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Anticoagulation use in perioperative atrial fibrillation after noncardiac surgery: a systematic review and meta-analysis

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Summary

BACKGROUND: Perioperative atrial fibrillation is associated with an increased risk of stroke, myocardial infarction, and death after noncardiac surgery. Anticoagulation therapy is effective for stroke prevention in nonsurgical atrial fibrillation, but its efficacy and safety in perioperative atrial fibrillation are unknown.

METHODS: We searched MEDLINE, EMBASE, and CENTRAL from database inception until January 2022. We included studies comparing anticoagulation versus no anticoagulation use in patients with perioperative atrial fibrillation after noncardiac surgery. Our study outcomes included stroke ± systemic embolism, bleeding, mortality, myocardial infarction, and venous thromboembolism. We pooled studies using fixed-effects models. We reported summary risk ratios (RRs) for studies reporting multivariable-adjusted results.

RESULTS: Seven observational studies but no randomised trials were included. Of the 27,822 patients, 29.1% were prescribed therapeutic anticoagulation. Anticoagulation use was associated with a lower risk of stroke ± systemic embolism (RR 0.73; 95% CI, 0.62–0.85; I^2 = 81%; 3 studies) but a higher risk of bleeding (RR 1.14; 95% CI, 1.04–1.25; 1 study). There was a lower risk of mortality associated with anticoagulation use (RR 0.45; 95% CI, 0.40–0.51; I^2 = 80%; 2 studies). There was no difference in the risk of myocardial infarction (RR 2.19; 95% CI, 0.97–4.96; 1 study). The certainty of the evidence was very low across all outcomes.

CONCLUSION: Anticoagulation is associated with a reduced risk of stroke and death but an increased risk of bleeding. The quality of the evidence is very poor. Randomised trials are needed to better determine the effects of anticoagulation use in this population.

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Introduction

Perioperative atrial fibrillation is the most commonly encountered arrhythmia after noncardiac surgery, with its incidence ranging between 5 and 12% [1]. Many clinicians regard perioperative atrial fibrillation as a transient and self-isolated clinical phenomenon [2]. However, recent studies have demonstrated that perioperative atrial fibrillation is associated with an increased risk of stroke, myocardial infarction, and death [3–5].

Oral anticoagulation reduces the long-term risk of ischemic stroke and systemic embolism in patients with atrial fibrillation diagnosed outside of the perioperative setting [6]. In contrast, the efficacy of anticoagulation for preventing stroke and systemic embolism has not been well established for patients with perioperative atrial fibrillation after noncardiac surgery. Oral anticoagulation prevents cardioembolic strokes in patients with clinical atrial fibrillation by inhibiting intracardiac thrombus formation [7]. If perioperative atrial fibrillation represents the first manifestation of clinical atrial fibrillation, oral anticoagulation may reduce the risk of future adverse outcomes. However, it is possible that the increased risks associated with perioperative atrial fibrillation simply reflect a higher burden of cardiovascular disease in this population and that anticoagulation is not expected to be effective in this setting [4]. Even if oral anticoagulation can effectively prevent arterial thromboembolism after perioperative atrial fibrillation, such benefits need to be carefully weighed against any increased risk of bleeding. Clinicians, therefore, remain uncertain about whether these medications should be routinely prescribed in this setting.

To address some of these uncertainties, we conducted a systematic review and meta-analysis assessing the efficacy and safety of anticoagulation use in patients with perioperative atrial fibrillation after noncardiac surgery.

Methods

We reported this systematic review and meta-analysis according to the Meta-analyses of Observational Studies in Epidemiology (MOOSE) reporting guidelines [8]. We registered the study protocol with PROSPERO (CRD42021257115).

Search methods

We identified relevant studies through a systematic literature search of MEDLINE, EMBASE, and CENTRAL from the time of database inception until January 25, 2022. Our search strategy combined keywords and terms related to surgery, atrial fibrillation, and anticoagulation (supplemental methods S1). We identified additional articles by reviewing reference lists from relevant studies and consulting experts in the field.

Study selection and outcome assessment

We considered cohort studies, case-control studies, and randomised controlled trials to be eligible for inclusion. We included studies if they (1) had patients undergoing noncardiac surgery; (2) reported one or more of the prespecified outcomes in patients with a comparison without anticoagulation use after surgery; (3) included ≥100 participants with perioperative atrial fibrillation; and (4) included patients ≥18 years of age. Studies reporting data on patients with perioperative atrial fibrillation after cardiac surgery were included in a separate systematic review [9]. We excluded studies published only as meeting abstracts. We did not exclude studies based on publication language. We conducted screening and full-text reviews independently and in duplicate and resolved discrepancies either through consensus or by consulting with a third independent reviewer. We defined the use of anticoagulation therapy as any anticoagulation drug prescribed at doses considered therapeutic for the treatment of stroke and systemic embolism. We chose to use a broad definition of anticoagulation therapy, as there are multiple options to treat clinical atrial fibrillation, and there is no consensus on the optimal type of drug or drug formulation that should be used to treat perioperative atrial fibrillation. We included therapeutic doses of anticoagulation, as subtherapeutic doses should not be used for stroke prevention in patients with clinical atrial fibrillation.

The main outcomes of interest were stroke, with or without systemic embolism, and bleeding. Acceptable definitions of stroke include any stroke, ischemic stroke, or embolic stroke. We accepted any definition of bleeding used by the individual study authors. Other study outcomes included all-cause mortality, myocardial infarction, and venous thromboembolism.

Data extraction

We performed the data extraction independently and in duplicate using standardised forms. We collected information on the study design, sample size, types of surgical procedures, baseline demographics, study definitions (i.e., perioperative atrial fibrillation, anticoagulation use, and study outcomes), number of perioperative atrial fibrillation patients with and without anticoagulation use, reported associations between anticoagulation use and outcomes, and covariates used for multivariable adjustment. We contacted the study authors to obtain unpublished data and to clarify the number of participants and outcome events.

Assessment of the risk of bias and certainty of the evidence

We used the Risk of Bias in Non-randomized Studies – of Interventions (ROBINS-I) tool to assess the risk of bias for nonrandomised studies [10]. The tool assesses seven bias domains and views each study as a hypothetical randomised controlled trial. We completed risk of bias assessments independently and in duplicate and resolved disagreements either through consensus or by consulting with a third independent reviewer.

We used the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework to assess the certainty of the evidence [11]. The tool was used to apply an overall rating to the body of evidence for each outcome of interest. The major domains of GRADE are risk of bias, imprecision, inconsistency, indirectness, and publication bias. Evidence is graded as very low, low, moderate, or high certainty of evidence. By definition, evidence from nonrandomised data starts with low certainty in the GRADE framework.

Statistical analysis

For our main analyses, we included only observational studies reporting multivariable-adjusted data. We estimated pooled risk ratios (RR) and their corresponding 95% confidence intervals (CIs) using the inverse variance method. Because several of the included studies were large and deemed to be of greater trustworthiness, and only a small number of studies were included in each of the main analyses, we chose to use fixed-effects models [12, 13]. We used tests of interaction to determine whether the summary results differed between studies with and without multivariable adjustments. When no significant differences were found, we additionally reported the pooled RR across both adjusted and unadjusted studies for each outcome. We quantified between-study statistical heterogeneity using the I^2 value. Heterogeneity was considered to be important when I^2 was >30% [14]. We calculated absolute risk differences (ARDs) and their corresponding 95% CIs for each outcome using the methods described in the Cochrane Handbook for Systematic Reviews of Interventions [15]. We estimated the baseline absolute long-term risk of events using the most representative data available from patients with perioperative atrial fibrillation.

We performed subgroup analyses of studies with multivariable adjustment at low or moderate versus high or critical risk of bias. For the outcome of stroke ± systemic embolism, we performed a sensitivity analysis excluding studies with multivariable adjustments that defined stroke as total stroke (i.e., included non-ischemic strokes). We also performed sensitivity analyses using random-effects

models for each outcome. We conducted all analyses using Review Manager (Cochrane Collaboration), version 5.4. Analyses were two-tailed with statistical significance set at $P < 0.05$.

Results

Study selection

We identified 21,212 unique citations through database searches. After reviewing the full text of 167 articles and undertaking consultations with field experts, 7 nonrandomised studies (including 1 unpublished analysis from the POISE trials) met our eligibility criteria [4, 16–21]. No randomised controlled trials were identified. A flow diagram of the study selection process is shown in supplemental figure S1. Of the 27,822 participants with perioperative atrial fibrillation included, 29.1% reported using anticoagulation after surgery. Three of the included studies provided multivariable adjusted results [4, 17, 18], of which 3 reported stroke ± systemic embolism, 2 reported mortality, 1 reported bleeding, and 1 reported myocardial infarction. No studies reported the risk of venous thromboembolism.

We contacted and received clarifications on the number of participants receiving anticoagulation from 1 study author [21] and the number of events from 1 study author [19]. We obtained the original study data from the POISE-1 and POISE-2 trials and conducted a combined observational analysis consisting of patients with perioperative atrial fibrillation using multivariable Cox regression analyses (supplemental methods S2) [4, 22–24].

Study characteristics

The main characteristics of the 7 included studies are outlined in table 1. Additional study characteristics are available in supplemental table S1. The average participant age was 75 years (SD 10.1), and 53.1% were female. Studies included patients undergoing noncardiac surgery (5 studies), thoracic surgery (1 study), and lung transplantation (1 study). All 3 studies reporting multivariable adjusted results reported long-term patient outcomes, with an average follow-up time of 4.1 years (range 0.7 to 4.3). Of the patients who received anticoagulation in these 3 studies, 99.9% were given an oral formulation of anticoagulation.

The diagnosis of perioperative atrial fibrillation was determined by retrospective chart review in 4 studies, International Classification of Diseases (ICD) codes from administrative databases in 2 studies, and prospective data collection from a randomised trial in 1 study. No studies included patients with preoperative atrial fibrillation. Postoperative anticoagulation status was determined at hospital discharge in 4 studies, during index hospitalisation in 2 studies, and within 30 days after discharge in 1 study. Anticoagulation use after discharge was assessed by 2 of the 5 studies reporting long-term outcomes [25, 26]. For the outcome of stroke ± systemic embolism, 2 studies reported a composite of ischemic stroke and systemic embolism, 2 studies reported stroke but did not provide an outcome definition, 1 study reported a composite of ischemic stroke and transient ischemic attack, and 1 study reported total stroke. For the outcome of bleeding, 1 study included multiple specific types of bleeding (i.e., intracranial, gastrointestinal, intra-ocular, haematuria, haemoptysis, epistaxis) [18], 1 study included events adjudicated as Bleeding Academic Research Consortium type 3 bleeding [19], and 1 study did not specify the definition of bleeding [20].

Table 1:
Baseline characteristics of the 7 included studies. Baseline characteristics are presented as anticoagulation group / no anticoagulation group where available.

Author	Year	Country	Type of Surgery	Surgery N	POAF N (%)	POAF Definition	Postoperative medications		CHADS2 Score	CHA_2DS_2-VASc Score	Follow up
							AC Use %	ASA Use %			
Barnes	2020	Australia	Lung transplantation	394	100 (25.4%)	Sustained atrial fibrillation confirmed by 12 lead ECG, causing symptoms, and occurring within 30 days of surgery	39.0	–	–	–	30 days
Butt	2018	Denmark	Noncardiac	1,520,109	3830 (0.3%)	Primary or secondary discharge diagnosis of atrial fibrillation during index hospitalisation by ICD 8 or 10	–	23.7	1.4	3.0	3.2 years
Elharram	2020	Canada	Noncardiac	–	22,007	Secondary diagnosis of atrial fibrillation or atrial fibrillation coded as complication of admission by ICD 9 or 10	29.4	26.2 / 46.2	–	–	4.3 years
Hyun	2021	South Korea	Noncardiac	322,688	315 (0.1%)	Atrial fibrillation diagnosed using ECGs as adjudicated by two authors, occurring before hospital discharge (up to 90 days after admission)	26.2	46.2	–	3.0 / 2.1	Up to 2 years
Makhija	2011	United States	Thoracic	–	759	Atrial fibrillation for >1 hour with ECG documentation; all patients were continuously monitored for 24 hours after surgery within 30 days of surgery or during the index hospitalisation	30.0	30.5 / 17.7	1.3 / 1.1	–	Up to 30 days or during index hospitalisation
POISE 1 & 2	–	International	Noncardiac	18,361	404 (2.2%)	Atrial fibrillation that resulted in angina, congestive heart failure, or symptomatic hypotension, or that required treatment with a rate controlling drug, antiarrhythmic drug, or cardioversion	14.6	–	2.2 / 1.8	4.0 / 3.6	Up to 1 year
Siontis	2020	United States	Noncardiac	–	452	Atrial fibrillation on ECG or rhythm strip during emergency visit, hospitalisation or echocardiogram report within 30 days of surgery	23.6	–	2	4	5.4 years

AC: anticoagulation; ASA: acetylsalicylic acid; CABG: coronary artery bypass surgery; $CHADS_2$ score: congestive heart failure, hypertension, age, diabetes, stroke/thromboembolism; CHA_2DS_2-VASc Score: congestive heart failure, hypertension, age, diabetes, stroke/thromboembolism, vascular disease, sex (female); ECG: electrocardiogram; POAF: perioperative atrial fibrillation

Risk of bias

Six of the seven studies were at a high or critical risk of bias. A summary of the risk of bias assessments is available in supplemental table S2.

Risk of stroke and systemic embolism

Among the studies that reported multivariable-adjusted results, the relative risk of stroke ± systemic embolism was significantly lower in patients using anticoagulation compared to those not using anticoagulation (RR 0.73; 95% CI, 0.62–0.85; p<0.0001; I^2 = 81%; 3 studies, n = 26,208). The results remained similar after pooling adjusted and unadjusted studies (RR 0.74; 95% CI, 0.64–0.86, I^2 = 69%; 7 studies, n = 27,819) (figure 1). The estimated long-term incidence of stroke ± systemic embolism was 1.2 events per 100 person-years in patients using anticoagulation versus 1.6 events per 100 person-years in patients not using anticoagulation (ARD –0.4; 95% CI, –0.6 to –0.2). The certainty of the evidence was very low and was rated down due to the presence of moderate to high statistical heterogeneity (supplemental table S3). Subgroup analyses demonstrated that a single study at moderate risk of bias had a lower relative risk of thromboembolism compared to two studies at high or critical risk of bias (P for interaction = 0.0001). The subgroup and sensitivity analyses are further detailed in supplemental table S4.

Risk of bleeding

A single study using multivariable adjustment found that patients using anticoagulation had a higher risk of bleeding than those not using anticoagulation (RR 1.14; 95% CI, 1.04–1.25; n = 22,007). The results remained similar after pooling adjusted and unadjusted studies (RR 1.15; 95% CI, 1.05–1.26; I^2 = 0%; 3 studies, n = 23,081) (figure 2). The estimated long-term incidence of bleeding was 3.8 per 100 person-years in patients using anticoagulation versus 3.3 per 100 person-years in patients not using anticoagulation (ARD 0.5; 95% CI, 0.1–0.8). The certainty of the evidence was very low and was rated down due to concerns regarding the risk of bias and the inability to assess consistency of the evidence with only a single study (supplemental table S3).

Risk of other outcomes

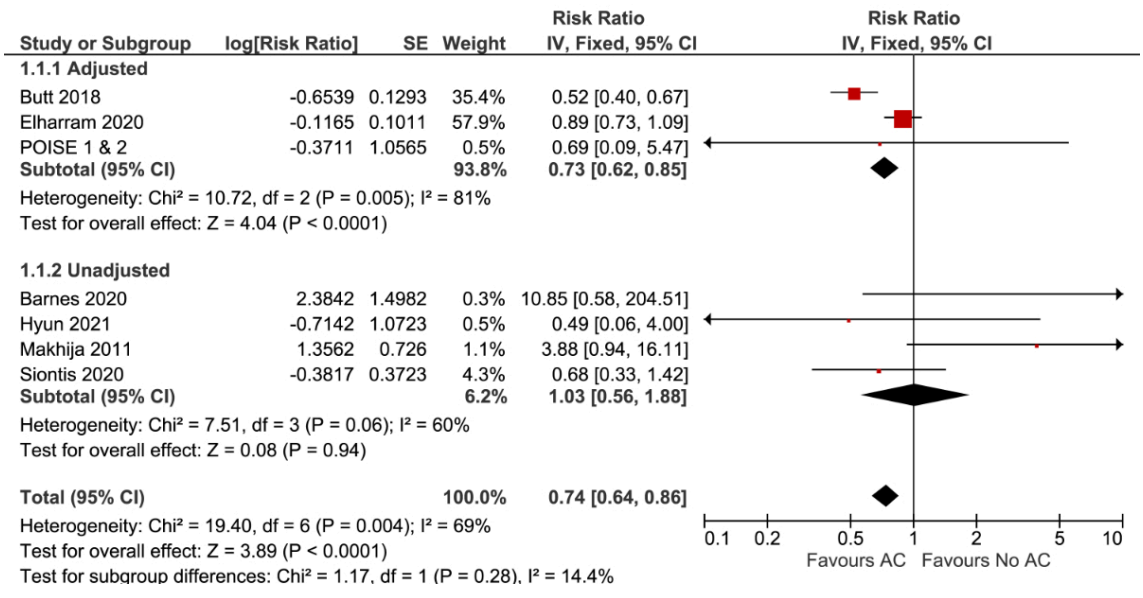
The study results for individual outcomes are summarised in table 2. Among studies reporting multivariable adjusted results, there was a statistically significant difference in mortality risk between patients with anticoagulation use compared to those without anticoagulation use (RR 0.45; 95% CI, 0.40–0.51; I^2 = 80%; 2 studies, n = 4154; very low certainty) (supplemental figure S2). A single study reporting multivariable-adjusted results found no significant difference in the risk of myocardial infarction (RR 2.19; 95% CI, 0.97–4.96; n = 364; very low certainty) (supplemental figure S3).

Discussion

In this systematic review and meta-analysis including over 25,000 participants with perioperative atrial fibrillation after noncardiac surgery, anticoagulation use was associated with a lower risk of stroke ± systemic embolism and death but a higher risk of bleeding. However, no randomised trials were identified in the review, and the overall certainty of the evidence was very low.

Patients with perioperative atrial fibrillation are sometimes prescribed anticoagulation after noncardiac surgery. Studies in our review reported that between 15 and 30% of patients are given anticoagulation shortly after perioperative atrial fibrillation, although it is likely that fewer patients continue to receive treatment during long-term follow-up. The heterogeneous uptake of anticoagulation use in this population likely reflects the fact that physicians hold differing opinions on whether perioperative atrial fibrillation is a transient postoperative phenomenon or the first manifestation of clinical atrial fibrillation requiring anticoagulation based on current risk stratification schemes [27]. In the absence of high-quality evidence, clinicians are faced with a difficult decision when it comes to balancing the po-

Figure 1: Forest plot for stroke ± systemic embolism stratified by the use of multivariable adjustment. AC: anticoagulation



tential risks and benefits of using anticoagulation in this population, and it is unclear whether patients are currently being under- or overtreated for this condition. Although some international atrial fibrillation guidelines have suggested the use of anticoagulation in patients with perioperative atrial fibrillation and additional stroke risk factors [28, 29], our review found no high-quality data available to support such recommendations.

One could argue that oral anticoagulation should be prescribed with caution in this population for several reasons. First, we found that the long-term absolute risk of stroke ± systemic embolism in this population was low, with an estimated incidence of 1.2 events and 1.6 events per 100 person-years in patients with and without anticoagulation use, respectively. As the absolute risk difference appears to be relatively small, and bleeding risk is generally higher in elderly populations that are anticoagulated [30], it is possible that the risks could outweigh any potential benefits. However, high-quality data are needed to establish the net benefit-to-risk ratio of anticoagulation in this population. Second, anticoagulation may be less effective in preventing thromboembolism in patients with perioperative atrial fibrillation than in those with non-operative atrial fibrillation. Whereas oral anticoagulation reduces the long-term relative risk of thromboembolism by 62 to 73% in non-operative atrial fibrillation [31], anticoagulation only led to a 27% relative risk reduction in perioperative atrial fibrillation patients. One potential explanation for these differences is that non-cardioembolic strokes may be more common in perioperative atrial fibrillation patients than in non-operative atrial fibrillation patients, and anticoagulation is usually much less effective in these stroke types. This hypothesis is supported by the fact that perioperative atrial fibrillation and atherosclerosis share many of the same risk factors and that a strong association between perioperative atrial fibrillation and myocardial infarction has been previously observed [4]. Third, the risk of clinically important bleeding with anticoagulation use is challenging to estimate for this population due to the heterogeneous bleeding definitions used in previous studies. For example, a retrospective cohort study of more than 20,000 Canadian patients demonstrated an increased bleeding risk with oral anticoagulation use after perioperative atrial fibrillation. However, the definition of bleeding used in this study also included potential minor bleeding events, such as epistaxis. The use of administrative data also limits the interpretation of these results [18, 32]. Of the two other studies included in this review that reported bleeding risk, one included only very serious bleeding events [19], while the other did not provide a definition of bleeding [20]. Large randomised controlled trials, such as the ASPIRE-AF trial, will provide better information on the safety and efficacy of anticoagulation use in this population [33]. Until such data are available, the decision to use anticoagulation in perioperative atrial fibrillation should be carefully considered based on individual thromboembolic and bleeding risks.

Our systematic review has limitations. We identified few studies with multivariable-adjusted data, observed a substantial degree of unexplained heterogeneity, and found that several studies were at increased risk of bias. Consequently, we determined that the certainty of the evidence was very low. Most studies did not account for whether

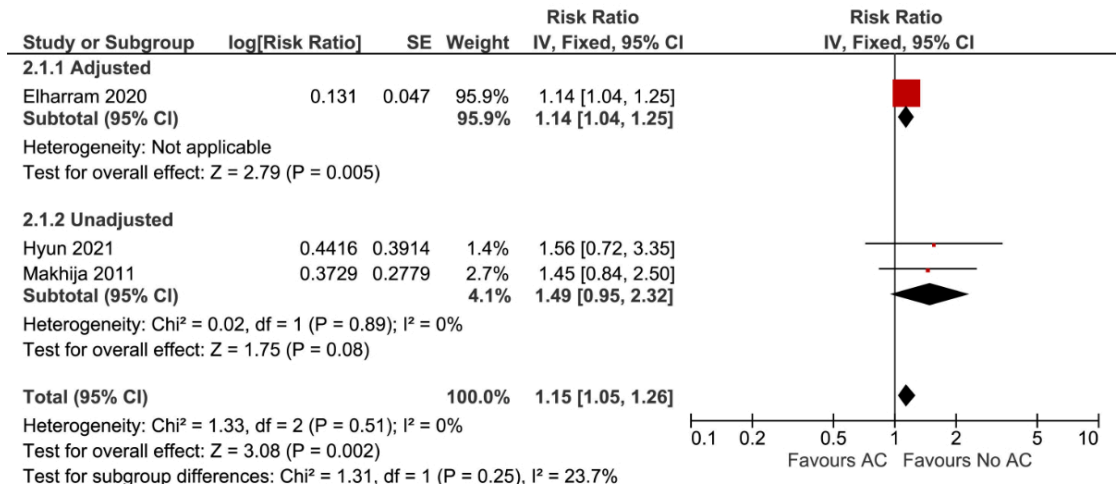


Figure 2: Forest plot for bleeding stratified by the use of multivariable adjustment. AC: anticoagulation.

Table 2:
Summary of study results.

Outcome	N of participants (N of studies)	Relative effect (95% CI)	Anticipated absolute effects in study population (95% CI) (Person-Years)			Certainty of the evidence
			Risk without anticoagulation	Risk with anticoagulation	Difference	
Stroke ± systemic embolism	26,208 patients (3)	0.73 (0.62–0.85)	1.6 per 100	1.2 per 100 (1.0 to 1.4)	0.4 fewer per 100 (0.6 fewer to 0.2 fewer)	⊕○○○ Very low
Bleeding	22,007 patients (1)	1.14 (1.04–1.25)	3.3 per 100	3.8 per 100 (3.4 to 4.1)	0.5 more per 100 (0.1 more to 0.8 more)	⊕○○○ Very low
Mortality	4154 patients (2)	0.45 (0.40–0.51)	14.8 per 100	6.7 per 100 (5.9 to 7.6)	8.1 fewer per 100 (8.9 fewer to 7.3 fewer)	⊕○○○ Very low
Myocardial Infarction	364 patients (1)	2.19 (0.97–4.96)	12.7 per 100	27.7 per 100 (12.3 to 62.7)	15.1 more per 100 (0.4 fewer to 50.1 more)	⊕○○○ Very low

anticoagulation was used beyond the early postoperative period. As it is likely that some patients had their anticoagulation discontinued over time, our risk estimates may have been underestimated. The 2 largest studies we included in our review diagnosed perioperative atrial fibrillation based on ICD codes from administrative databases. As the use of ICD codes has not been validated for the diagnosis of perioperative atrial fibrillation, diagnostic misclassification may have occurred. Patients with perioperative atrial fibrillation are sometimes prescribed single antiplatelet therapy in lieu of anticoagulation. Antiplatelet therapy may have an effect on outcomes similar to those of anticoagulation in this population. Therefore, risk estimates may have been underestimated in studies that did not account for antiplatelet use in their analyses. It is possible that there are other unpublished data apart from the POISE trials that we included. Other unpublished data, apart from the POISE trials from research groups not involved in the current meta-analysis, may exist.

Conclusion

In this systematic review and meta-analysis of patients with perioperative atrial fibrillation after noncardiac surgery, anticoagulation use was associated with a reduced risk of stroke ± systemic embolism and mortality but an increased risk of bleeding. The certainty of the evidence is very low, and the net benefit remains uncertain. Randomised trials are needed to address this frequently encountered problem after noncardiac surgery.

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Potential competing interests

Dr. Blum has received grants from the Swiss National Science foundation, the Mach-Gaensslen foundation and the Bangerter-Rhyner foundation outside the submitted work. Dr. McIntyre has received speaking fees from Bayer, Servier, and Boehringer Ingelheim, outside the submitted work. Dr. Healey has received grants and speaking fees from Abbott, BMS/Pfizer, Bayer, Boston Scientific, Medtronic, and Servier, outside the submitted work. Dr. Devereaux has received grants from Abbott Diagnostics, Boehringer Ingelheim, Philips Healthcare, Roche Diagnostics and Siemens, outside the submitted work. Dr. Devereaux has participated in advisory board meetings for Boehringer Ingelheim, Bayer and Quidel Canada, and has attended an expert panel meeting with Boehringer Ingelheim, outside the submitted work. Dr. Conen has received consultancy fees from Roche Diagnostics and Trimedics, and speaker fees from BMS/Pfizer and Servier, outside the submitted work. All other authors have no conflicts of interest to declare.

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Appendix

Supplemental methods S1. EMBASE search strategy.

1. exp atrial fibrillation/
2. atrial fibrillation.mp.
3. poaf.mp.
4. af.mp.
5. afib.mp.
6. 1 or 2 or 3 or 4 or 5
7. exp surgery/
8. exp perioperative period/
9. exp postoperative care/
10. exp postoperative complication/
11. surg*.mp.
12. periop*.mp.
13. postop*.mp.
14. operati*.mp.
15. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. exp anticoagulation/
17. exp anticoagulant agent/
18. anticoag*.mp.
19. antithromb*.mp.
20. noac.mp.
21. oac.mp.
22. warfarin.mp.
23. edoxaban.mp.
24. rivaroxaban.mp.
25. apixaban.mp.
26. dabigatran.mp.
27. lmwh.mp.
28. ufh.mp.
29. heparin.mp.
30. dalteparin.mp.
31. enoxaparin.mp.
32. tinzaparin.mp.
33. nadroparin.mp.
34. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35. 6 AND 15 AND 34
36. animals/ NOT (humans/ AND animals/)
37. meeting abstract.pt. or conference abstract.pt. or meta-analysis.pt. or review.pt. or systematic review.pt. or editorial.pt. or comment.pt. or case reports.pt.
38. 35 NOT 36 NOT 37

Supplemental methods S2. Analysis methods of unpublished data from the POISE trials.

Data Source

This is a retrospective secondary analysis of the POISE-1 and POISE-2 randomized controlled trials. The study methods, study results, and associations between perioperative atrial fibrillation (POAF) and adverse outcomes have been described elsewhere.[1-5] In brief, POISE-1 randomized 8,351 patients undergoing noncardiac surgery to extended-release metoprolol succinate or placebo. Study drug was started 2-4 hours before surgery and continued for 30 days. The primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal cardiac arrest. POISE-2 was a 2-by-2 factorial trial that randomized 10,010 patients undergoing noncardiac surgery to aspirin versus placebo for either 7 or 30 days and clonidine versus placebo for up to 72 hours after surgery. The primary outcome in both studies was a composite of death or nonfatal myocardial infarction at 30 days.

Patient Consent

Patients in the POISE-1 and POISE-2 trials gave written informed consent to participate in the respective studies.

Study Population

Adult patients were enrolled into POISE-1 and POISE-2 if they met all of the following inclusion criteria: (1) undergoing noncardiac surgery; (2) 45 years of age or greater; (3) expected to require at least a 24-hour (for POISE-1) or an overnight (for POISE-2) in-hospital stay after surgery; (4) met one of several high cardiovascular risk eligibility criteria.

Patients enrolled in POISE-1 and POISE-2 were included in the current analysis if all the following criteria were met: (1) Documented POAF within 30 days after surgery; (2) POAF that was either symptomatic or required acute treatment (i.e., rate and/or rhythm control use); (3) no history of pre-operative AF. The index date was defined as the date of POAF occurrence.

Exposure, Outcomes, and Post-Discharge Oral Anticoagulation Use

POAF events were documented by research assistants during the index hospitalization. Stroke, myocardial infarction, and death were documented during the index hospitalization and on each follow-up visit. Patients were followed for up to 1 year after randomization. In POISE-1, warfarin use was documented on discharge. In POISE-2, warfarin and therapeutic non-vitamin K oral anticoagulant (NOAC) use was documented on discharge. The definition of stroke included ischemic stroke, hemorrhagic stroke, and strokes of uncertain subtype. Outcome events were reviewed by a blinded event adjudication committee.

Statistical Analysis

A complete case analysis approach was used. Patients with missing covariate data (including anticoagulation use) were excluded from the main analysis. Patients were censored at the time of the adverse outcome, time of death, or when the study end date was reached.

Cox regression analysis was used to estimate adjusted hazard ratios with 95% confidence intervals for the association between anticoagulation use and each outcome, adjusted for the CHA_2DS_2-VASc score. The CHA_2DS_2-VASc score was forced into the model. As effect modification between co-variates was not clinically anticipated, interaction terms were not tested in the model. Ties were handled using the Breslow approximation. The proportional hazards assumption was tested by assessing the statistical significance the Schoenfeld residuals test. Statistical analyses were conducted using STATA 16.0 (StataCorp LLC). All analyses were performed on a 2-sided significance level of 0.05.

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Supplemental table S1. Additional study characteristics.

a. Patient demographics and co-morbidities.

Author	Year	Age	Male sex (%)	CHF (%)	Hypertension (%)	BMI	Diabetes (%)	Stroke ± TIA (%)	ATE (%)	Vascular disease (%)	CAD (%)	PAD (%)	MI (%)	Smoker (%)
Barnes	2020	60 (9)	59	–	23	NR	8	NR	NR	NR	NR	NR	NR	NR
Butt	2018	77 [8]	42	14	30	NR	3	NR	17	NR	15	6	NR	NR
Elharram	2020	76 (9) / 75 (11)	52 / 55	21 / 17	65 / 59	NR	28 / 24	7 / 3	NR	22 / 18	37 / 37	NR	NR	NR
Hyun	2021	68 (10) / 66 (10)	56 / 67	4 / 1	62 / 48	23 (4)	33 / 24	NR	NR	22 / 18	NR	NR	NR	NR
Makhija	2011	72 [?] / 71 [?]	75 / 67	8 / 3	50 / 46	NR	14 / 13	8 / 6	NR	27 / 17	32 / 26	21 / 12	NR	71 / 71
POISE 1 & 2	-	74 (8)	62	7	76	28 (6)	25	17	NR	56	31	22	NR	22
Siontis	2020	75 [8]	52	23	77	29 [4]	29	15	NR	NR	NR	14	17	NR

Footnotes: Results are reported separately as anticoagulation / no anticoagulation, where applicable. Results are reported as mean (age) or median [IQR], where applicable. NR – not reported. ATE – arterial thromboembolism; BMI – body mass index; CAD – coronary artery disease; CHF – congestive heart failure; MI – myocardial infarction; PAD – peripheral arterial disease; TIA – transient ischemic attack.

b. Surgical subtypes.

Author	Year	Orthopedic	Abdominal	Thoracic	Vascular	Urology	Neurosurgery	Gynecology	Head and Neck	Other
Barnes	2020	0	0	100	0	0	0	0	0	0
Butt	2018	35	29	14	7	3	NR	2	1	2
Elharram	2020	26 / 22	24 / 28	30 / 29	14 / 9	10 / 14	6 / 8	2 / 2	2 / 2	<1 / <1
Hyun	2021	25 / 14	41 / 44	19 / 23	9 / 5	NR	4 / 9	1 / 1	1 / 4	0 / <1
Makhija	2011	0	0	100	0	0	0	0	0	0
POISE 1 & 2	NR	21	28	15	28	NR	NR	NR	NR	9
Siontis	2020	32	27	25	NR	8	8	NR	NR	20

Footnotes: All values are given as percentages. Results are reported separately as anticoagulation / no anticoagulation, where applicable. NR – not reported.

Supplemental table S2. Risk of bias assessed using the ROBINS-I tool.

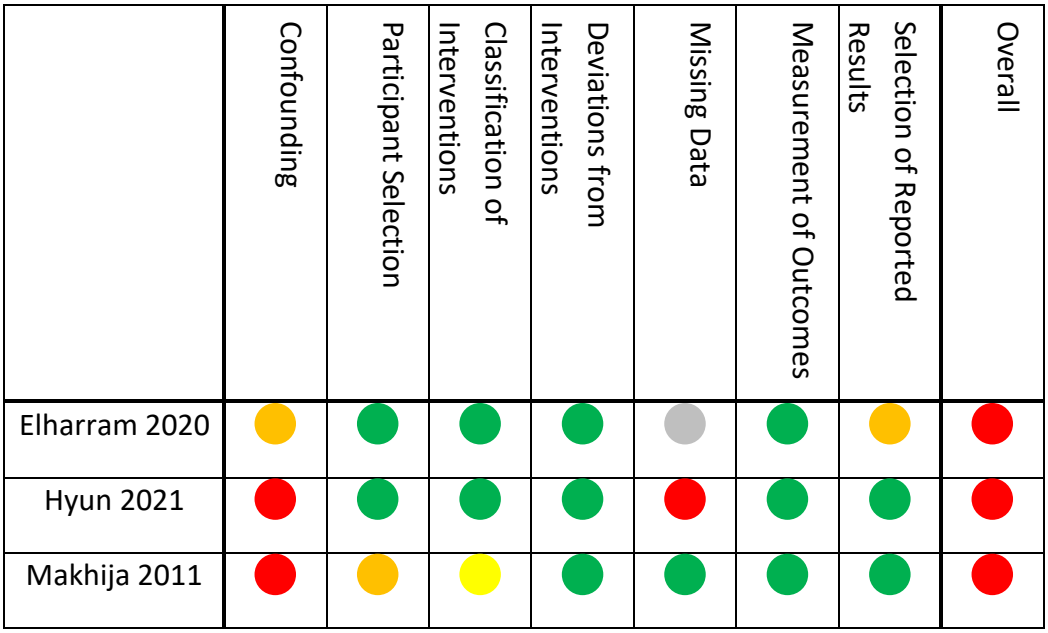
a. Risk of bias legend

Low	
Moderate	
Serious	
Critical	
No Information	

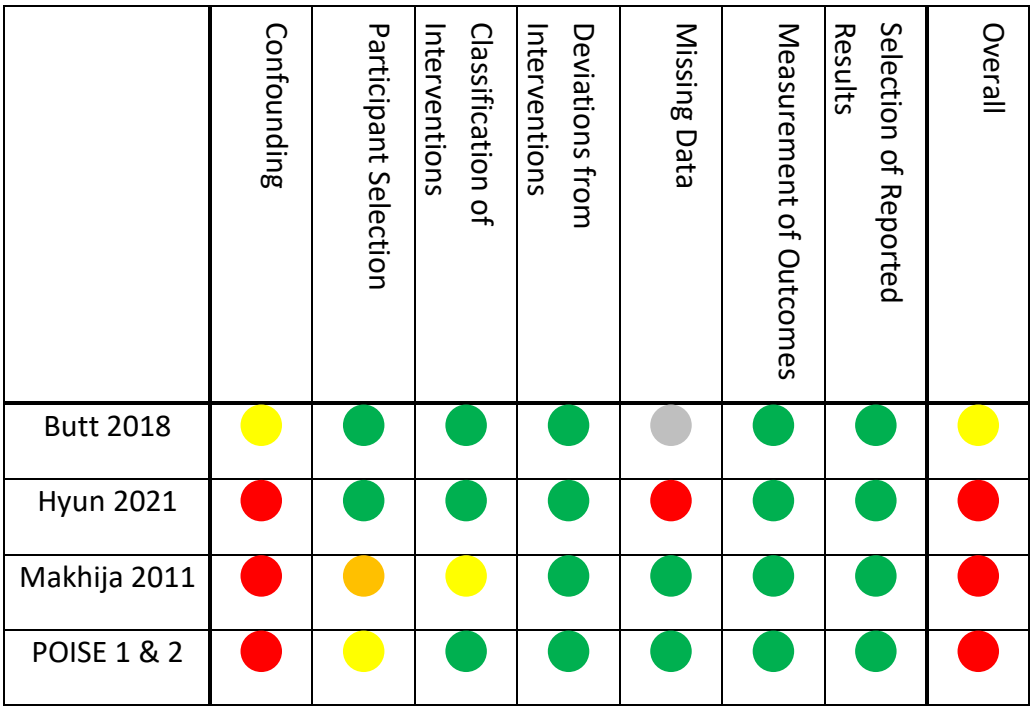
b. Stroke ± systemic embolism

	Confounding	Participant Selection	Classification of Interventions	Deviations from Interventions	Missing Data	Measurement of Outcomes	Selection of Reported Results	Overall
Barnes 2020								
Butt 2018								
Elharram 2020								
Hyun 2021								
Makhija 2011								
POISE 1 & 2								
Siontis 2020								

c. Bleeding



d. Mortality



e. Myocardial Infarction

	Confounding	Participant Selection	Classification of Interventions	Deviations from Interventions	Missing Data	Measurement of Outcomes	Selection of Reported Results	Overall
POISE 1 & 2								

Supplemental table S3. Summary of GRADE assessment.

Outcome	N of participants (studies)	Factors that may increase or decrease certainty of evidence				
		Risk of bias	Indirectness	Inconsistency	Imprecision	Other
Stroke ± Systemic Embolism	26161 patients 3 studies	Borderline [a]	No	Serious [d]	No	No
Bleeding	22007 patients 1 study	Serious [b]	No	Serious [e]	No	No
Mortality	4154 patients 2 studies	Serious [c]	No	Serious [d]	No	No
Myocardial Infarction	324 patients 1 study	Serious [c]	No	Serious [e]	Serious [f]	No

[a] Some studies conducted statistical analyses adjusting for some but not all potential confounders.
[b] The sole included study conducted analyses adjusting for some but not all potential confounders and conducted multiple analyses.
[c] Some studies had conducted analyses adjusting for few of the potential confounders.
[d] A moderate to high heterogeneity was demonstrated by the I^2 statistic.
[e] The certainty was rated down due to an inability to assess inconsistency with only one study.
[f] The optimal information size criterion was not met.

Supplemental table S4. Subgroup and sensitivity analyses.

a. Subgroup analyses for the outcome of stroke ± systemic embolism.

Subgroup	**Relative Risk (95% CI) [studies]**
High or critical risk of bias	0.89 (0.73-1.08) [2]*
Low or moderate risk of bias	0.52 (0.40-0.67) [1]*

* P for interaction < 0.0001.

b. Sensitivity analysis for the outcome of stroke ± systemic embolism.

Sensitivity Analysis	**Relative Risk (95% CI) [studies]**
Excluding studies reporting total strokes	0.72 (0.62-0.85) [2]

c. Sensitivity analyses using random-effects models for studies with multivariable adjustment.

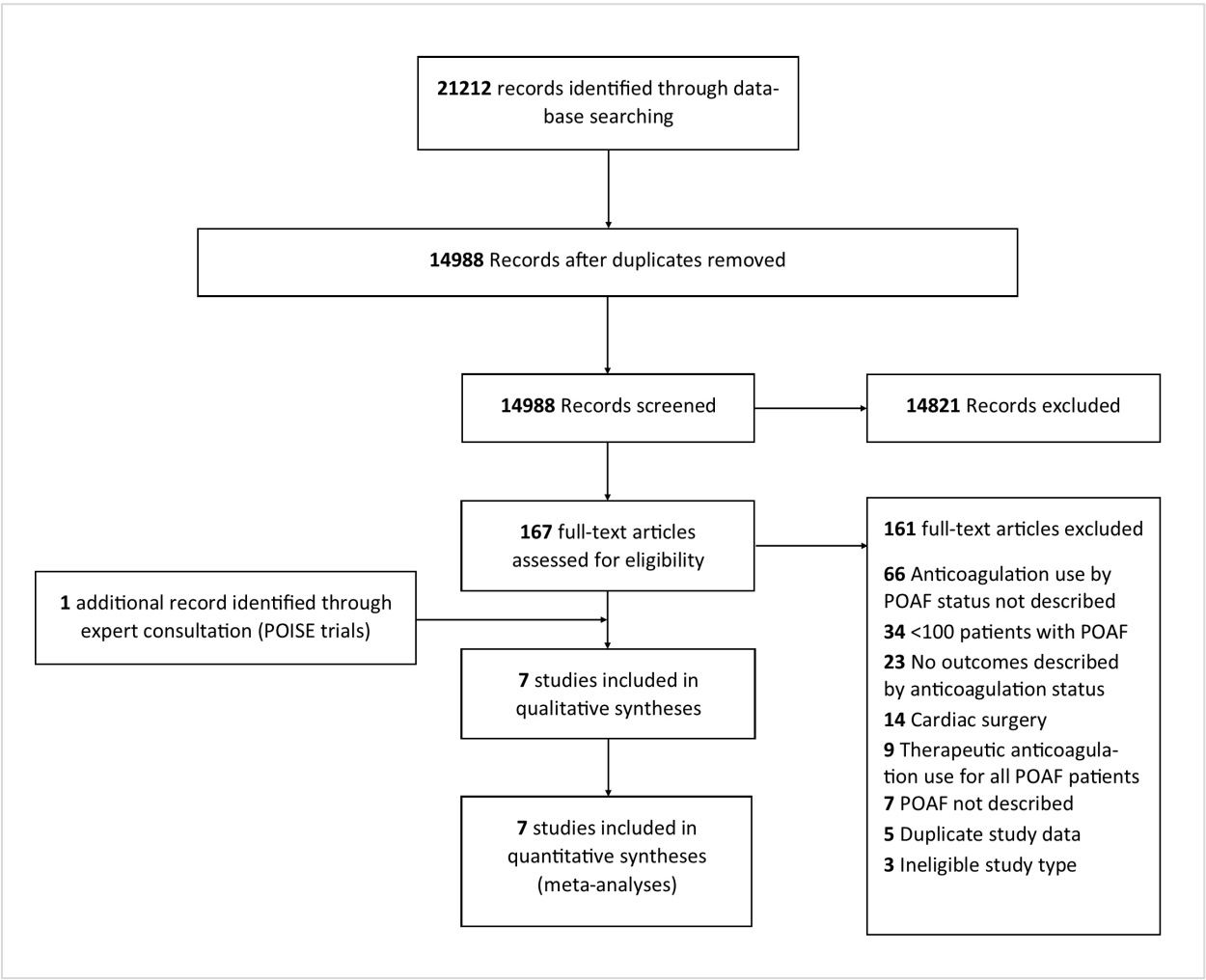
Outcome	**Relative Risk (95% CI) [studies]**
Stroke ± systemic embolism	0.69 (0.42, 1.11) [3]
Bleeding	1.14 (1.04, 1.25) [1]
Mortality	0.63 (0.27, 1.45) [2]
Myocardial infarction	2.19 (0.97, 4.96) [1]

d. Sensitivity analyses using random-effects models, pooling adjusted and unadjusted studies.

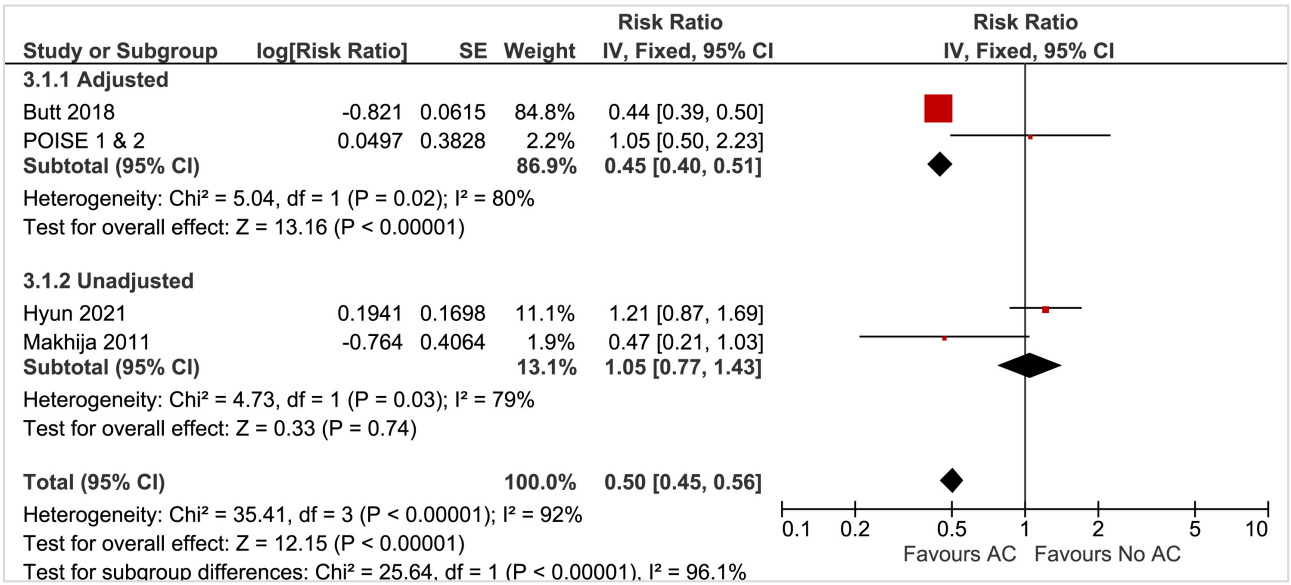
Outcome	**Relative Risk (95% CI) [studies]**
Stroke ± systemic embolism	0.82 (0.52, 1.28) [7]
Bleeding	1.15 (1.05, 1.26) [3]
Mortality	-*
Myocardial infarction	2.19 (0.97, 4.96) [1]

*Not conducted due to statistically significant subgroup differences between adjusted and unadjusted studies in the main meta-analy

Supplemental figure S1. PRISMA flow diagram.


21212 records identified through database searching
14988 Records after duplicates removed
14988 Records screened
14821 Records excluded
167 full-text articles assessed for eligibility
161 full-text articles excluded
66 Anticoagulation use by POAF status not described
34 <100 patients with POAF
23 No outcomes described by anticoagulation status
14 Cardiac surgery
9 Therapeutic anticoagulation use for all POAF patients
7 POAF not described
5 Duplicate study data
3 Ineligible study type
1 additional record identified through expert consultation (POISE trials)
7 studies included in qualitative syntheses
7 studies included in quantitative syntheses (meta-analyses)

Supplemental figure S2. Forest plot for mortality, stratified by use of multivariable adjustment.



Supplemental figure S3. Forest plot for myocardial infarction.