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SYSTEMATIC REVIEW

Non-steroidal anti-inflammatory drugs and postoperative atrial fibrillation in patients having non-cardiac surgery: a systematic review

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Abstract

Increasing evidence suggests an association between non-steroidal anti-inflammatory drugs (NSAIDs) and atrial fibrillation in the general population. A systematic review was conducted to characterize the association of perioperative NSAIDs with atrial fibrillation after non-cardiac surgery (POAF). PubMed and Scopus were searched for relevant studies. We excluded review articles, case studies, articles not published in English, and animal studies. The primary objective was to investigate the relationship between the perioperative use of NSAIDs and POAF during the first 30 postoperative days (from the day of surgery), at hospital discharge, and at 30 and 90 days after hospital discharge. Four studies were identified, a pooled analysis of two randomized double-blind clinical trials and three observational studies. A *post-hoc* sensitivity analysis for acetylsalicylic acid (aspirin) *vs.* other NSAIDs revealed that the former seems to decrease the incidence of POAF although non-significantly (Relative Risk (RR) (95% Confidence Interval (CI)): 0.92 (0.81, 1.04); $p = 0.165$). After excluding acetylsalicylic acid from the analysis, NSAIDs were associated with an increased risk of POAF development (RR (95% CI): 1.15 (1.07, 1.23); $p < 0.001$). In conclusion, perioperative administration of non-aspirin NSAIDs may be associated with an increased risk of POAF development. Further studies investigating the role of NSAIDs and the potential protective role of aspirin in POAF are justified.

Keywords

Non-steroidal antiinflammatory drugs; Perioperative; Atrial fibrillation; Surgery; Non-cardiac surgery

1. Introduction

Postoperative atrial fibrillation (POAF), defined as new-onset atrial fibrillation in the immediate period after surgery, is the most important type of secondary atrial fibrillation [1]. It complicates 20–40% of cardiac and up to 30% of non-cardiac surgical procedures [1–3]. The peak incidence of POAF occurs 1 to 3 days postoperatively and has been positively correlated with patient age, preoperative heart rate, and male sex [3].

Postoperative atrial fibrillation is associated with adverse consequences such as hemodynamic instability, increased risk of stroke and lengthened hospital stay [1, 2]. The underlying mechanisms have not been investigated in depth, but POAF can be triggered by myocardial ischemia and sympathetic activation [1, 2, 4]. In addition, the relation between inflammation and atrial fibrillation is well-established and supported by clinical studies indicating that even local myocardial inflammation contributes to the pathogenesis [2, 4, 5]. Inflammation may lead to atrial remodeling, conduction disturbances facilitating re-entry, altered molecular expression, increase oxidative stress, and infiltration of inflammatory cells these phenomena together with surgical stress can initiate POAF [1].

Several studies investigated the association of non-steroidal anti-inflammatory drugs (NSAIDs) with atrial fibrillation in the general population. NSAID use was associated with a 44% increase in the risk of permanent atrial fibrillation [6]. Also, 40–70% increase in relative risk of atrial fibrillation was reported in new NSAID users compared to non-users [7]. Moreover, a meta-analysis of 114 randomized double-blind clinical trials reported that some NSAIDs show increased risk of arrhythmia [8].

Much less is known about the epidemiological and clinical features of POAF and its association with NSAIDs in patients undergoing non-cardiac surgical operations. The present systematic review investigated whether perioperative administration of NSAIDs is associated with an increased risk of POAF

after non-cardiac surgery.

2. Materials and methods

2.1 Study protocol

The protocol was registered in the PROSPERO international prospective register of systematic reviews on 10 March 2023 (CRD42023402997). This systematic review was reported according to the Preferred Reporting Items for Systematic Re-views And Meta-Analyses (PRISMA) checklist (**Supplementary Table 1**) [9].

2.2 Objectives

The primary objective was the relationship between perioperative NSAID use and POAF after non-cardiac surgery during the first 30 postoperative days (from the day of surgery), upon discharge from the hospital, and at 30 and 90 days after hospital discharge. Secondary objectives were the association of POAF with hospital length of stay, days of mechanical ventilation, length of stay in the intensive care unit, and mortality at hospital discharge, at 30 days and at 90 days. The comparators were patients not treated with NSAIDs.

2.3 Search strategy

We included randomized controlled trials, clinical trials, comparative studies, cohort studies, pragmatic clinical trials, validation studies and observational studies. Exclusion criteria included review articles, case studies, articles not published in English, and animal studies. Four authors (NN, NP, EL, AC) designed the strategy, which intended to explore all available clinical studies from 01 January 2000 to 31 March 2023. An initial search was performed in PubMed (MEDLINE) and Scopus for articles containing the following terms in the abstract or title: the MeSH® terms postoperative; atrial fibrillation; non-cardiac surgery; the wildcard terms postop*; fibril*; or any of the terms: anti-inflammatory; inflammation; anti-inflammatory treatment; anti-inflammatory drug; or non-steroidal anti-inflammatory drugs (**Supplementary Table 2**). Thereafter, we searched for articles meeting the above criteria AND any of the following MeSH® terms: postoperative; surgery; or surgical or the following non-MeSH terms: complications; outcome; or survival. Another search was conducted with the reference lists of all identified reports and articles for additional studies, and a grey literature search was conducted on Google Scholar. ClinicalTrials.gov website was also searched for articles containing any of the following terms: postoperative; atrial fibrillation; and non-cardiac surgery. A last search for relevant articles was performed on 31 December 2023.

2.4 Data extraction

The titles and abstracts of studies obtained were independently screened by three review authors (NN, NP, EL) to identify studies that potentially meet the inclusion criteria outlined above. The full text of potentially eligible studies was independently assessed for eligibility by four review team members (NN, NP, EL, AC). Any disagreement was resolved through discussion among all authors.

Data extracted included publication details, study information, types and dose of NSAIDs, and information to assess risk of bias. Three authors (NN, NP, EL) extracted data independently using a pre-designed Excel spreadsheet. Disagreements or discrepancies regarding study eligibility were resolved through discussion among all authors. Missing data were obtained from the corresponding author of the included studies.

2.5 Assessment of methodological quality

Articles identified for retrieval were assessed by three independent authors (NN, NP, AC) for methodological quality using standardized critical appraisal tools. The quality of the included studies was assessed using the MINORS and the Risk of Bias 2.0 (RoB 2.0) tools. Potential publication bias were assessed by visual inspection of funnel plots. Any disagreements were resolved through discussion among all authors.

3. Results

Altogether, 46,307 citations were identified. Of the 204 records that were initially collected, eight clinical studies were selected for full review and were further assessed (Fig. 1). Data extraction was feasible in four studies (Table 1) [10–13].

3.1 Study characteristics

One study was a pooled analysis of two randomized double-blind clinical trials [10], while the remaining were observational studies [11–13].

The study by Gan *et al.* [10] included data regarding the administration of $\geq$1 dose of hydroxypropyl-β-cyclodextrin-diclofenac (HPβCD-diclofenac) or ketorelac in 608 patients (mean age ~48 years; 331 abdominal/pelvic surgery; 277 orthopedic surgery) and the emergence of POAF as an adverse event. Intravenous HPβCD-diclofenac did not increase the risk of cardiovascular adverse events, as compared to treatment with placebo over the observation period employed (30- to 37-day follow-up), while most cardiovascular adverse effects reported were mild or moderate in severity. Only one (0.3%) patient in the HPβCD-diclofenac group developed POAF. The analysis by Gan *et al.* [10] found that HPβCD-diclofenac was not associated with a significantly risk of increased cardiovascular adverse events in patients >65 years old; however, the number of these patients was relatively low (n = 72).

Butt *et al.* [11] included data from 1,520,109 non-cardiac surgery patients with no history of atrial fibrillation. All patients had received NSAIDs (ATC-code M01A). Median age of participants was 77 years (IQR: 69 to 84 years; 43.2% men), while the most frequent type of surgery was orthopedic (30.2%). Of them, 6048 (0.4%) patients developed in-hospital POAF. Patients with POAF were older and had more cardiovascular comorbidities compared to non-POAF individuals [11]. Also, the POAF group had more non-cardiovascular comorbidities, with the exception of cancer and chronic obstructive pulmonary disease. In the study by Butt *et al.* [11] patients with POAF had a significantly lower risk of rehospitalization

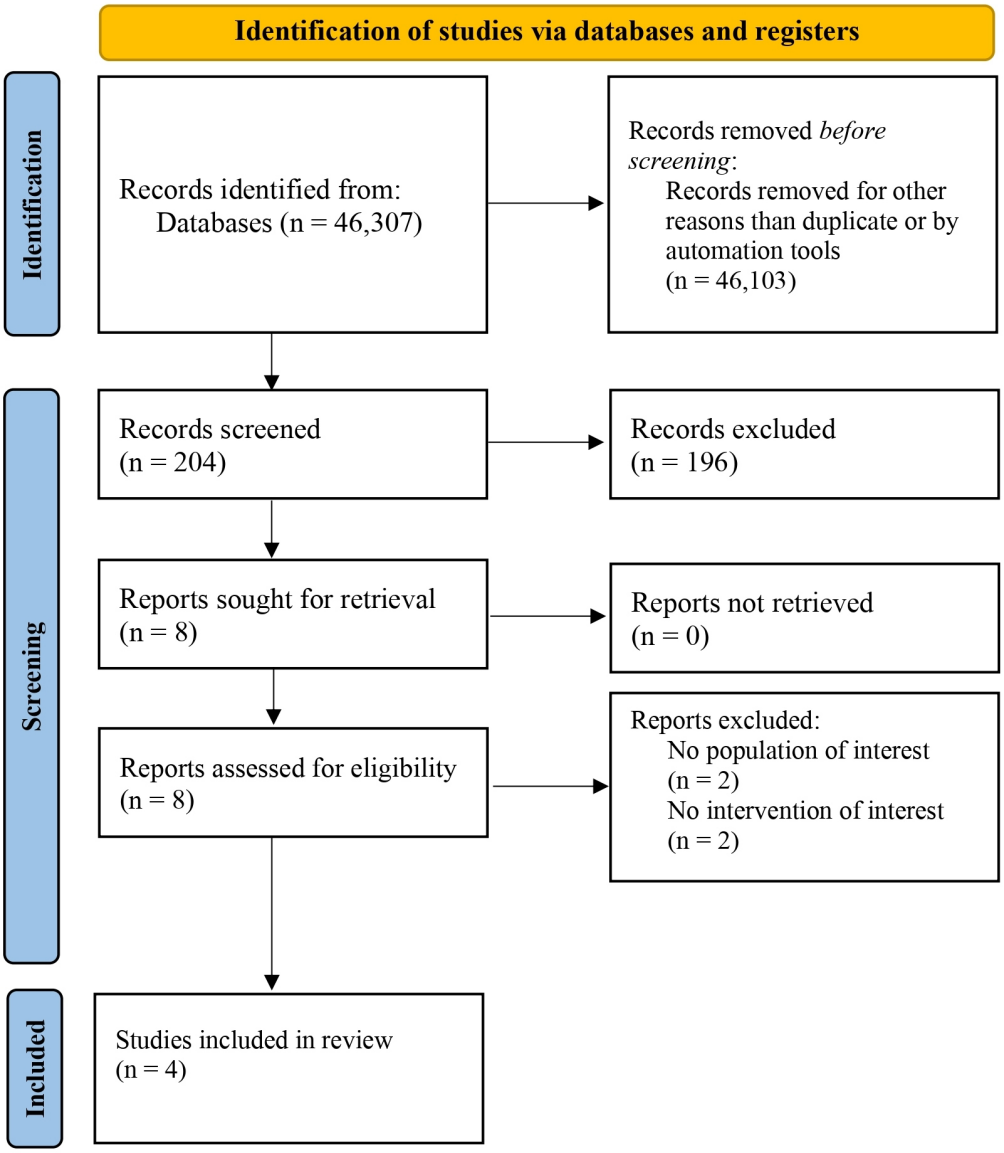

FIGURE 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram.

TABLE 1. Characteristics of the included studies.

Author, year	Type of study	No. of patients without NSAID	POAF without NSAID	No. of patients with NSAID	POAF with NSAID
Amar *et al.* [13], 2005	Prospective observational study	93	24	38	14
Gan *et al.* [10], 2016	Pooled analysis of two randomized, double-blind, placebo- and active comparator-controlled phase III clinical trials	148	0	460	1
Butt *et al.* [11], 2018	Retrospective registry-based observational study—Aspirin Subgroup	15,320	4028	3830	906
	Retrospective registry-based observational study—NSAID subgroup	15,320	3028	3830	869
Stronati *et al.* [12], 2022	Retrospective observational study	2004	697	44	17

NSAID, non-steroidal anti-inflammatory drugs; POAF, postoperative atrial fibrillation.

due to atrial fibrillation, but they exhibited significantly higher risk of all-cause mortality during the first year (Hazard Ratio (HR): 1.83; 95% CI: 1.67 to 2.01). After 1 year, a similar risk of all-cause mortality was found in both groups (HR: 1.00; 95% CI: 0.93 to 1.07) [11].

Stronati *et al.* [12] assessed independent predictors of POAF in 2048 consecutive patients (1350 men; aged 72 $\pm$ 12 years; no previous diagnosis of atrial fibrillation) having all types of elective non-cardiac surgery. Of them, 44 (2.1%) patients experienced POAF. Only age (76.4 $\pm$ 7.7 *vs.* 71.8 $\pm$ 12.3, $p < 0.001$), body mass index (21.7 $\pm$ 43 *vs.* 23.6 $\pm$ 5.4, $p = 0.041$), hypertension (41 (93%) *vs.* 1490 (74%), $p = 0.005$), and thyroid dysfunction (11 (25%) *vs.* 216 (11%), $p = 0.012$) were significantly different between patients with and without POAF. Surgery risk was generally higher in the POAF group ($p < 0.001$), while the revised cardiac risk index was similar between the two groups ($p = 0.913$) [12]. Of note, 17 (39%) POAF and 697 (35%) non-POAF patients received acetylsalicylic acid ($p = 0.621$) before surgery. Median time from surgery to POAF diagnosis was 3 days (first to third quartile range: 2 – 4 days) [12].

Amar *et al.* [13] conducted a prospective study to determine whether an elevated C-reactive protein level is associated with development of POAF. They also evaluated whether statin use reduces the incidence of POAF after thoracic surgery. The authors included 131 consecutive patients (age >60 years) who were at risk for POAF development. In that study, an increase in POAF incidence was observed in the NSAID group (Odds Ratio (OR) 1.43) [13]. The study was published in 2005 and included a specific group of patients (thoracic surgery), while aspirin was not separated from the NSAID group.

3.2 Risk of bias, quality of evidence

The overall MINORS score for the observational studies of Butt *et al.* [11], Stronati *et al.* [12], and Amar *et al.* [13] are 18, 17, and 16, respectively. The ROB-II plot for the randomized study [10] is presented in Fig. 2.

3.3 Primary objective

The majority of patients received acetylsalicylic acid at low doses, mainly due to its antithrombotic rather than anti-inflammatory effect. Therefore, we conducted a *post-hoc* sensitivity analysis for acetylsalicylic acid (aspirin) *vs.* other NSAIDs. p values were considered to be significant when < 0.05. All statistical analyses were performed in R v4.2. Acetylsalicylic acid seems to decrease the incidence of POAF although non-significantly (RR (95% CI): 0.92 (0.81, 1.04); $p = 0.165$). After excluding acetylsalicylic acid from the analysis, NSAIDs were associated with an increased risk of POAF development (RR (95% CI): 1.15 (1.07, 1.23); $p < 0.001$) (Table 2).

3.4 Secondary objectives

The data were insufficient for assessing our secondary objectives.

4. Discussion

Postoperative atrial fibrillation is a common problem in cardiac surgery, occurring in about one-third of patients, and associated with increased cost and longer hospital stays [1, 14]. The frequency and clinical course of POAF after non-cardiac surgery has not been studied adequately, possibly due to the incompletely understood pathophysiology, heterogeneous patient populations, and non-standardized electrocardiographic monitoring protocols. Nevertheless, the number of patients undergoing non-cardiac surgery is much larger than cardiac surgery patients, and characterizing the causes, risk factors and triggers of POAF after non-cardiac surgery is paramount.

Non-steroidal anti-inflammatory drugs are extensively used in perioperative medicine and modern pre-emptive/preventive, multimodal analgesic strategies [15, 16]. In addition, they are increasingly used as opioid-sparing analgesic regimens, especially amid the current opioid epidemic in the United States and other countries. These agents are known to attenuate the body's response to surgical injury and the subsequent release of inflammatory mediators [17–20]. On the other hand, NSAIDs are associated with several adverse events, such as bleeding, acute kidney injury, gastrointestinal ulceration, and cardiovascular disease [21–25].

The results of the present systematic review are interesting although they are based on only two studies. The first study, a very large, registry-based, retrospective analysis reporting separately on patients taking aspirin and patients taking other NSAIDs, concluded that acetylsalicylic acid reduce the incidence of POAF [11]. The second study is smaller and did not show a similar reduction in POAF incidence, nor does it inform us about any drug co-administration [12]. Whether the potential protective effect of acetylsalicylic acid on POAF development is due solely to its pharmacological properties or due to the co-administration of other cardiovascular risk-reducing drugs, such as β-blockers or angiotensin-converting enzyme inhibitors, deserves further investigation. On the other hand, patients taking NSAIDs together with aspirin may lose the cardioprotective benefits of the latter due to their subtle differences within the framework of a common mechanism of action; although both bind to the same site on the cyclooxygenase (COX)-1 enzyme, NSAIDs bind earlier, thereby inhibiting aspirin binding (competitive interaction) [26–32].

Whether perioperative NSAID use increases the risk of POAF after non-cardiac surgery remains poorly answered. The data reported in this systematic review are hypothesis generating and should be validated in a randomized controlled trial setting. This becomes more imperative when one considers a relatively recent Cochrane review that showed inconsistent and non-clinically important evidence that pre-emptive and preventive NSAIDs reduce both postoperative pain and morphine consumption [24]. Also, a retrospective cohort study with 452 patients who had their first-ever documented episode of POAF within 30 days after non-cardiac surgery reported that POAF was associated with a significantly increased risk of stroke or transient ischemic attack [33].

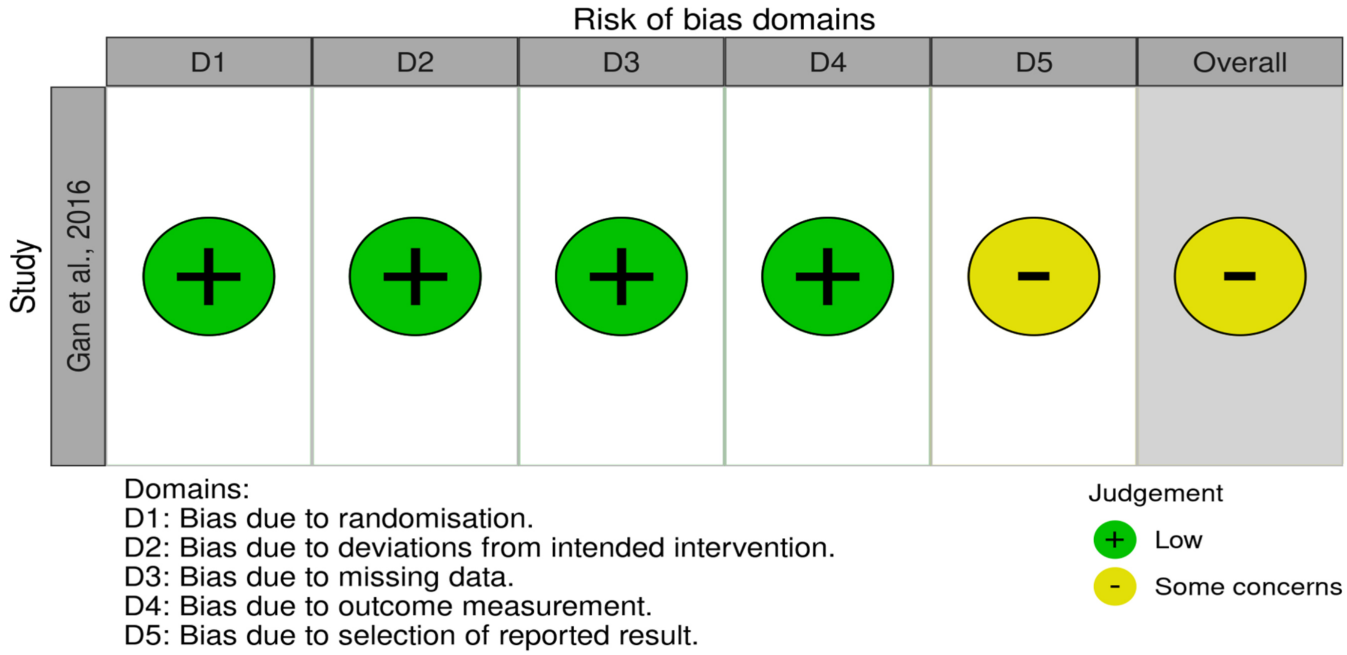

FIGURE 2. Traffic lights plot for risk of bias assessment.

TABLE 2. Effects of NSAIDs with and without acetylsalicylic acid on POAF development.

NSAIDs including acetylsalicylic acid							
Number of studies: 2	N (Total)	Estimate (RR)	*p*-Value	95% CI	I^2	Q	*p* (Q)
	21,198	0.92	0.165	0.81–1.04	14.38%	1.168	0.280
NSAIDs excluding acetylsalicylic acid							
Number of studies: 2	N (Total)	Estimate (RR)	*p*-Value	95% CI	I^2	Q	*p* (Q)
	19,758	1.15	<0.001	1.07–1.23	0%	0.011	0.917

NSAID, non-steroidal anti-inflammatory drugs; POAF, postoperative atrial fibrillation; RR, relative risk; CI, confidence interval.

4.1 Effectiveness of NSAIDs in reducing POAF

Data from experimental and clinical studies are diverse regarding the effectiveness of NSAIDs in reducing the frequency of atrial fibrillation [24]. In canine models, ibuprofen failed to suppress the inflammatory response, prevent the electrophysiological changes leading to atrial fibrillation, and decrease the duration of arrhythmia [34]. Several clinical studies showed that administration of NSAIDs is significantly associated with the development of atrial fibrillation [7, 35, 36]. Also, studies with cardiac surgery patients reported that NSAIDs are effective in preventing POAF without increasing the rate of renal failure (defined as serum creatinine >2.0 mg·dL^{-1}) [37, 38]. However, an interim analysis of a randomized, double-blind, placebo-controlled, single-center trial comparing the effectiveness of naproxen versus placebo showed that naproxen failed to reduce the rate of POAF and increased the frequency of acute kidney injury after cardiac surgery [39]. Of note, the joint 2014 American College of Cardiology/American Heart Association guidelines recommended that POAF should prompt investigation into underlying causes including drug toxicity [3]. The aforementioned data together with the findings of the present systematic review possibly suggest a causal relationship between NSAIDs and POAF after non-cardiac surgery. Until more data are available, it appears advisable to consider NSAIDs should probably be carefully considered on an individual basis and after conducting risk-benefit assessments, taking into account that the dosage and duration of administration may play an important role on POAF development [20].

4.2 Translational evidence on arrhythmogenic mechanisms of NSAIDs

The mechanisms by which NSAIDs increase the risk of POAF development remain unclear [8, 36, 40, 41]. These drugs exert cardiotoxic effects, which are attributed to the cytochrome p450-mediated alteration of arachidonic acid metabolism and reduction of monoepoxides derived from polyunsaturated fatty acids [25, 42, 43]. They also induce the formation of reactive oxygen species in different cell types, including cardiac and cardiovascular-related cells, thereby altering key intracellular signaling pathways [44]. In addition, NSAIDs may affect left ventricular function, even after a short treatment exposure [45], and disturb the production of thromboxane and prostacyclin by inhibiting COX-1 and COX-2 enzymes, shifting the prothrombotic/antithrombotic balance on endothelial surfaces

towards thrombosis [36, 46]. Of note, prostacyclin may act as an endogenous antiarrhythmic by directly inhibiting epicardial sympathetic nerve activity [46].

In an animal study recording action potentials in isolated rabbit pulmonary vein, sinoatrial node, and atrial preparations, selective inhibition of COX-2 (in clinically relevant concentrations) suppressed pulmonary vein and sinoatrial node spontaneous beating rates, which are known to induce burst firings facilitate, delayed afterdepolarizations, and enhance atrial arrhythmogenesis [47]. Also, inhibition of COX-2 shortened the action potential duration in both atria, which may facilitate the maintenance of re-entrant circuits. Some NSAIDs, *e.g.*, indomethacin, may shorten the action potential duration only in the left atrium, which creates an inter-atrial dispersion and reentrant circuits [47]. In other experimental studies, selective deletion of cardiomyocyte COX-2 expression induced interstitial and perivascular fibrosis, which predisposes to ischemic arrhythmias [48].

Inhibition of COX-2 affects sodium current in ganglion cells (and reduces spontaneous firing rate) and burst firings in pulmonary veins, opens voltage-gated potassium channels and blocks L-type calcium channels, and changes the vascular tone and excitability [47, 49]. In addition, NSAIDs may cause acute kidney injury leading to fluid retention, electrolyte disturbances, and hypertension [50–53]. These important side effects, together with the generous amounts of fluids often given intraoperatively, may lead to volume overload and venous congestion, activation of the renin-angiotensin and sympathetic systems, tissue hypoperfusion and edema, and cellular hypoxia [54–56], thus dysregulating postoperative physiology.

4.3 Limitations

This systematic review included non-randomized and randomized studies with different characteristics. There were no data on type and dose of NSAIDs, duration of treatment, and data after hospital discharge. The findings of the *post-hoc* sensitivity analysis are limited by the high degree of uncertainty of the evidence (derived from only two studies), which could include a significant confounding by indication. In addition, the data were insufficient for assessing our secondary objectives; whether POAF affects hospital length of stay, days of mechanical ventilation, length of stay in the intensive care unit, and mortality after non-cardiac surgery remains unknown.

5. Conclusions

Perioperative use of non-aspirin NSAIDs may be associated with an increased risk of POAF in patients undergoing non-cardiac surgery. Whether the potentially protective effect of acetylsalicylic acid on the development of POAF is due solely to its pharmacological properties or to the co-administration of other cardiovascular risk-reducing drugs remains unclear. Data from this systematic review should be investigated in a randomized controlled trial setting.

AVAILABILITY OF DATA AND MATERIALS

Data can be made available upon request after publication through a collaborative process. Researchers should provide a methodically sound proposal with specific objectives in an approval proposal. Please contact the corresponding author for additional information.

AUTHOR CONTRIBUTIONS

NN and AC—Conceptualization, writing-original draft preparation. NN, NP, EL, AC—methodology, investigation, validation, data curation, visualization. NN, NP, EL, KE, NI, TX and AC—resources, writing-review and editing. AC—supervision, project administration. NP, EL—software. NP—formal analysis. All authors have read and agreed to the published version of the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Athanasios Chalkias is serving as one of the Editorial Board members of this journal. We declare that Athanasios Chalkias had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to MGI.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae.com/mre-signavitae/article/1831927256384978944/attachment/Supplementary%20material.pdf.

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