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Review

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# Stroke risk and anticoagulation in the setting of post-cardiac surgery atrial fibrillation: a systematic review of the literature

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## Abstract
Postoperative atrial fibrillation (POAF) affects up to 50% of patients undergoing cardiac surgery. It remains unclear to what extent POAF increases the stroke risk and whether anticoagulation is warranted in this setting. The primary objective of this review was to conduct a systematic review of the evidence for a correlation between POAF and stroke. Further, we sought to evaluate the published evidence on anticoagulation in the setting of POAF to prevent stroke. To this end, we performed a comprehensive literature search to identify studies on POAF in patients undergoing cardiac surgery with stroke as an outcome. To date, eight meta-analyses providing pooled estimates of the stroke risk associated with POAF in patients undergoing cardiac surgery have been published. The reported pooled odds ratios range from 1.36 to 4.09 for unadjusted estimates. Additionally, five studies were identified that evaluated the impact of anticoagulation on stroke in the setting of POAF. Of these, three supported the use of anticoagulants, and two studies were inconclusive. This systematic review did not find strong supporting evidence that POAF is causally related to stroke, despite a strong correlation with comorbidities and all-cause mortality in the literature. Available evidence to date suggests an elevated risk of bleeding with no clear reduction in stroke or other thromboembolic events when anticoagulation is initiated in the setting of POAF. An upcoming randomized clinical trial by the Cardiothoracic Surgery Network group will hopefully provide clarification on the recommendations for anticoagulation in the setting of POAF after cardiac surgery.

**Keywords:** Postoperative atrial fibrillation, anticoagulation, stroke, cardiac surgery

## INTRODUCTION

Patients undergoing cardiac surgery commonly develop postoperative atrial fibrillation (POAF)[1,2]. The exact pathophysiology of atrial fibrillation and its origins remains poorly understood, but an increasing body of evidence points towards an inflammatory process propagated and sustained by anatomic remodeling of the atria[3]. An inflammatory response is believed to be both a trigger for atrial fibrillation as well as a consequence of atrial fibrillation. Patients subject to cardiac surgery are exposed to a host of insults that predispose them to POAF. These include the inflammatory cascade triggered by the stress responses to perioperative physiological changes and direct tissue trauma. Direct trauma to atrial tissue results from ischemia, incisions, and other surgical manipulation, while tissue stretch due to a change in loading conditions in the perioperative period and electrolyte disturbances[4,5].

The incidence of POAF is thought to vary based on the type of procedure as well as predisposing factors. Reports show the incidence of POAF ranges from approximately 20% after coronary artery bypass graft (CABG) surgery to as high as 50% after combined CABG and valve surgery, with the most significant predisposing risk factors being age, male sex, history of heart failure, peripheral arterial disease, and previous stroke[5-7].

Though often self-limited and partially preventable, it continues to significantly affect outcomes after cardiac surgery[8]. POAF has been associated with an increased incidence of heart failure, reintubation, length of hospital stay, hospital costs, and long-term all-cause mortality[1,5-7]. Atrial fibrillation is strongly associated with stroke, other morbidities, and mortality in the general population[9]. This is particularly pronounced in patients with additional risk factors and has led to guideline recommendations to use oral anticoagulation in patients with atrial fibrillation persisting for 48 hours or longer[9]. Whether POAF carries the same morbidity and mortality as other atrial fibrillation due to or associated with other causes remains controversial. Robust evidence for the management of postoperative atrial fibrillation is lacking.

Here we present a systematic literature review of the association between POAF and stroke and the evidence for the use of anticoagulation in the setting of POAF to prevent stroke.

## METHODS

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were followed to perform a systematic review of the literature on the association between POAF and stroke, including the evidence for the benefits and harms of anticoagulation for the specific purpose of preventing stroke in the setting of POAF[10].

### Definitions

A major challenge in the literature is the inconsistent definition of POAF as well as methods used to detect it in all phases of care. For studies to be included in this systematic review, any definition of POAF and duration was acceptable. Clinical and imaging-based stroke definitions were permissible, including ischemic and non-ischemic strokes, disabling, non-disabling strokes, and transient ischemic attacks. All classes and any duration of anticoagulants used postoperatively studied and reported were included in this review.

### Search strategy for the identification of publications

We performed a PubMed search to identify pertinent literature on POAF and stroke as an outcome in patients undergoing cardiac surgery. The following search term was created to identify eligible publications: {("Cardiac Surgical Procedures"[Mesh] OR "heart surgery"[tiab] OR "cardiac surgery"[tiab]) AND ("Atrial Fibrillation"[Mesh] OR "atrial fibrillation"[tiab]) AND "postoperative" AND "anticoagulation" NOT "percutaneous"[tiab] NOT "transcatheter"[tiab]} OR {("Cardiac Surgical Procedures"[Mesh] OR "heart surgery"[tiab] OR "cardiac surgery"[tiab]) AND ("Atrial Fibrillation"[Mesh] OR "atrial fibrillation"[tiab]) AND "postoperative" AND "stroke" NOT "percutaneous"[tiab] NOT "transcatheter"[tiab]}. We included English-language studies published any time through July 2021, the last month studied. Peer-reviewed journal papers and conference proceedings papers were included; extended abstracts were excluded. Additionally, we evaluated bibliographies of retrieved studies.

## RESULTS

### Evidence on POAF and stroke

Our initial literature search yielded 889 articles, of which 199 were reviewed in more detail to compile evidence on the association between POAF and stroke. A large number of retrospective and some prospective, observational studies have focused on this association. In addition, several randomized-clinical trials designed to evaluate the safety and efficacy of various interventions to prevent POAF has also reported on postoperative strokes stratified by incident POAF. That data should also be considered observational. Over the last decade, there have been 8 meta-analyses [Table 1] providing pooled estimates of the stroke risk associated with POAF in patients undergoing cardiac surgery[11-18]. Five meta-analyses were published within 12 months of our literature search[14-18]. The included studies in the meta-analyses to obtain pooled estimates vary considerably. However, the association of POAF with an elevated risk of stroke is directionally (qualitatively) consistent across all studies [Table 1 shows pooled odds ratios (OR) ranging from 1.62 to 4.09].

In 2013, Hernandez *et al.*[11] reported on the association of obesity and POAF in 18 studies and included a subgroup analysis of 10 studies that also reported cumulative incidence of stroke during follow-up. The pooled OR for stroke was 1.77 (1.36-2.31). In 2017, Megens *et al.*[12] conducted a meta-analysis of studies on the association of POAF and long-term stroke in patients undergoing CABG. Long-term stroke was defined as stroke after 6 months or greater following CABG with a median follow-up period of 2.05 years. Outcomes were pooled on the log-ratio scale using a random-effects model and reported as exponentiated effect-sizes. They reported a pooled estimate for the OR of the cumulative incidence of stroke during follow-up of 1.36 (1.12-1.65), including 16 studies. In a separate analysis, the authors also pooled adjusted risk estimates reporting a pooled effect estimate of 1.25 (1.09-1.43). The level of adjustment varied considerably between the studies and resulted in inconsistent changes in the effect estimate compared to the unadjusted estimates[12].

The next meta-analysis was published in 2019 by Lin *et al.*[13] included only 8 studies on patients undergoing CABG and/or valve procedures and one non-cardiac surgery study on the association of POAF and stroke. Further, they divided studies based on stroke occurrence within the first 30 days after surgery or thereafter. The pooled estimate for the 30-day stroke OR was 1.62 (1.47-1.80) (6 studies), and lower at 1.37 (1.07-1.77) for the follow-up after 30 days (4 studies).

The remaining 5 meta-analyses were all published within 12 months of our literature search. Kerwin *et. al*[14] included 12 studies in an unadjusted OR analysis [pooled OR 2.15 (1.82-2.53)] in patients after CABG, and 3 studies for a pooled estimate of adjusted OR for stroke [1.88 (1.02-3.46)]. Woldendorp *et al.*[15] published

**Table 1. Unadjusted estimates: Reported unadjusted estimates of association between POAF and stroke in eight separate meta-analyses. Characteristics of pooled primary studies used to obtain these estimates are also described**

| Year & Name | Population | Included studies | Total subjects | Pooled estimate & CI | Average time to follow-up for creating estimate |
|---|---|---|---|---|---|
| Hernandez *et al.*[11], 2013 | CABG, Valve, CABG + Valve | 10 | 17,127 | OR 1.77 (95%CI: 1.36-2.31) | not reported |
| Megens *et al.*[12], 2017 | CABG, CABG + Valve | 13 | 108,711 | ES 1.36 (95%CI: 1.12-1.65) | 2.05 years |
| Lin *et al.*[13], 2019 | CABG, Valve, CABG + Valve | 6 | 33,319 | OR 1.62 (95%CI: 1.47-1.80) | 30 days |
| Kerwin *et al.*[14], 2020 | CABG | 12 | 89,498 | OR 2.15 (95%CI: 1.82-2.53) | not reported |
| Woldendorp *et al.*[15], 2020 | CABG, Valve, Other Cardiac | 61 | 239,018 | OR 2.29 (95%CI: 1.97-2.66) | 30 days |
| Caldonazo *et al.*[18], 2021 | Any cardiac surgery | 57 | 246,340 | OR 2.17 (95%CI: 1.90-2.49) | 30 days |
| Chau *et al.*[17], 2021 | CABG | 3 | 28,003 | RR 1.57 (95%CI: 1.27-1.95) | 4.79 years |
| Eikelboom *et al.*[16], 2021 | CABG, CABG + Valve | 4 | 9,072 | OR 4.09 (95%CI: 2.49-6.72) | 6.1 years |

the arguably most comprehensive analysis of the association of POAF and stroke in patients undergoing cardiac surgery. The unadjusted, pooled OR for stroke during follow-up in this study is 2.29 (1.97-2.66) and derived from 61 studies. No confounder-adjusted estimate was reported in this meta-analysis. A 2021 study by Eikelboom *et al.*[16] reported an unadjusted, pooled OR estimate from 4 studies on patients undergoing CABG and/or valve procedures, that is significantly higher [4.09 (2.49-6.72)] compared to the other meta-analyses. And Chau *et al.*[17] (2021) included 3 studies of patients undergoing CABG and reported a pooled OR estimate of 1.57 (1.27-1.95). Finally, Caldonazo *et al.*[18] reported their pooled estimate for the unadjusted OR for stroke in patients with POAF at 2.17 (1.90-2.49), including 57 studies in patients undergoing cardiac surgery.

Several published studies on POAF and stroke were not included in the meta-analyses cited above. A notable example is a report from the SWEDHEART registry on this topic. SWEDHEART is an observational, nationwide, population-based, longitudinal registry-based cohort study including all Swedish residents > 18 years receiving cardiovascular care. This study included 24,523 patients with no previous history of atrial fibrillation, no taking anticoagulation preoperatively, undergoing first-time CABG. Thirty percent developed POAF (within 30 days of the index procedure)[19]. At 5 years follow-up, POAF was associated with an increased risk of ischemic stroke [HR 1.18 (1.05-1.32)] after adjustment for variables differentiating them from the group without POAF.

### Evidence on anticoagulation in POAF to prevent stroke

The evidence for anticoagulation in the setting of POAF is relatively sparse. We identified 5 studies evaluating the impact of anticoagulation on stroke in the setting of POAF [Table 2][20-24]. Of these, 3 studies had results that supported the use of anticoagulants[20-22], and two studies had inconclusive evidence or noted no adverse effects of anticoagulation[23,24].

Current guidelines[9] suggest using anticoagulation in patients with POAF are based primarily on one study (new-onset atrial fibrillation predicts long-term mortality after coronary artery bypass graft)[25] and the experience in patients with atrial fibrillation in general.

**Table 2. Articles in literature search that met inclusion criteria and discussed the use of anticoagulation in POAF**

| Year, Author | Population (Surgery) | Total Subjects | % of study population with POAF | % stroke in patients with POAF | Relative stroke risk with anticoagulation | Time to follow up for creating estimate |
|---|---|---|---|---|---|---|
| Hata *et al.*[21], 2013 | CABG | 447 | 151 (33.5%) | 12.9% in patients with two types of antiplatelets; 1.7% in patients treated with antiplatelet and warfarin | Absence of warfarin therapy in patients with POAF conferred an increased odds ratio for stroke. Odds ratio: 13.037 | Three months after surgery |
| Biancari *et al.*[24], 2013 | CABG | 1226 | 384 (31.3%) | 2.5% | Postoperative atrial fibrillation (relative risk [RR] 1.483; 95% confidence interval [CI] 1.009-2.179) was an independent predictor of stroke. All POAF patients were treated medically with an anticoagulant | Mean follow-up of 7.2 ± 4.5 years |
| Ayoub *et al.*[23], 2018 | Cardiac surgery | 61 | 61 (N/A) | 10% | No significant difference in stroke/TIA between cardiac and non-cardiac surgery (HR 3.1; 95%CI: 0.72-13.3; $P$ = 0.26). Anticoagulants given to 13% at discharge and all patients for whom AF recurred | From 30 days after hospital discharge to either the last recorded clinical encounter or until a study endpoint was met |
| Butt *et al.*[33], 2018 | CABG | 7,524 | 2108 (30.9%) | Incidence was 18.3 events per 1000 person-years for patients with POAF on OACs | HR 0.55; 95%CI: 0.32-0.95; $P$ = 0.03 | > 1 year after discharge |
| Nauffal *et al.*[20], 2021 | Cardiac surgery | 26,522 | 26,522 (N/A) | 0.2% in NOAC group, 0.3% in warfarin group | No association between type of anticoagulant and 30-day stroke/transient ischemic attack (ORNOAC/warfarin 0.94, 95%CI: 0.53-1.67) | 30 days after discharge |

The SWEDEHEART study on POAF investigated the benefit and harm of anticoagulation. For the 7368 patients with POAF, the authors also explored the prescription of oral anticoagulation and its association with stroke and major bleeding. They report a non-significant association between oral anticoagulation and stroke in patients with POAF [HR 1.08 (0.80-1.45)] and other thromboembolic events [HR 1.01 (0.77-1.33)] but a significantly increased risk of major bleeding [HR 1.40 (1.08-1.82)][19].

In a recent analysis of the Society of Thoracic Surgeons (STS) Database, Matos *et al.*[26] found that roughly 25% of patients with POAF were discharged on anticoagulation. This was not associated with lower 30-day stroke rates [adjusted odds ratio 0.87 (0.65-1.16)] but resulted in increased adjusted 30-day readmissions for major bleeding [4.30 (3.69-5.03)]. Further, among those discharged off anticoagulation, there was no significant difference in adjusted 30-day stroke rates based on amiodarone use at discharge [1.19 (0.85-1.66)]. The authors concluded that a formal RCT is needed to recommend anticoagulation in the setting of POAF.

At least three meta-analyses have investigated the association between prophylactic antiarrhythmic use and stroke in patients undergoing cardiac surgery[27-29]. Zimmer *et al.*[28] pooled estimates from 5 studies and found no effect on cerebrovascular accidents. Contrarily, Gillespie (pooling data from eight trials, 2,077 patients) suggested a significant reduction in stroke with prophylactic amiodarone compared to placebo [OR 0.47 (0.23-0.96)][29], as did a study by

Aasbo *et al.*[27], also pooling estimates from eight trials (some being the same as in the Gillespie meta-analysis), reporting an OR 0.39 (0.21-0.76).

## DISCUSSION

We present a systematic review of the literature on POAF and associated stroke risk, as well as on anticoagulation for stroke prevention in patients with POAF after cardiac surgery. Eight meta-analyses of the data on POAF and stroke were published in the last few years [Tables 1 and 3]. All of them report an increased risk of stroke to be associated with POAF. The reported pooled odds ratios range from 1.36 to 4.09 for unadjusted estimates. This is consistent with the higher short- and long-term mortality that has also been reported in the same meta-analyses and the underlying studies, respectively[15-18]. Importantly, this is strong evidence that POAF and stroke are correlated. However, it is not proof that POAF is the cause of the higher stroke incidence.

Atrial fibrillation and stroke share many risk factors, including age, smoking, hypertension, and prior stroke, among others[11,30]. Furthermore, the most studied tool to estimate the risk of stroke in patients with atrial fibrillation, the $CHA_2DS_2$-VASc score, has been found to predict the onset of POAF. A meta-analysis summarizing the data of 12 studies with over 18,000 patients suggests $CHA_2DS_2$-VASc is an independent predictor of POAF after cardiac surgery [OR 1.46 (1.25-1.72)][31]. The score consists of points for hypertension, stroke, diabetes, and peripheral vascular disease, among others. In this context, it is evident that even a strong association between POAF and stroke is not sufficient to establish causality. In fact, it may be considered to support the notion that POAF is a *risk marker*, rather than a risk factor that warrants clinical attention and possibly further investigation during follow-up[32]. Butt *et al.*[33] reported recently from a large Danish cohort study that patients with CABG with and without POAF had similar long-term thromboembolic risk. They compared long-term outcomes between patients with POAF and matched nonsurgical patients with incident nonvalvular atrial fibrillation. Interestingly, patients with POAF after CABG had markedly better long-term outcomes than nonvalvular atrial fibrillation patients in terms of lower thromboembolic risk, lower mortality risk, and lower risk of recurrent hospitalization for AF. Other investigators have also shown that the overall rate of stroke is not statistically different between post-cardiac surgery patients with and without atrial fibrillation[34,35].

Only two meta-analyses published to date reported pooled odds ratios from adjusted estimates of the association of POAF and stroke (OR 1.25; 1.88)[12,14]. The level of adjustment is rather variable between the studies, and the meta-analyses could only include a few studies providing adjusted estimates, as most studies did not provide such information. Residual confounding remains a significant concern in the included original studies.

Historically, POAF has been thought to be associated with an increased risk of thromboembolic events and a negative impact on morbidity. To reduce the risk of stroke in the setting of POAF, some studies have suggested using anticoagulants[25,36,37]. This is also reflected in guidelines proposed for the management of POAF by the American College of Chest Physicians, the Canadian Cardiovascular Society, and the European Association for Cardio-Thoracic Surgery[38-40]. Matos *et al.*[26] found that post-CABG anticoagulation for new atrial fibrillation in the STS Database was associated with increased bleeding events, but no difference in stroke at 30 days postoperatively. In a recent review by Greenberg *et al.*[41], they conclude that the benefits of anticoagulation in POAF may lose to the risk of bleeding in patients with certain risk factors, including advanced age, uncontrolled hypertension, and history of bleeding. Similarly, a report from the SWEDEHEART study showed harm and no benefit with anticoagulation in patients with POAF[19]. Two out of three meta-analysis pooling estimates from RCT on the use of amiodarone and beta-

**Table 3. Adjusted estimates: Reported adjusted estimates of association between POAF and stroke in the same eight meta-analyses presented in Table 1**

| Year & Name | Population (surgery) | Included of studies | Total subjects | Pooled estimate & CI | Time to follow up for creating estimate |
|---|---|---|---|---|---|
| Megens *et al.*[12], 2017 | CABG, CABG + Valve | 16 | 108,711 | ES 1.25 (95%CI: 1.09-1.42) | 2.05 years |
| Kerwin *et al.*[14], 2020 | CABG | 3 | 15,102 | OR 1.88 (95%CI: 1.02-3.46) | Not reported |

blockers for the prevention of POAF suggested a reduced stroke incidence with these drugs. It remains unclear from these meta-analyses, and the respective RCT, whether this effect is attributable to a lower POAF burden or rather other effects of these drugs on the stroke risk. All pharmacological interventions used for the prevention of POAF have effects on the heart rate and blood pressure that could also reduce the stroke risk overall.

An upcoming trial by the Cardiothoracic Surgery Network group will address the question of anticoagulation in patients with POAF after cardiac surgery. This will be a randomized study comparing anticoagulation (warfarin or direct oral anticoagulants) with antiplatelet therapy, the Anticoagulation for New-Onset Post-Operative Atrial Fibrillation After CABG (PACES) (NCT04045665). This trial should provide more definitive answers regarding the benefit or absence of anticoagulation in patients with POAF; it is less likely that it will contribute significant new information on whether POAF is the cause of cerebrovascular incidents or rather is an intermediate variable in the causal association of comorbidities and stroke. While awaiting new evidence, it may be reasonable to consider anticoagulation for patients with POAF at low risk for bleeding complications, and not use it in those with high risk of bleeding, weighing both conflicting evidence and current guidelines.

## CONCLUSION

In summary, this systematic review did not find strong supporting evidence that POAF is causally related to stroke. However, substantial evidence exists for the said association, and several lines of evidence suggest that interventions known to lower cardiovascular risk overall may reduce long-term stroke risk, especially in high-risk individuals. An upcoming randomized clinical trial will hopefully provide a more definitive answer to whether anticoagulation in the setting of POAF provides benefits.

## DECLARATIONS

### Authors' contributions

Writing of the manuscript: Rademacher N, Spellman C, Wyler von Ballmoos MC, Almassi GH
Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Wyler von Ballmoos MC, Rademacher N, Spellman C
Contributed to the conception of the study: Almassi GH

### Availability of data and materials

Not applicable.

### Financial support and sponsorship

None.

### Conflicts of interest
All authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate
Not applicable.

### Consent for publication
Not applicable.

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