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Anticoagulation therapy in patients with post-operative atrial fibrillation: Systematic review with meta-analysis

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ABSTRACT

Background: Post-operative atrial fibrillation (POAF) is a relevant complication after surgery. Several studies have shown that POAF has important consequences for long-term morbidity and mortality, by increasing the risk of thromboembolic events. However, the use of oral anticoagulation (OAC) is not well established in this context.
Methods: We searched MEDLINE, CENTRAL, PsycInfo and Web of Science for clinical trials and observational studies evaluating anticoagulation vs. no anticoagulation in patients with POAF (after cardiac or non-cardiac surgery). Data were screened and extracted by two independent reviewers. We performed a random- effects model to estimate the pooled odds ratio (OR) with 95% Confidence Intervals (CI), and heterogeneity was evaluated by I^2 statistics. The outcomes of interest were all-cause mortality, thromboembolic events, and bleeding events.
Results: Overall, 10 observational retrospective studies were included: 5 studies with 203,946 cardiac surgery POAF patients, and 5 studies with 29,566 patients with POAF after non-cardiac surgery. In cardiac surgery POAF, the OAC use was associated with lower risk of thromboembolic events (OR 0.68; 95%CI 0.47–0.96, $I^2 = 31\%$; 4 studies) and the bleeding risk was significantly increased (OR 4.30; 95%CI 3.69 to 5.02, 1 study). In non-cardiac surgery POAF, OAC did not significantly reduce the risk of thromboembolic events (OR 0.71, 95%CI 0.33–1.15; $I^2 = 79\%$; 5 studies) but was associated with increased risk of bleeding (OR 1.20, 95%CI 1.10–1.32, $I^2 = 0\%$; 3 studies). Mortality was not significantly reduced in both cardiac and non-cardiac surgery POAF.
Conclusion: Oral anticoagulation was associated with a lower risk of thromboembolic events in patients with POAF following cardiac surgery but not in non-cardiac surgery. Bleeding risk was increased in both settings. The confidence on pooled results is at most low, and further data, namely randomized controlled trials are necessary to derive robust conclusions.

1. Introduction

Post-operative atrial fibrillation (POAF) is a clinically relevant complication that may occur after surgery [1,2]. Its incidence varies depending on the type of surgery, being higher after cardiac surgery, reaching around 30% of patients after isolated coronary artery bypass grafting (CABG) surgery [1–6], 40% after valve replacement or repair [1–3,5] and 50% after combined procedures [2,3,5]. The incidence of POAF after non-cardiac surgery is about 0.4% to 3% [7–9], with a higher risk after abdominal, orthopedic and vascular surgery [7,10,11]. Despite the uncertainty about the POAF management, several studies have already demonstrated that POAF is associated with several complications as greater risk of stroke [12–18], prolonged hospital stays [4,9,13,14,18] and long-term mortality [4,9,15,19].

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Several mechanisms have been suggested for pathogenesis of POAF. There best known mechanisms for AF that develops after cardiac surgery are pericardial inflammation, excessive production of catecholamines, autonomic imbalance and changes in volume, pressure and neurohumoral environment, beyond any previous structural heart disease [3]. When AF develops after non cardiac surgery, it suggests a more systemic inflammation mechanism [8]. Several risk factors were already identified to more likely cause POAF such as advanced age, male gender, hypertension, heart failure, cardiac chambers enlargement, higher body mass index (BMI) and diabetes [3,8,12]. Previous unknown paroxysmal AF may also be uncovered by surgery as shown a retrospective study in patients with cardiac devices [20].

Due to the increased risk of stroke related with AF, anticoagulation should be one of the considered measures in the management of these patients. However, the anticoagulation in the post-operative setting poses some challenges as a greater risk of bleeding is expected due to the importance of haemostasis in the internal and external scarring process [21]. Therefore, the bleeding risks in these group of patients should meticulously balanced against the thromboembolic hazards [22]. In American and European guidelines, oral anticoagulation in patients with POAF is a IIA class recommendation [23,24].

Once it is well established that the risk of thromboembolic events is similar in patients with POAF and AF, it is crucial to have more information regarding efficacy and safety of anticoagulation therapy in POAF. This is an important question because POAF is associated with increased costs due to medication and prolonged hospital stay.

In this review we intend to gather all the existing data on anticoagulation in patients with POAF and to conclude if there is a clinical impact in the prognosis of patients with this arrhythmia.

2. Methods

This systematic review was conducted and reported using PRISMA [25] and MOOSE [26] guidelines. This review was registered in PROSPERO with the following reference CRD42020183205.

2.1. Eligibility criteria

We considered eligible all longitudinal studies (clinical controlled trials and observational studies, whether prospective or retrospective) in patients with POAF, evaluating oral anticoagulation with non-anticoagulated control group. Case series (including self-controlled case series), case reports, cross-sectional studies, reviews and commentaries were not included. Studies/data comparing different schemes of anticoagulation were also excluded.

The outcomes of interest were all-cause mortality, thromboembolic events (defined as stroke of systemic embolism; if studies reported only stroke we included the data in this outcome) and bleeding events (preferentially major bleeding according to the International Society of Thrombosis and Haemostasis definitions [27,28], or a defined by investigators).

2.2. Information sources and search strategy

We searched MEDLINE, CENTRAL, PsycInfo and Web of Science for clinical trials and observational studies (last search in August 2021). Two reviewers (DC and IN) independently screened the titles and abstracts yielded by search according to the eligibility criteria. The full reports were independently read and determined whether they meet the inclusion criteria. Discrepancies were solved by consensus.

2.3. Risk of bias

The risk of bias was assessed by ROBINS-I [29] (Risk of Bias In Non-randomized Studies – of Interventions) tool. The confounding domains considered relevant were factors considered in the CHA2DS2-VASc (Congestive heart failure/LV dysfunction, Hypertension, Age $\geq$ 75 years, Diabetes mellitus, stroke/transient ischemic attack, vascular disease, Age 65–74 years, sex category) score. After assessing the risk of bias for different domains, the overall risk of bias was estimated for each study.

2.4. Data synthesis

We used RevMan 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) to derive plots and to perform statistical analysis. Meta-analysis was performed using the inverse variance method and a random effects model. Statistical heterogeneity was assessed using the chi-square test (threshold $P > 0.10$) and through I^2, considering studies with $I^2 > 50\%$ to have substantial heterogeneity. We reported pooled outcomes using ORs and respective 95% confidence intervals (CIs). We performed subgroup analysis according to type of surgery (cardiac or non-cardiac).

We planned to assess publication bias, through the Egger's test and funnel plot if at least 10 studies were included for analysis.

2.5. Confidence in cumulative evidence

Two authors (IN and DC) used the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) criteria to evaluate the quality of the pooled evidence for each outcome. The certainty in the evidence for each outcome was graded as high, moderate, low, or very low [30]. Discrepancies were solved by a third party.

3. Results

3.1. Included studies

The search returned 1113 records and after screening the records and full-text assessment, we included ten studies [4,7,12,18,21,31–35] (Fig. 1).

All the 10 included studies were observational retrospective cohorts. No randomized controlled trials (RCTs) matching eligibility criteria were found. Five studies were carried out in patients who underwent cardiac surgery (4 with CABG surgery [4,31–33], one left-side heart valve surgery [12]). Five studies were performed in the non-cardiac surgery setting: one in thoracic surgery (non-cardiac) [18], and the remaining studies included various types of non-cardiac surgery [7,34–36]. All studies excluded patients with AF diagnosed prior to surgery.

The total number of patients with POAF that were evaluated in the studies of cardiac surgery and non-cardiac surgery were 203,946 and 29,566, respectively.

The mean age of the patients ranged between 66.4 years and 77 years.

POAF was defined as a rhythm requiring either medical therapy or cardioversion, and/or coded in administrative databased through ICD-8, ICD-9 or ICD-10 (Supplementary data 2). The percentage of POAF patients who received oral anticoagulation varied from 3.2% to 62.9%. Only one study stated that the burden of POAF was a determinant of anticoagulation, as anticoagulated patients had a median time o AF duration of 6 days and non-anticoagualated a median of 1 day [18]. In the seven studies, the most used anticoagulant was warfarin (62.9–100%). Only two studies reported data of non-vitamin K antagonists oral anticoagulants (NOACs) with rates of use of 19% and 26% [21,35], respectively, within the patients anticoagulated. The mean CHA_2Ds_2VASc score ranged between 2.9 and 4 in the studies that reported this data [4,7,12,32,34,35]. Three studies reported the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR [international normalized ratio], elderly, drugs/alcohol concomitantly) score that ranged between 1.9 and 2.2 [4,7,12]. The control was no anticoagulant treatment in all

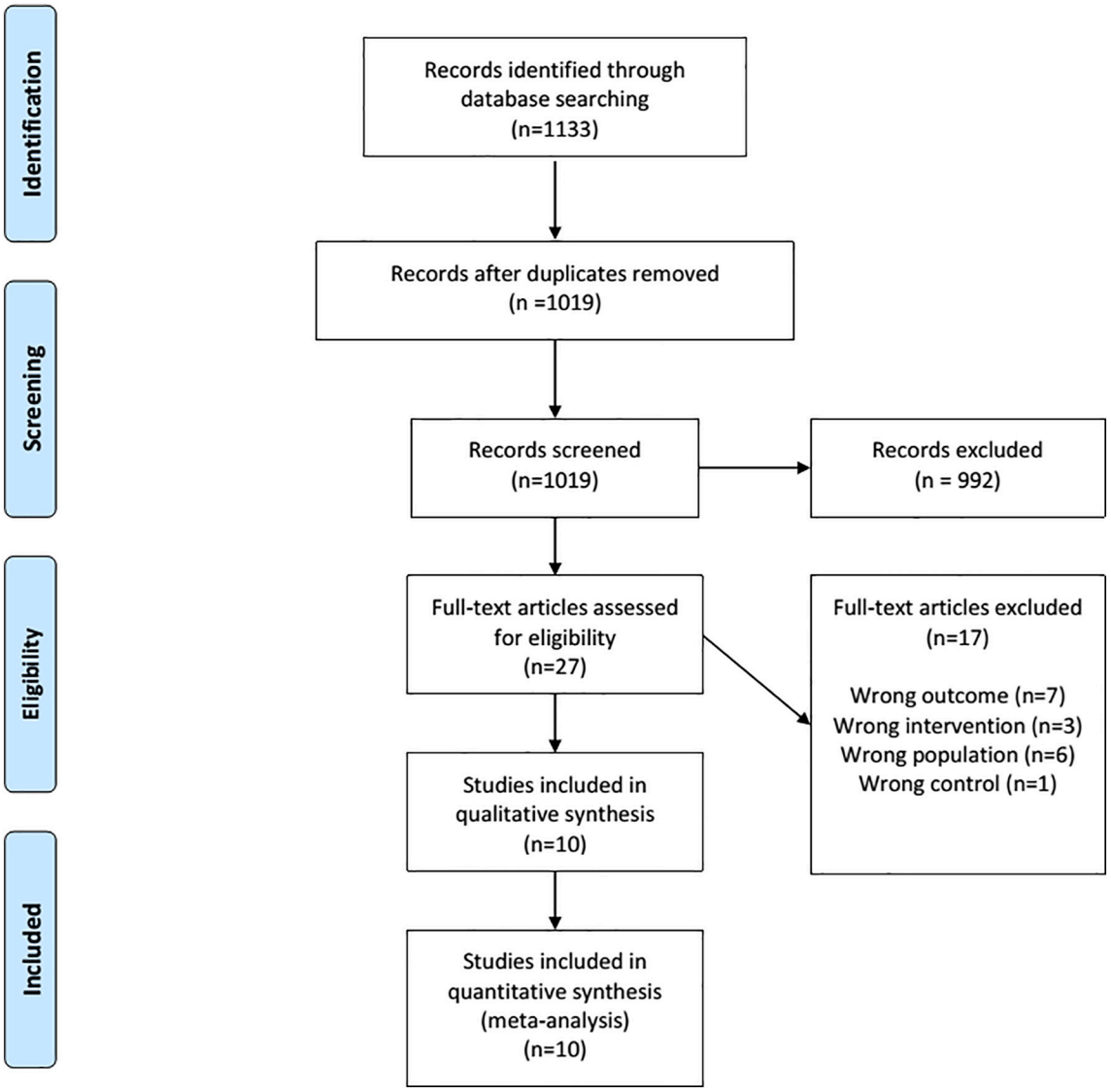

Fig. 1. Flowchart of studies selection.

studies.

The mean follow-up of patients ranged between 30 days and six years.

General characteristics of each study are described in Table 1 and Supplementary Data 2.

3.2. Risk of bias

The overall risk of bias in the included studies was moderate in five studies [4,7,12,21,31] and serious for four studies [18,33–35] (Supplementary Data 3). The study of Matos et al. was considered of moderate risk of bias but for the bleeding outcome it was classified as at high risk of bias due to selective reporting bias as bleeding was not a predefined outcome [32].

The main source of risk of bias was the absence of baseline and time-varying adjustments for confounding factors.

3.3. Anticoagulation in POAF after cardiac surgery

The meta-analysis enrolling patients with POAF after cardiac surgery (Fig. 2) showed a significant association between anticoagulation and thromboembolism risk reduction (OR = 0.68, 95% CI 0.47 to 0.96; I^2 = 31%; 4 studies; 200,961 patients) without significantly reducing the risk of all-cause mortality (OR = 0.93, 95% CI 0.70 to 1.22; I^2 = 83%; 5 studies; 203,782 patients). Bleeding risk was based in only one study with a significant risk increase with an OR 4.30 (95%CI 3.69 to 5.02; 1 study; 166,747 patients) [32].

3.4. Anticoagulation in POAF after non-cardiac surgery

The use of anticoagulation in patient with POAF after non-cardiac surgery (Fig. 3) was not associated with a significant reduction in both risks of death (OR 0.64, 95% CI 0.30 to 1.39, I^2 = 88%; 3 studies; 7122 patients) and thromboembolic events (OR 0.71, 95% CI 0.33 to 1.15; I^2 = 79%; 5 studies; 29,566 patients). The meta-analyis of bleeding data showed an positive association between the use of anticoagulation and the bleeding risk (OR 1.20, 95% CI 1.10 to 1.32, I^2 = 0%; 3 studies; 23,081 patients).

3.5. Secondary analyses

Evaluating the data excluding the studies at serious risk of bias, the results were similar to the primary analysis with a significant decrease of the thromboembolic risk in POAF after cardiac surgery but not non-

Table 1
Summary of studies characteristics.

Identification	Design	Surgery setting	Nr Patients with POAF (% receiving OAC)	Anticoagulation	CHA_2DS_2VASc/HAS-BLED	Mean age female %	Follow-up (mean)
Butt 2018 Denmark	Retrospective Cohort	Coronary Artery Bypass Graft Surgery (Cardiac)	2108 (8.4%)	83.4% warfarin 16.6% OAC not specified	3.1 2.2	69.2 y 17.7%	5.1 years
Butt 2018 Denmark	Retrospective Cohort	Noncardiac surgery	3830 (24.4%)	76.4% warfarin 23.6% OAC not specified	3 1.9	77 y 66.8%	3.2 years
Butt 2019 Denmark	Retrospective Cohort	Left-sided heart valve surgery (Cardiac)	712 (62.9%)	62.9% warfarin 27.1% OAC not specified	2.9 2.1	71 y 40.7%	4.2 years
Makhija 2011 U.S.A.	Retrospective Cohort	General thoracic surgery (Noncardiac)	759 (30.0%)	OAC type was not specified	Not specified	71 y 30.6%	27.6 months
Matos 2019 U.S.A.	Retrospective Cohort	Coronary Artery Bypass Graft Surgery (Cardiac)	166,747 (25.7%)	Warfarin	3.2 HAS-BLED not specified	70 y 21.0%	30 days
El-Chami 2009 U.S.A.	Retrospective Cohort	Coronary Artery Bypass Graft Surgery (Cardiac)	2985 (20.5%)	Warfarin	No data available	67.5 y 27.0%	6 years
Ahlsson 2009 Sweden	Retrospective Cohort	Coronary Artery Bypass Graft Surgery (Cardiac)	165 (3.6%)	Warfarin	No data available	69.2 y 18.8%	6.9 years
Siontis 2020 U.S.A.	Retrospective Cohort	Non-cardiac surgery	437 (49.4%)	OAC type was not specified	4 HAS-BLED not specified	75 y 48.2%	5.4 years
Elharram 2020 Canada	Retrospective Cohort	Non-cardiac surgery	22,007 (29.4%)	Warfarin (81%) NOACs (19%)	CHA_2DS_2VASc high in 42% HAS-BLED high in 41%	75 y 46%	4.3 years
Hyun 2021 South Korea	Retrospective Cohort	Non-cardiac surgery	315 (25.4%)	Warfarin (74%) NOACs (25%)	2.3	66.4 y	2 years

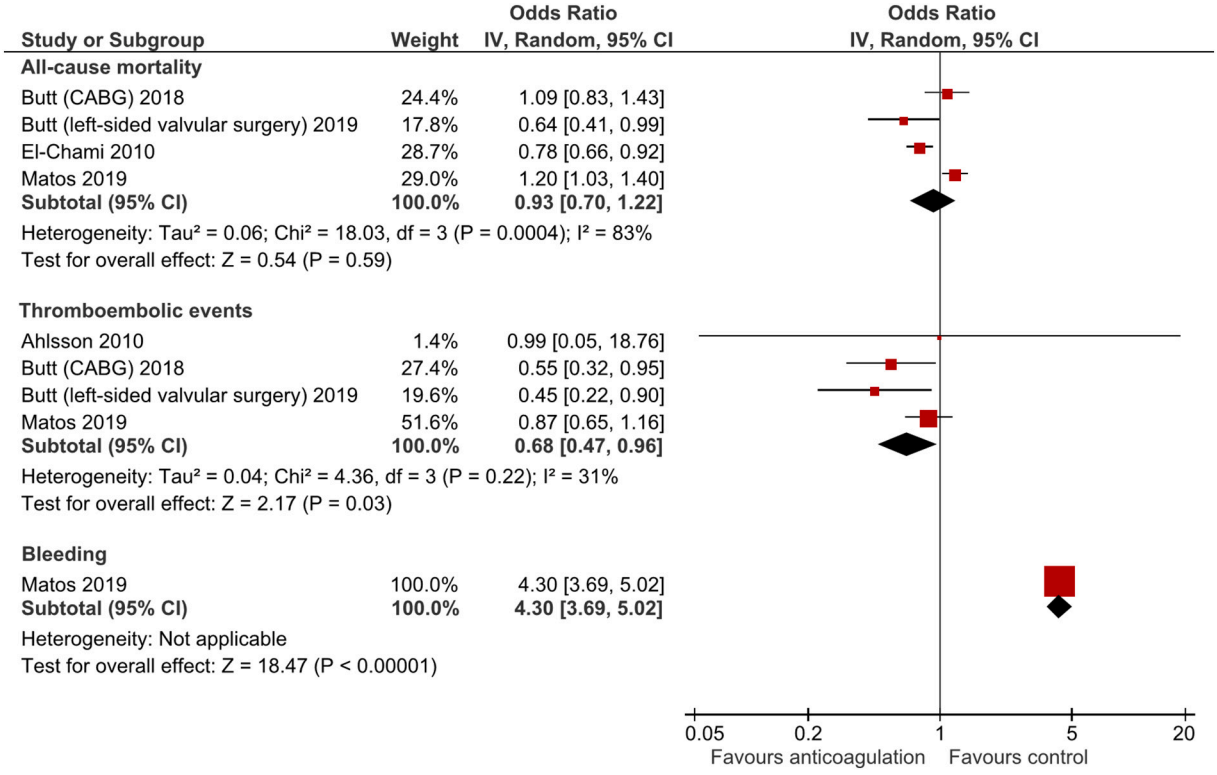

Fig. 2. Pooled and individual estimates of the mortality, thromboembolic and bleeding risks associated with anticoagulation in POAF after cardiac surgery.

cardiac surgery (Supplementary Fig. 1 and Supplementary Fig. 2). The remaining outcomes kept non-significant.

In a secondary analysis we also evaluated the OAC exposure in POAF patients irrespectively of having cardiac or non-cardiac surgery (i.e. both groups were merged for this analysis) (Supplementary Fig. 3). The analysis showed that anticoagulation was associated with significantly

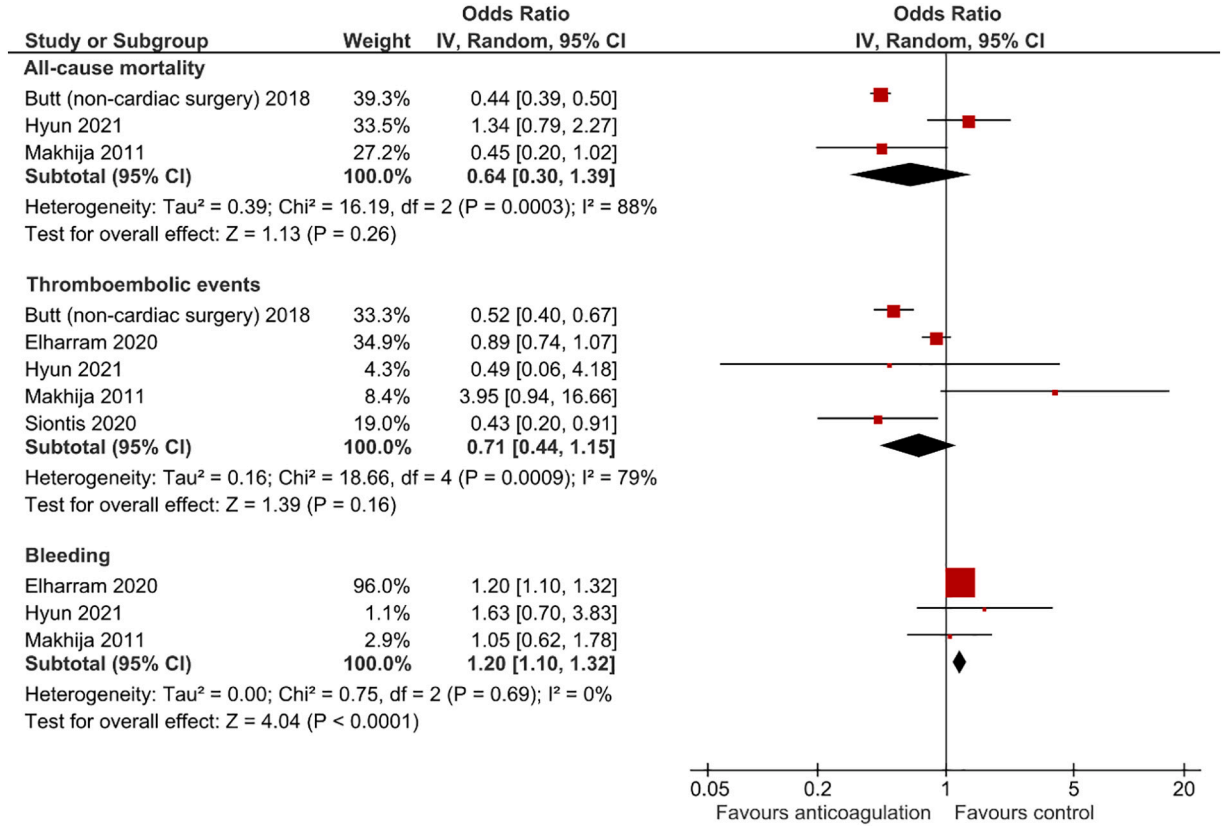

Fig. 3. Pooled and individual estimates of the mortality, thromboembolic and bleeding risks associated with anticoagulation in POAF after non-cardiac surgery.

lower risk of thromboembolic events in POAF with OR = 0.68 (95% CI 0.51 to 0.90, $I^2 = 65\%$; 9 studies) (Supplementary Fig. 3). No statistically significant results were found for mortality and bleeding.

3.6. Assessment of confidence in cumulative evidence

Table 2 presents a summary of the findings obtained according to certainty of evidence (GRADE). The highest confidence degree obtained in this analysis was 'Low' for thromboembolic risk decrease in POAF after cardiac surgery, and bleeding risk increase in POAF after non-cardiac surgery. In both situations, despite the significant relative effect results, the absolute effects seem modest: decrease of 7 thromboembolic events for each 1000 POAF anticoagulated after cardiac surgery; increase of 7 bleeding events for each 1000 POAF anticoagulated after non-cardiac surgery. The remaining evaluations were considered with 'Very Low' confidence according to GRADE. Further details about classification and reasons for downgrading in GRADE assessments are depicted in Supplementary Data 4.

4. Discussion

In this systematic review with meta-analysis, we observed an association between OAC use and decreased of thromboembolic events in patients with POAF after cardiac surgery. The current evidence is not significant for thromboembolic risk decrease in non-cardiac surgery POAF, nor mortality in both cardiac and non-cardiac surgery. The use of anticoagulation expectedly showed a significant increase in bleeding risks. The overall confidence in the results according GRADE evaluation was 'low' or 'very low' which means that further studies are required.

The occurrence of post-operative arrythmias are clinically relevant and AF is one of the commonest sustained arrhythmias. Despite the known risk of stroke associated with AF, POAF was typically seen as a benign/reversible condition [4,7], demonstrating the uncertainty regarding the stroke prevention management in the context of POAF. The key argument for the use of oral anticoagulation is that the intervention reduces significantly the risk of thromboembolic events in patients with AF (other than POAF) [37]. In fact, our data showed that in cardiac surgery POAF the risk of thromboembolic events was similarly significantly decreased. This phenomena is well shown in the studies of Butt and colleagues in both CABG and valvular surgery where the risk of thromboembolism does not differ significantly among patients with POAF and 'conventional' non-surgical atrial fibrillation [4,12]. Patients undergoing cardiac surgery might have a substrate that makes them more susceptible to the development of arrhythmias such as AF. In addition, several studies have demonstrated an increased risk of thromboembolic events and long-term morbidity in those who develop POAF [38–40]. Despite the observed risk reduction in thromboembolic events, OAC did not reduce the all-cause mortality. In the presence of high statistical heterogeneity, the removal of studies at higher risk of bias, did not change substantially the statistical heterogeneity nor the results, meaning that results might be influenced by other factors not captured in this systematic review.

Regarding POAF after non-cardiac surgery, OAC did not reduce substantially the risk to thromboembolic events in the pooled analysis. Only the Danish study of Butt and colleagues showed a statistically significant result with a magnitude of risk reduction of thromboembolic events similar to the risk reduction observed in the cardiac surgery, and also in the placebo-controlled trial in AF (other than POAF) [37]. A larger study by Elharram and colleagues suggested an absence of clinical impact of anticoagulation in non-cardiac surgery POAF [21]. This suggests that the lower incidence of POAF in non-cardiac surgery can lead to misleading results in studies with methodological pitfalls. Thus, there is a need for further studies in new-onset POAF after non-cardiac surgery.

The main concerning when anticoagulating these post-operative patients is major bleeding. Our pooled data revealed a significant increase in the bleeding risk associated with OAC treatment in both

Table 2
Summary of findings according to GRADE.

Outcomes	Studies	Certainty of the evidence (GRADE)	Odds ratio (95% CI)	Anticipated absolute effects	
				Risk with no anticoagulation	Risk difference with Anticoagulation
POAF after cardiac surgery					
POAF cardiac surgery - all-cause mortality	4 observational studies	⨁◯◯◯ VERY LOW [a,b,c,d]	OR 0.93 (0.70 to 1.22)	CABG 47 per 1000** Valvular surgery 42 per 1000**	3 fewer per 1000 (14 fewer to 10 more) 3 fewer per 1000 (12 fewer to 9 more)
POAF cardiac surgery - thromboembolic events	4 observational studies	⨁⨁◯◯ LOW [a]	OR 0.67 (0.47 to 0.96)	CABG 18 per 1000** Valvular surgery 22 per 1000**	6 fewer per 1000 (10 fewer to 1 fewer) 7 fewer per 1000 (11 fewer to 1 fewer)
POAF cardiac surgery - bleeding	1 observational study	⨁◯◯◯ VERY LOW [a,e]	OR 4.30 (3.69 to 5.02)	Only CABG data available 2 per 1000***	6 more per 1000 (5 more to 8 more)
POAF after non-cardiac surgery					
POAF non-cardiac surgery - all-cause mortality	3 observational studies	⨁◯◯◯ VERY LOW [a,b,c,d]	OR 0.64 (0.30 to 1.39)	133 per 1000[#]	44 fewer per 1000 (89 fewer to 43 more)
POAF non-cardiac surgery - thromboembolic events	5 observational studies	⨁◯◯◯ VERY LOW [a,b,c,d]	OR 0.71 (0.44 to 1.15)	32 per 1000[#]	9 fewer per 1000 (18 fewer to 5 more)
POAF non-cardiac surgery - bleeding	3 observational studies	⨁⨁◯◯ LOW [a]	OR 1.20 (1.10 to 1.32)	39 per 1000[##]	7 more per 1000 (4 more to 12 more)

CI: Confidence interval; OR: Odds ratio.
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
Explanations:
[a]Presence of studies at serious risk of bias in ROBINS-I.
[b]Substantial heterogeneity with I2 > 75%.
[c]The estimate includes OR 1.0 in the interval.
[d]The estimate fails to exclude clinically relevant harm.
[e]Data from a single retrospective study.
Source of data for control group in absolute effect calculations:
**Crude data from Butt et al. (CABG).
***Crude data from Butt et al. (valvular surgery).
***From Matos et al.
[#]Crude data from Butt et al. (non-cardiac surgery).
[##]Crude data from Elharram et al.

cardiac and non-cardiac surgery POAF. This result was expected but the data is scarce regarding any further details. Most of the studies did not evaluate bleeding events because they were not designed to evaluate bleeding and this is probably the main reason for the absence of bleeding data in most studies, as well absence of details on how bleeding was managed (e.g. use of vitamin K, frozen plasma, prothrombin complex concentrate, and/or transfusion of red blood cell packs or platelets). Nevertheless, it is expected that bleeding risk increases with oral anticoagulation (compared with no anticoagulation) and data are required to better establish the benefit-risk evaluation [22].

This systematic review aimed to analyze the clinical impact of oral anticoagulation on POAF. The differences of cardiac- and noncardiac surgery POAF were already considered in the split analysis. Nevertheless within these types of surgery there are substantial differences in background risk factors and AF incidence. Despite all the limitations it is conceivable that physicians prescribe oral anticoagulants in patients with POAF in accordance with current guidelines [20,21], and our limited and observational pooled data.

Further data are required either prospective observational studies adjusting adequately for baseline and time-varying factors (including the anticoagulation) and/or properly designed and powered randomized controlled trials, such as the Anticoagulation for Stroke Prevention In Patients With Recent Episodes of Perioperative Atrial Fibrillation After Noncardiac Surgery (ASPIRE-AF, NCT03968393) trial. These studies should also monitor prospectively patients for AF outside of the acute post-operatory period to determine the frequency of AF recurrence, their predictors and the potential influence of anticoagulation. A recent systematic review assessing the AF after non-cardiac surgery emphasized that studies evaluating AF recurrence after POAF mostly did not use a prospective systematic monitoring protocol (only one study performed such evaluation [41]) [42], and that POAF incidence and AF recurrence depends also in the type and intensity of ECG monitoring as well of surgery type (POAF incidences high in surgeries such as esophagectomy, pulmonary resection/transplant or other thoracic surgeries [42], as well as in abdominal, orthopedic and vascular surgery [7,10,11]) [42]. It is also important different burden/duration of POAF should be studied to determine its relevance for anticoagulation purposes.

The wider use of Non-Vitamin K antagonist oral anticoagulants (or direct oral anticoagulants) as well the safer and efficacious profile of these drugs warrants further evaluation in future studies [43–46].

4.1. Limitations

One of the main limitations of this study is that it only contains data from retrospective observational studies, with the risk of bias associated with each of the studies, especially due to confounding domain. The GRADE confidence in the pooled evidence was ‘low’ or ‘very low’, mainly due to the risk of bias, high heterogeneity of the results and imprecision of data.

A limiting aspect of this study is that it does not have more detailed information on all patients included, namely on factors such as the value of CHA_2Ds_2VASc score or echocardiography elements that clarify why some patients have been anticoagulated and others have not.

Another important note is that other pharmacological measures or lifestyle changes were not considered, which could also contribute to a decreased cardiovascular risk and, hence, reduction of thromboembolic events.

5. Conclusion

The available evidence showed that oral anticoagulation was associated with a decreased risk of thromboembolic events in cardiac surgery and an increased risk of bleeding events. The low or very-low confidence in the pooled evidence emphasizes the need of RCTs to establish the efficacy and safety of oral anticoagulation in patients with POAF.

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None.

Statement

Authors state the manuscript is a systematic review with meta-analysis of metadata of published studies and informed consent is not required in this context.

Declaration of Competing Interest

DC has no conflicts of interest in the last 3 years. JJF had speaker and consultant fees with Grünenthal, Fundação MSD (Portugal), TEVA, MSD, Allergan, Medtronic, GlaxoSmithKline, Novartis, Lundbeck, Solvay, BIAL, Merck-Serono, Merz, Ipsen, Biogen, Acadia, Allergan, Abbvie, Sunovion-Pharmaceuticals. FJP had consultant and speaker fees with Astra Zeneca, Bayer, BMS, Boehringer Ingelheim and Daiichi Sankyo.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vph.2021.106929.

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