)</td>
<td>n = 3023</td>
<td>Isolated CABG</td>
<td>24.3%</td>
<td>8.3%</td>
<td>X</td>
</tr>
<tr>
<td>*Madsen, 202128 Denmark</td>
<td></td>
<td>Retrospective cohort of Eastern Danish Heart Registry (1996-2016)</td>
<td>n = 7944 patients with STEMI treated with percutaneous coronary intervention</td>
<td>3.7% new AF</td>
<td>38%</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

All studies were retrospective. POAF, Postoperative atrial fibrillation; OAC, oral anticoagulation; CABG, coronary artery bypass grafting; TAVR, transcatheter aortic valve replacement; STEMI, ST-elevation myocardial infarction; AF, atrial fibrillation. *Used in qualitative analysis only.
HOW SHOULD PATIENTS WITH POSTOPERATIVE ATRIAL FIBRILLATION BE ANTICOAGULATED?

Vitamin K antagonists (VKAs) have long been the cornerstone of OAC management for AF. In a large systematic review of patients with any type of AF, the mean time in the therapeutic range (TTR) was 64% (range, 25%-90%); longer TTR was associated with fewer major bleeding complications but no significant improvement in stroke or systemic embolism rates. In general AF, patients at highest risk for bleeding (those with renal dysfunction, heart failure, or previous stroke) typically had the lowest TTR rates. Moreover, patients typically spend less time in the therapeutic range during the first 3 to 6 months of VKA therapy, which has implications for those who develop POAF after cardiac surgery. We found no publications that reported TTR rates specifically for patients with POAF.

Increasingly, direct oral anticoagulants (DOACs) are used as an alternative to VKAs for AF, with similar effectiveness, less bleeding, and less need for monitoring. A systematic review analyzed 12 studies comparing DOACs with VKAs (n = 8587) for POAF: 5 randomized trials (n = 1435; 8.5% of the overall sample) and 7 observational studies (n = 15,467; 91.5% of the overall sample). The major neurological event (stroke) rate for DOACs was 0.9%, compared with 1.4% for warfarin, yielding a 37% relative risk reduction (RR, 0.63; 95% CI, 0.48-0.83; P = .01) and a 0.5% AR reduction (NNT 204). Pooled mortality was 1.7% (95% CI, 0.7-4.2) for patients receiving DOACs, with no difference in mortality between patients treated with DOACs versus warfarin (RR, 1.02; 95% CI, 0.77-1.35; P = .9). The bleeding rate was 2.1% in the DOAC group and 2.8% in the warfarin group, for a 26% relative risk reduction (RR, 0.74; 95% CI, 0.62-0.89; P = .01) and a 0.7% AR reduction favoring DOACs (NNT 143). These results suggest that DOACs may be slightly more beneficial than VKAs in patients with POAF.

KNOWLEDGE GAPS AND NEXT STEPS IN POSTOPERATIVE ATRIAL FIBRILLATION ANTICOAGULATION

The widespread heterogeneity in clinical practice reflects a high degree of uncertainty about the optimal indications for OAC in POAF. The question remains as to whether POAF is fundamentally the same as nonoperative AF or whether it is a distinct entity with different risks for stroke and bleeding, which would require a different approach, with new trials offering important insights. Increasing our understanding requires the following (Table 2).

1. High-quality prospective trials on anticoagulation for POAF. Currently, the Anticoagulation for New-Onset Post-Operative Atrial Fibrillation After CABG (PACES) trial is randomizing patients to either antiplatelet therapy alone or antiplatelet therapy with OAC, either a VKA or DOAC; accrual (n = 3200) should be completed by December 2024. Trial results are eagerly awaited to help identify the optimal role of anticoagulation for patients who have undergone CABG. Moreover, questions such as the duration of OAC, especially in patients who have returned to sinus rhythm, should be addressed. Similar trials for POAF after heart valve surgery might be considered.

2. Improved characterization of AF burden for POAF. Rather than a simple “Yes/No” to the presence of POAF, characterizing its duration, frequency, or presence/absence at discharge might better define postoperative stroke risk, helping identify patients likely to benefit from anticoagulation.

3. Better scoring tools for anticoagulation-related bleeding after cardiac surgery. Although validated scoring systems are available for assessing bleeding risk in patients with AF generally, scoring systems for anticoagulation-related perioperative bleeding may provide better guidance for clinicians. This could include factors not typically included in traditional AF bleeding risk considerations, such as reoperative surgery, duration of cardiopulmonary bypass, and concomitant antiplatelet therapy.

4. Earlier consideration of wearable technology to identify at-risk patients. Wearable devices that monitor heart rate may identify patients developing POAF postdischarge. Knowledge about POAF burden may inform decision making about initiating or continuing OAC.

CONCLUSIONS

Postoperative AF after cardiac surgery appears to be distinct from general AF and even noncardiac surgical POAF. Anticoagulation strategies should be individualized by the type of surgical procedure, bleeding risk, potentially the CHA2DS2-VASc score, and other factors. The evidence does not support a clear advantage of DOACs over VKAs. That said, the evidence base underlying published recommendations is not robust: Most recommendations are based on decidedly heterogeneous observational trials and post hoc analyses of randomized trials never designed to evaluate POAF and OAC. Ongoing clinical trials that include POAF are critically important for shedding light on optimal patient management strategies and informing the next iteration of practice guidelines.

Conflict of Interest Statement
S.C. has served on advisory boards for Edwards Lifesciences, La Jolla Pharmaceutical Company, Eagle Pharmaceuticals, and Baxter Pharmaceuticals. N.A. serves as a consultant to Medtronic, AtriCure, LivaNova USA, and Left Atrial Appendage Occlusion, LLC; and serves on advisory boards for Vascular Graft Solutions, Ltd, and CardioSight. V.B. serves as a consultant to Abbott.
TABLE 2. Knowledge gaps and next steps in understanding postoperative atrial fibrillation

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Rationale</th>
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<tbody>
<tr>
<td>High-quality prospective trials on anticoagulation for POAF</td>
<td>- Current studies have found inconsistent results on benefits of routine anticoagulation for POAF</td>
</tr>
<tr>
<td>Guideline-recommended strategies to prevent POAF</td>
<td>- Strong evidence showing that amiodarone and beta-blockers can prevent POAF</td>
</tr>
<tr>
<td>Improved characterization of AF burden for POAF</td>
<td>- Current binary approach to POAF</td>
</tr>
<tr>
<td>Better scoring tools for anticoagulation-related bleeding after cardiac surgery</td>
<td>- Well developed in patients with AF of any type</td>
</tr>
<tr>
<td>Better characterization of the role of LAA occlusion in POAF</td>
<td>- LAA occlusion in patients with AF undergoing cardiac surgery is associated with lower rates of late stroke</td>
</tr>
<tr>
<td>Better identification of candidate patients to identify at-risk patients</td>
<td>- POAF may occur outside of the hospital</td>
</tr>
<tr>
<td>Earlier consideration of wearable technology to identify at-risk patients</td>
<td>- Better identification of patients at higher risk for developing stroke and thromboembolic complications</td>
</tr>
</tbody>
</table>

POAF, Postoperative atrial fibrillation; AF, atrial fibrillation; LAA, left atrial appendage.

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References


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