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STATE OF THE ART REVIEW
Cardiac and vascular surgery

Postoperative atrial fibrillation: from mechanisms to treatment

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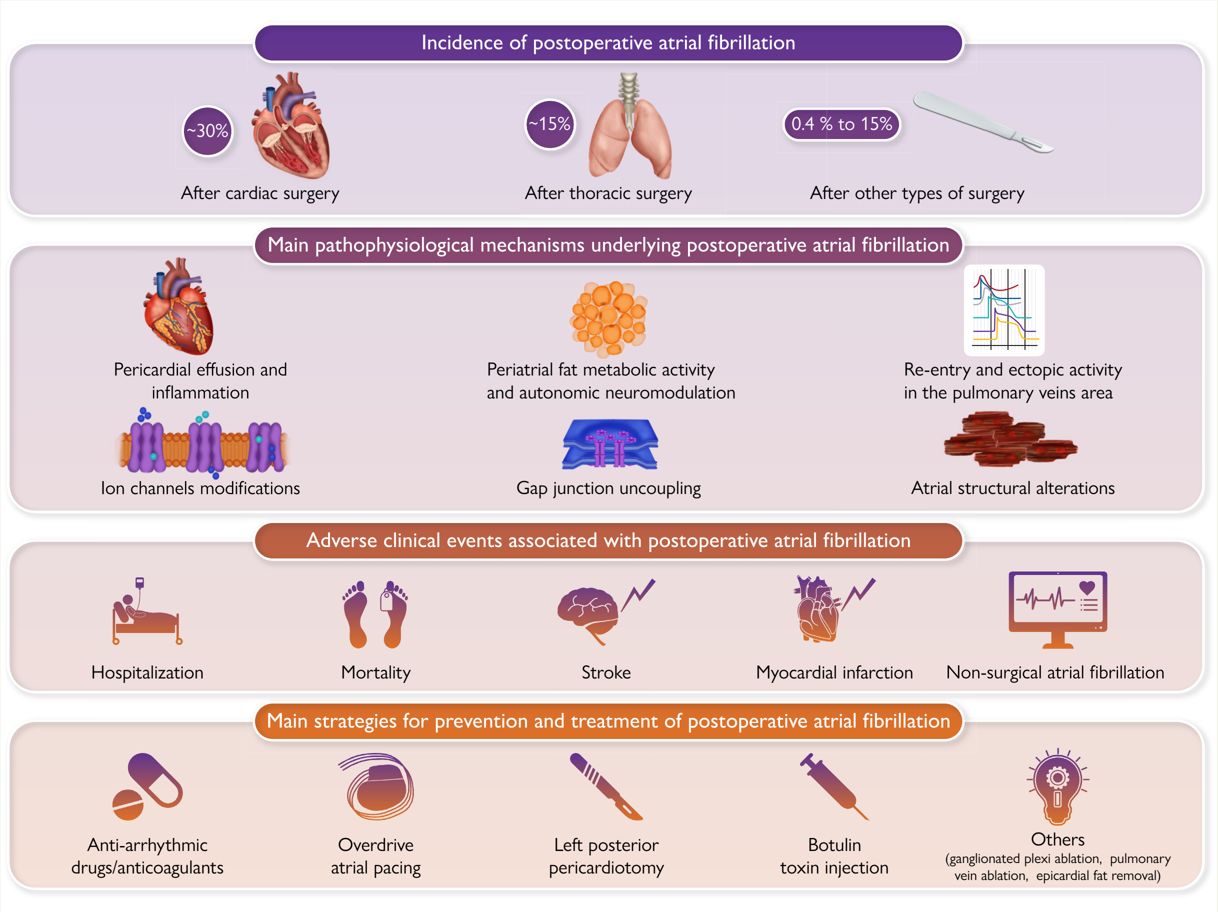
Graphical Abstract



Summary of the epidemiology, pathophysiology, associated clinical events, prevention, and treatment strategies for postoperative atrial fibrillation.

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Abstract

Postoperative atrial fibrillation (POAF) is the most common type of secondary atrial fibrillation (AF) and despite progress in prevention and treatment, remains an important clinical problem for patients undergoing a variety of surgical procedures, and in particular cardiac surgery.

POAF significantly increases the duration of postoperative hospital stay, hospital costs, and the risk of recurrent AF in the years after surgery; moreover, POAF has been associated with a variety of adverse cardiovascular events (including stroke, heart failure, and mortality), although it is still unclear if this is due to causal relation or simple association.

New data have recently emerged on the pathophysiology of POAF, and new preventive and therapeutic strategies have been proposed and tested in randomized trials.

This review summarizes the current evidence on the pathogenesis, incidence, prevention, and treatment of POAF and highlights future directions for clinical research.

Keywords Postoperative atrial fibrillation • Mechanisms • Treatment

Introduction

Postoperative atrial fibrillation (POAF) is the most common type of secondary atrial fibrillation (AF) and the most common complication after cardiac surgery.[1] POAF significantly increases in-hospital stay and costs and has been associated with a variety of adverse cardiovascular events (including stroke, heart failure, and mortality), although it is unclear if this is due to causal relation or simple association.[2–4] POAF also significantly increases the risk of recurrent AF in the years after surgery.[5,6]

In the last decade, new data have emerged on the pathophysiology of POAF, and new preventive and therapeutic strategies have been proposed and tested in randomized clinical trials (RCTs) (*Figure 1*).

We provide a summary of the current evidence on the pathogenesis, incidence, prevention, and treatment of POAF and highlight future directions for clinical research. To facilitate the reader, each section starts with a textbox highlighting key concepts.

Details of the search strategy and study selection are provided in the Supplementary material online, *Appendix*.

POAF definition and incidence

Incidence
After cardiac surgery
• Overall: ∼30%
• CABG: ∼20%
• Valve surgery: 40%–50%
• Aortic surgery: ∼30%
• Heart transplant: ∼4%
After thoracic surgery
• Overall: ∼15%
• Pneumonectomy: ∼30%
After other types of surgery
• 0.4%–15%

While POAF is generally defined as newly occurring AF immediately after surgery, there is no consensus on the details of its definition. Different authors have defined POAF either as postoperative AF requiring treatment[7] (a definition that ignores patients with self-terminating arrhythmias and those with contraindications to treatment, estimated at approximately 9600/year in the USA[8]), any postoperative AF episode lasting >30 s,[9] any postoperative new-onset AF,[10] or postoperative AF lasting longer than 10 min.[11]

Although POAF has been best studied after cardiac surgery, it is also a common and costly complication after non-cardiac surgery, such as thoracic and general surgery. Regardless of the type of surgical operation, patients who develop POAF have longer in-hospital and intensive care stays, higher hospital costs, and higher rates of both short- and long-term adverse cardiovascular events.[6,12–17]

The incidence of POAF has remained relatively stable over time, despite continued awareness of its impact on clinical outcomes, and a plethora of new and old preventative strategies.[18,19]

POAF incidence following cardiac surgery

Overall, approximately 30% of cardiac surgical patients develop POAF.[20] However, POAF occurs at different rates depending on the type of cardiac operation. The incidence of POAF is higher after valve replacement surgery (up to over 50%), and lower following coronary artery bypass grafting (CABG: 20% of the patients).[20] Cohort studies reported an incidence of approximately 30% in patients undergoing aortic surgery,[21] and higher rates in the case of the combined valve and CABG operations.[12,22] POAF incidence after a heart transplant is low (∼4%), possibly due to denervation of the implanted heart and morphologically normal implanted left atrium.[23]

The variable spectrum of reported POAF incidence may be attributed to differences in the baseline risk profiles of the patients and details of the surgical intervention, but also to heterogeneity in postoperative rhythm monitoring, and POAF definition.[11,24] For example, the use of continuous ECG monitoring has been associated with a higher rate of POAF when compared to the daily 12-lead electrocardiogram (ECG).[25]

POAF incidence following transcatheter structural heart interventions

Available data on new-onset AF following transcatheter structural heart interventions are mostly limited to patients undergoing

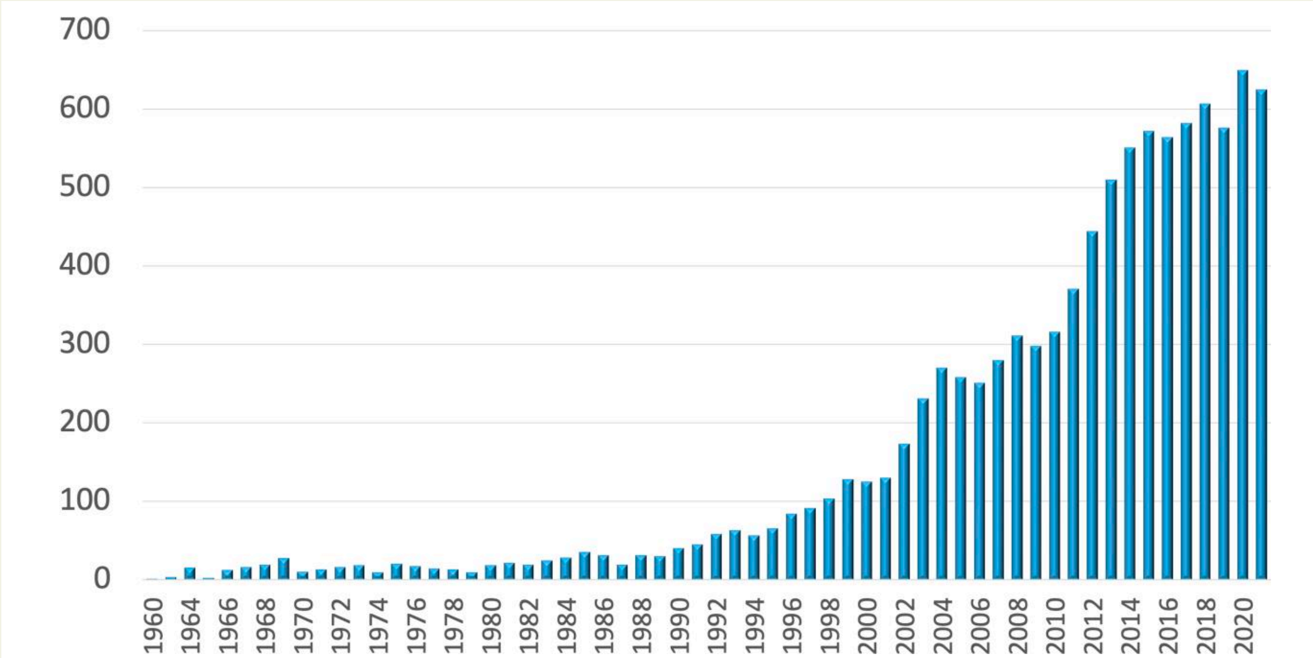

Figure 1 Number of articles on POAF published each year between 1960 and 2021.

transcatheter aortic valve replacement (TAVR). In the PARTNER (Placement of Aortic Transcatheter Valve) 3 trial, in-hospital POAF occurred in 4.3% vs. 36.6% of TAVR vs. surgical aortic valve replacement (SAVR) patients, respectively ($P < 0.0001$).[26]

In the published series, POAF incidence after TAVR ranges between 1% and 32%,[27–29] with higher rates after transapical vs. transfemoral procedures (6%–38% and 1%–16%, respectively).[29–31]

POAF incidence following thoracic surgery

POAF is relatively frequent after thoracic surgery, although its incidence is lower on average (10%–20%) compared to cardiac surgery, likely due to the better baseline cardiac status of non-cardiac surgical patients.[20,32–35] More invasive operations such as pneumonectomy, lung transplant, and esophagectomy have a higher risk of POAF (around 30%) suggesting that the extent of the surgical trauma may play a pathogenetic role.[33,36]

POAF incidence following other types of surgery

The incidence of POAF after non-cardiac and non-thoracic surgery is lower, ranging from 0.4% to 15%.[37–44] In a large cohort study (80 653 779 patients of whom 294 112 developed POAF),[44] cesarean section had the lowest risk of POAF occurrence, while colorectal surgery had the highest.

In a retrospective analysis of administrative data of 370 447 adult patients undergoing major non-cardiac surgery at 375 US hospitals,[42] 10 957 (3.0%) developed clinically significant POAF, of which 7355 (67%) had a history of previous AF episodes.

POAF pathophysiology

Main pathophysiological theories
• Atrial structural alterations
• Pericardial effusion and inflammation
• Gap junction uncoupling
• Peri-atrial adipose tissue metabolic activity
• Myocardial ischemia
• Ion channels modifications
• Autonomic neuromodulation
• Re-entry and ectopic activity in the pulmonary veins

The majority of the information on the pathophysiology of POAF is derived from the cardiac surgery series. The pathophysiology of POAF after cardiac surgery is unique relative to AF outside the perioperative period (non-surgical AF). While cardiovascular risk factors and comorbidity burden contribute to the risk of POAF, cardiac surgery imposes a unique set of circumstances that might facilitate POAF occurrence, including direct injury to the atrial myocardium, such as venous cannulation via right atriotomy or manipulation and suturing of the perivalvular atrial tissue in mitral and tricuspid surgery. Myocardial injury leads to inhomogeneity of conduction and anisotropic conduction which in turn favor dynamic re-entry and POAF.[45]

Inflammation is a key mechanism that promotes POAF. Peak concentrations of inflammatory markers like C-reactive protein occur at the same time as the peak incidence of POAF.[46] The ability of anti-inflammatory interventions to reduce the risk of POAF highlights the critical role of inflammation in the development of this arrhythmia. Of note, corticosteroid and possibly colchicine therapy have been associated with significant reductions in the occurrence of POAF.[47,48]

Models of sterile pericarditis highlight how inflammation in the pericardium can lead to the induction of atrial arrhythmias. Pre-clinical works suggest that activation of epicardial fibroblasts in the atrium leads to the loss of epicardial myocytes and changes in connexins. Decreases in connexin 40 and 43 in the epicardium and midmyocardium lead to conduction slowing, which is non-uniform and proarrhythmic.[49] Interestingly, the application of gap junction modifiers improved conduction and prevented AF in a pre-clinical model of pericarditis.[50] Shed mediastinal blood that remains in the pericardial space also leads to oxidation and inflammation.[51] Epicardial adipose tissue has been demonstrated to be a source of pro-inflammatory paracrine effects that increase the risk and severity of AF.[52,53] The secretome of atrial epicardial adipose tissue appears to promote electrical changes that directly favor AF, including reduced conduction velocity and increased heterogeneity of conduction in cardiomyocytes.[54] More recently, it has been observed that epicardial adipose-mediated interleukin (IL)-1β secretion is significantly higher in those who develop POAF compared with those individuals who do not develop POAF.[55] Proteomic and gene expression analysis of epicardial adipose tissue in individuals with and without POAF after CABG demonstrated associations of proteins involved in both inflammation and ion channel regulation with POAF.[56] Epicardial adipose mediators of inflammation and altered conduction may represent an attractive therapeutic target for localized strategies to prevent POAF since it is easily accessible at the time of cardiac surgery. Also, strategies aimed at draining the pericardium after cardiac surgery have been shown to be highly effective in reducing the incidence of POAF.[57]

Myocardial ischemia also plays an important role in the pathogenesis of POAF. Coronary obstruction in the atrial branches has been associated with the development of AF outside of surgery.[58] Ischemia-reperfusion injury to the atrial myocardium during and after the cardioplegic arrest has also been implicated in the development of POAF.[59] On-pump coronary artery bypass, which is associated with greater myocardial ischemia (and inflammation) is also associated with a higher risk of POAF than off-pump bypass.[60]

While traditional risk factors and altered atrial substrate predispose to all forms of AF, the degree to which acute factors and traditional risk factors contribute to the development of POAF is not entirely clear. Advancing age and comorbidity burden are associated with the probability of POAF.[19,61] On the other hand, while differences in ion channel activity and expression often underlie the development of non-surgical AF, it is not clear whether changes in ion channel activity and expression are critical for the induction of POAF. The aggregate evidence does not strongly support any key differences in intracellular calcium levels or potassium channel activity between patients with and without POAF.[62,63]

Autonomic influences appear to be critical in the pathogenesis of both non-surgical AF and POAF.[64–66] In particular, sympathetic activation seems to play an important role in the initiation of POAF and elevated catecholamine levels predict the onset of POAF.[67,68] Sympathetic activity leads to increased calcium gradients and afterdepolarizations that can trigger arrhythmia, particularly in the presence of concomitant parasympathetic stimulation. Parasympathetic stimulation leads to shortening of atrial-effective refractory periods.[69] For example, calcium-induced afterdepolarizations in the presence of acetylcholine have been shown to increase pulmonary vein firing.[69] Outside of the perioperative setting, pulmonary vein ectopy is known to be an important trigger of AF, and isolation of the pulmonary veins with catheter ablation leads to significant reductions in recurrent AF.[70]

Given the important role that autonomic influences and sympathetic activation have in the development of POAF, it is not surprising that beta-blocker therapy is protective against POAF. Cardiac denervation reduces the risk of POAF.[71,72] Similarly, suppression of epicardial ganglionated plexi with either injection of calcium chloride (irreversible injury) or botulinum toxin (reversible suppression) has been shown to decrease the risk and severity of POAF.[72–74] As our understanding of the autonomic changes that induce POAF improves, so too will our ability to treat and prevent POAF.

The main pathophysiological theories for POAF are summarized in *Figure 2*.

The possible overlap in risk factors for POAF following cardiac vs. non-cardiac surgery is summarized in *Figure 3*.

Association of POAF with adverse clinical events

Adverse clinical events associated with POAF
• Hospitalization for heart failure
• Mortality
• Stroke
• Myocardial infarction
• Non-surgical AF

POAF is usually an asymptomatic, self-terminating event occurring 2 to 4 days after surgery. However, the clinical relevance of POAF is not only due to the arrhythmic episode *per se*, but also to its association with increased short- and long-term complications, such as prolonged in-hospital stay, stroke, myocardial infarction, heart failure, and mortality.

Patients who develop POAF are generally older and with more complex comorbidities compared to those who do not develop the arrhythmia and the risk factors for POAF are often also risk factors for adverse cardiovascular events, complicating any attempt at defining causality. When unadjusted for confounders, POAF is strongly associated with increased morbidity and mortality.[75] In most of the published series, the association holds true even after multivariable adjustments.[75,76]

It has been shown that gene expression changes suggestive of extracellular matrix structural atrial remodeling are associated with non-surgical AF, but not with POAF.[4] However, almost all patients (83%) with non-surgical AF also experience POAF,[4,14] suggesting that while POAF and non-surgical AF are two separate entities with different underlying mechanisms, POAF could be an early predictor of the development of non-surgical AF in the years after surgery and may be the mediator of the association between POAF and adverse cardiovascular events (*Figure 4*).[3,20]

Clinical events associated with POAF following cardiac surgery

In a cohort study using administrative claims data across 11 states in the USA including 76 536 cardiac surgical patients, there was a strong

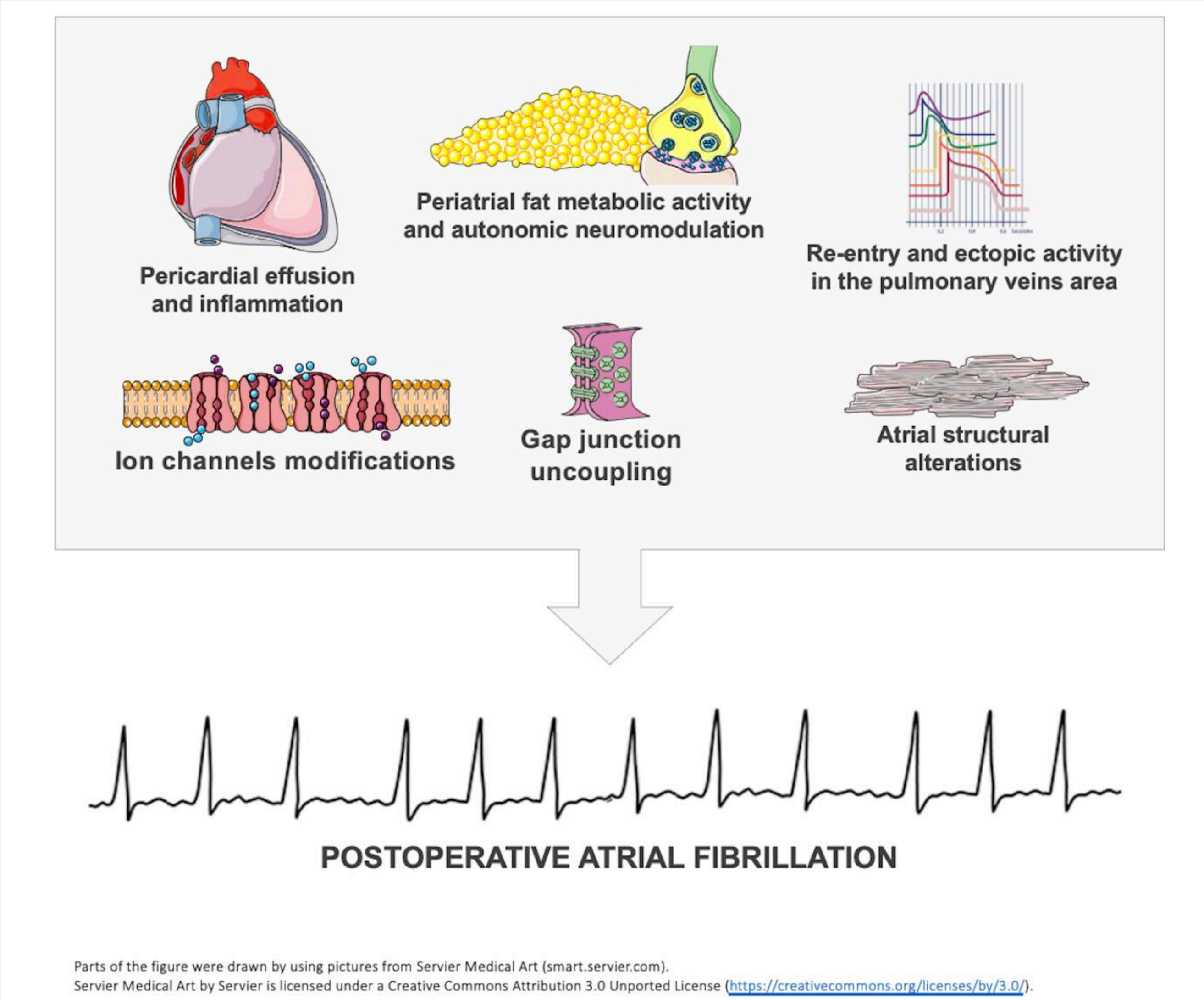

Figure 2 Summary of the main pathophysiological mechanisms underlying POAF.

and statistically significant association between POAF and hospitalization for heart failure (hazard ratio [HR] 1.33, 95% confidence interval [CI] 1.25–1.41).[77] A meta-analysis of 57 studies and 246 340 patients found that POAF was associated with perioperative mortality (odds ratio [OR] 1.92, 95%CI 1.58–2.33), stroke (OR 2.17, 95% CI 1.90–2.49), myocardial infarction (OR 1.28, 95% CI 1.06–1.54), and acute renal failure (OR 2.74, 95% CI 2.42–3.11) as well as long-term mortality and stroke.[78] In another meta-analysis of 32 studies (155 575 patients) long-term mortality was significantly higher in patients with POAF, even after adjusting for confounders (HR 1.25, 95% CI 1.2–1.3; $P < 0.01$); 1-year mortality was 6% vs. 4% (OR 1.69, 95% CI 1.1–2.6; $P = 0.02$), 5-year mortality was 15% vs. 10% (OR 1.6, 95% CI 1.52–1.68; $P < 0.0001$), and 10-year mortality was 29% vs. 23% (OR 1.51, 95% CI 1.43–1.60; $P < 0.0001$). Moreover, stroke occurred four times more frequently in patients with POAF (1% vs. 4%; OR 4.09, 95%CI 2.49–6.72; $P < 0.00001$).[79] The risk of developing non-surgical AF has been reported to be 8 times higher in patients who developed POAF.[14]

The economic impact of POAF is also relevant. In a sub analysis of the Veterans Affairs Randomized On/Off Bypass Follow-up Study including 2203 patients, adjusted first-year costs after CABG were $15 300 greater for patients with POAF.[80] If extrapolated to the number of cardiac surgery operations and assuming the reported incidence of POAF the extra cost related to POAF could exceed $2 billion/year in the USA only.[81,82]

Clinical events associated with POAF following non-cardiac surgery

In a study including 2 929 854 non-cardiac surgical patients, POAF was strongly associated with hospitalization for heart failure (HR 2.02, 95%CI 1.94–2.10).[77] A meta-analysis of 28 studies (2 612 816 patients) found that POAF after non-cardiac surgery was associated with an increase in the risk of stroke of almost three-fold at 1-month (weighted mean 2.1% vs. 0.7%; OR 2.82, 95%CI 2.15–3.70; $P < 0.001$) and four-fold at 12-month follow-up (weighted mean 2.0% vs. 0.6%; OR 4.12, 95% CI 3.34–5.11; $P < 0.001$).[36] POAF was associated with an increased risk of myocardial infarction (weighted mean 12.4% vs. 3.2%; OR 4.11, 95%CI 2.72–6.22;

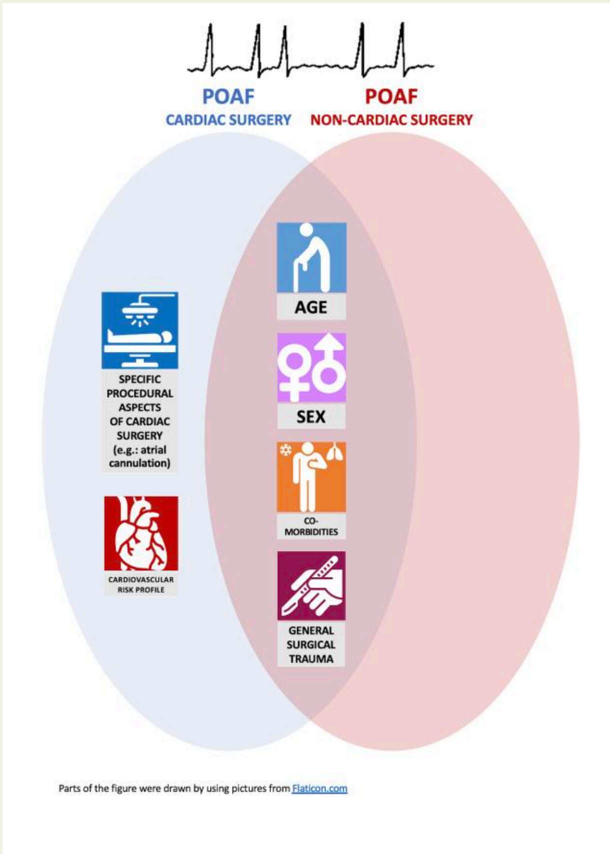

Figure 3 Overlap in risk factors for POAF following cardiac vs. non-cardiac surgery.

$P < 0.001$) and with a three-fold increased risk of mortality at ≥1-year follow-up (weighted mean 14.2% vs. 5.0%; OR 3.36, 95%CI 2.13–5.31; $P < 0.001$).

In another meta-analysis of 35 studies (2 458 010 patients), POAF was more strongly associated with stroke in patients undergoing non-cardiac surgery (HR 2.00; 95%CI 1.70–2.35) than in patients undergoing cardiac surgery (HR 1.20; 95%CI 1.07–1.34).[83] In a retrospective analysis of 370 447 patients undergoing major non-cardiac surgery,[42] patients with POAF had higher mortality (adjusted OR 1.72, 95%CI 1.59–1.86; $P < 0.001$), longer length of stay (adjusted relative difference, +24.0%, 95% CI +21.5% to +26.5%; $P < 0.001$), and higher costs (adjusted difference, +US$4,177, 95%CI +3764 to +4590; $P < 0.001$).

In patients who developed POAF after for non-cardiac surgery the incidence of non-surgical AF is approximately 18% within the first postoperative 1 year. The risk of stroke or death is similar between those who experience POAF after non-cardiac surgery and those who have non-surgical AF.[43]

Among patients who developed POAF following non-cardiac surgery procedures, those who underwent colon resections (OR 4.67, 95%CI 4.03–5.40), who had preoperative coagulopathy (OR 3.30, 95%CI 2.83–3.85), congestive heart failure (OR 2.08, 95%CI 1.81–2.40), and preoperative fluid and electrolyte disorders (OR 3.21, 95%CI 2.82–3.66) have the highest risk of death; elective procedures (OR 0.23, 95%CI 0.19–0.27) and female sex (OR 0.88, 95%CI 0.78–0.99) are associated with lower mortality rates among patients with POAF.[44]

Details of selected studies evaluating outcomes of patients developing POAF after cardiac or non-cardiac surgery are summarized in *Table 1*.[36,42,75–80,83]

POAF prevention

Strategies for POAF prevention	Strength of evidence	Mechanisms of action
• Beta-blockers	+++	- Antiadrenergic activity
• Amiodarone	+++	- Inhibition of the inward potassium current - Antiadrenergic activity - Calcium channel blockade - Sodium channel blockade
• Sotalol	++	- Potassium channel blockade - Beta-adrenergic receptor blockade
• Other antiarrhythmic drugs	(+)	- Calcium channel blockade - Sodium channel blockade - Potassium channel blockade
• Magnesium	(+)	- Unclear (might act via calcium channel blockade)
• Colchicine	(+)	- Anti-inflammatory properties
• Statins	–	- Anti-inflammatory and antioxidant properties
• Glucocorticoids	–	- Anti-inflammatory properties
• Polyunsaturated fatty acids	–	- Unclear (might act via modulation of ion channel activity)
• Overdrive atrial pacing	++	- Reduced bradycardia - Reduced atrial ectopic beat burden
• Left posterior pericardiotomy	++	- Reduced postoperative pericardial effusion
• Botulinum toxin injection	(+)	- Autonomic blockade - Autonomic neuromodulation
• Intraoperative epicardial fat removal	(+)	- Autonomic neuromodulation
• Ganglionated plexi ablation	(+)	- Autonomic blockade - Autonomic neuromodulation
• Pulmonary vein ablation	(+)	- Isolation of rapidly firing foci in or close to the pulmonary veins

Beta-blockers

Perioperative beta-blockers are the mainstay for POAF prophylaxis in patients undergoing cardiac surgery, as recommended by international guidelines (Class of Recommendation I, Level of Evidence A in the 2020 European Society of Cardiology [ESC] guidelines for the diagnosis and management of AF).[84] However, available data

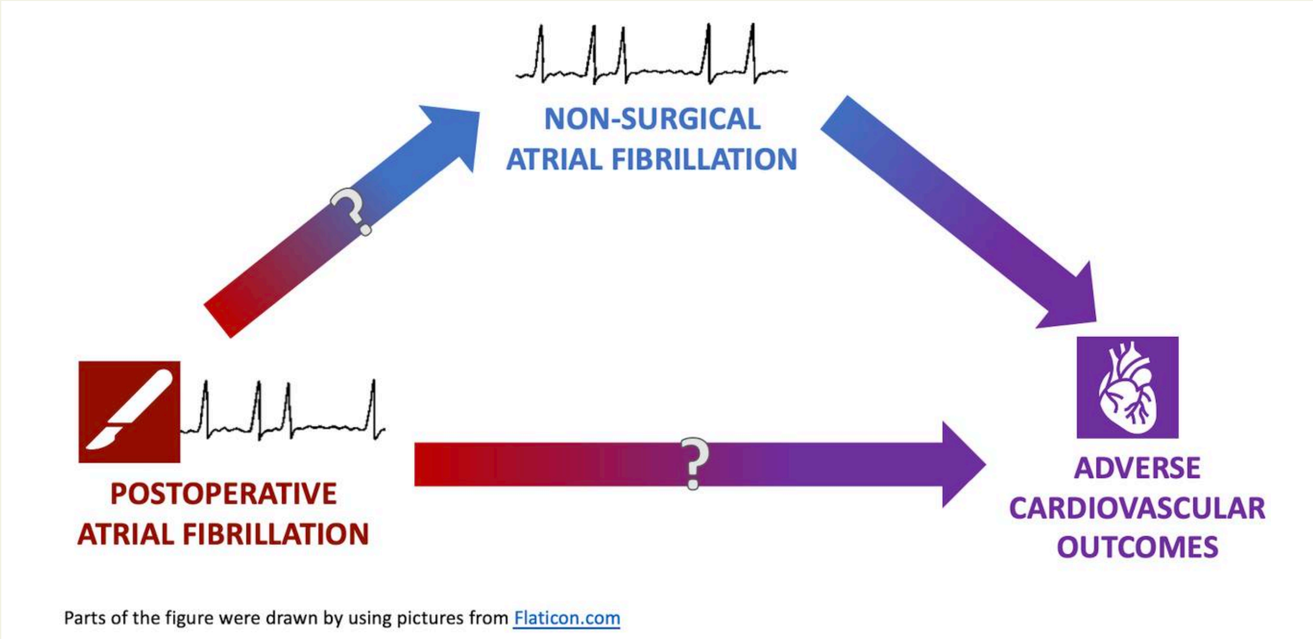

Figure 4 Association between POAF and adverse cardiovascular outcomes. Available evidence shows that POAF is strongly associated with increased rates of adverse cardiovascular outcomes; nevertheless, POAF is also an early predictor of development of non-surgical atrial fibrillation in the years after surgery, which may be the mediator of this association.

show that in clinical practice beta-blocker therapy has been limited by imperfect utilization and high rates of postoperative withdrawal (up to 25%).[19]

In a meta-analysis including 13 studies and 25 496 patients undergoing cardiac surgery, Kim et al.[85] reported significantly lower rates of POAF in those receiving perioperative beta-blockers (OR 0.56, 95% CI 0.35–0.91 and OR 0.70, 95%CI 0.55–0.91 in randomized and non-randomized studies, respectively). POAF reduction did not translate into improved clinical outcomes, as perioperative stroke and length of stay did not differ between groups. These findings are consistent with data from a Cochrane meta-analysis[86] of 33 RCTs showing reduced POAF incidence in cardiac surgical patients randomized to beta-blockers (OR 0.33, 95%CI 0.26–0.43), with no effects on length of stay, stroke rate, or mortality. A significant reduction of POAF occurrence in patients receiving prophylactic beta-blockers was also reported in a meta-analysis of 10 RCTs (2556 total patients)[87] (20% vs. 32.8% in control subjects; $P < 0.001$) that also found that carvedilol was the most effective beta-blocker for POAF prevention (55% RR reduction vs. metoprolol; $P < 0.001$).

The prophylactic us of beta-blockers in non-cardiac surgery has been associated with an increase in serious postoperative adverse events and is discouraged by international guidelines (Class of Recommendation III harm, Level of Evidence B in the 2020 ESC guidelines for the diagnosis and management of AF).[84] In an RCT involving 190 hospitals in 23 countries and a total of 8351 non-cardiac surgery patients randomized to receive metoprolol succinate immediately before surgery and then for 30 days or placebo, patients in the metoprolol group had lower risk of the composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal cardiac arrest (5.8% vs. 6.9%; HR 0.84, 95%CI 0.70–0.99; $P = 0.04$) and of myocardial infarction (4.2% vs. 5.7%; HR 0.73, 95%CI 0.60–0.89; $P = 0.001$) but higher mortality (3.1% vs. 2.3%; HR 1.33, 95%CI 1.03–1.74; $P = 0.03$) and stroke (1.0% vs. 0.5%; HR 2.17, 95%CI 1.26–3.74; $P = 0.005$).[88] In a Cochrane review of 83 RCTs including 14 967 non-cardiac surgery patients,[89] no significant differences between beta-blockers vs. control was found in postoperative mortality (risk ratio [RR] 1.17, 95%CI 0.89–1.54) and cerebrovascular events (RR 1.65, 95%CI 0.97–2.81), while lower incidence of myocardial infarction (RR 0.72, 95%CI 0.60–0.87) and postoperative AF or flutter (RR 0.41, 95%CI 0.21–0.79) were found in favor of beta-blockers.

Amiodarone

Amiodarone may exert beneficial effects in reducing POAF occurrence via multiple mechanisms, including, suppressing ectopic triggers as well as reentrant activity.[90] The evidence for its use in cardiac surgical patients is derived from multiple RCTs; the largest was the PAPABEAR (Prophylactic Amiodarone for the Prevention of Arrhythmias that Begin Early After Revascularization, Valve Replacement, or Repair) trial (601 patients),[91] where oral amiodarone led to a significant reduction in the incidence of postoperative atrial tachyarrhythmias (16.1% vs. 29.5%; HR 0.52; 95%CI 0.34–0.69; $P < 0.001$) compared to placebo, although no difference in postoperative complications or in-hospital death was reported. In a Cochrane metanalysis,[86] amiodarone was found effective in reducing POAF incidence (OR 0.43, 95%CI 0.34–0.54) and length of hospital stay (−0.95 days, 95%CI −1.37 to −0.52 days) vs. placebo, without differences in stroke rate or mortality. In a meta-analysis of 14 RCTs and 2864 patients preoperative initiation of amiodarone was not more effective than postoperative administration in reducing POAF after cardiac surgery (OR 0.50, 95%CI 0.39–0.63 vs. OR 0.48, 95%CI 0.37–0.63 for preoperative and postoperative initiation, respectively; $P = 0.86$), but a total dose of 3000 mg or higher was more effective than lower doses.[92]

Table 1 Selected studies evaluating outcomes of patients developing POAF after cardiac or non-cardiac surgery

Study, year	Type of study	Number of patients	Setting	Main results
LaPar et al., 2014[75]	Retrospective observational study	49 264	Cardiac surgery	Patients with POAF had a higher unadjusted incidence of mortality, morbidity, hospital readmission, longer intensive care unit and postoperative length of stay, and higher hospital costs. After risk adjustment, POAF was associated with a two-fold increase in the odds of mortality (adjusted OR 2.04, $P < 0.001$), greater hospital resource utilization, and increased costs.
Benedetto et al., 2020[76]	Post hoc analysis	3023	Cardiac surgery	At 10 years, the cumulative incidence of cerebrovascular accidents was 6.3% (4.6%–8.1%) in patients with POAF vs. 3.7% (2.9%–4.5%) in patients in sinus rhythm. POAF was an independent predictor of cerebrovascular accidents at 10 years (HR 1.53, 95%CI 1.06–2.23; $P = 0.025$) even when cerebrovascular accidents that occurred during the index admission were excluded from the analysis (HR 1.47, 95%CI 1.02–2.11; $P = 0.04$).
Goyal et al., 2022[77]	Retrospective cohort study	76 536 cardiac surgery patients 2 929 854 non-cardiac surgery patients	Cardiac and non-cardiac surgery	POAF was associated with hospitalization for heart failure among patients undergoing both cardiac (HR 1.33, 95%CI 1.25–1.41) and non-cardiac surgeries (HR 2.02, 95%CI 1.94–2.10).
Caldonazo et al., 2021[78]	Meta-analysis	246 340	Cardiac surgery	POAF was associated with perioperative mortality (OR 1.92, 95% CI 1.58–2.33), stroke (OR 2.17, 95% CI 1.90–2.49), MI (OR 1.28, 95% CI 1.06–1.54), and acute renal failure (OR 2.74, 95%CI 2.42–3.11) as well as long-term mortality (IRR 1.54, 95%CI 1.40–1.69) and stroke (IRR,1.33, 95%CI 1.21–1.46).
Eikelboom et al, 2021[79]	Meta-analysis	155 575	Cardiac surgery	Long-term mortality was significantly higher in patients with POAF, even after adjusting for confounders (HR 1.25, 95%CI 1.2–1.3; $P < 0.01$). In patients with and without POAF 1-year mortality was 6% vs. 4% (OR 1.69, 95%CI 1.1–2.6; $P = 0.02$), 5-year mortality was 15% vs. 10% (OR 1.6, 95%CI 1.52–1.68; $P < 0.0001$), and 10-year mortality was 29% vs. 23% (OR 1.51, 95%CI, 1.43–1.60; $P < 0.0001$). Stroke occurred four times more frequently in patients with POAF (1% vs. 4%; OR 4.09, 95%CI 2.49–6.72; $P < 0.00001$).
Almassi et al., 2021[80]	Post hoc analysis	2203	Cardiac surgery	Adjusted first-year post-CABG costs were $15 300 greater for patients with POAF.
AlTurki et al., 2020[36]	Meta-analysis	2 929 854	Non-cardiac surgery	POAF after non-cardiac surgery was associated with an increase in the risk of stroke of almost three-fold at 1-month (weighted mean 2.1% vs. 0.7%; OR 2.82, 95%CI 2.15–3.70; $P < 0.001$) and four-fold at 12-month follow-up (weighted mean 2.0% vs. 0.6%; OR 4.12, 95%CI 3.34–5.11; $P < 0.001$). POAF was also associated with an increased risk of MI (weighted mean 12.4% vs. 3.2%; OR 4.11, 95% CI 2.72–6.22; $P < 0.001$) and with a three-fold increased risk of mortality at ≥1-year follow-up (weighted mean 14.2% vs. 5.0%; OR 3.36, 95%CI 2.13–5.31; $P < 0.001$)
Lin et al., 2019[83]	Meta-analysis	2 458 010	Cardiac and non-cardiac surgery	POAF association with stroke was stronger in patients undergoing non-cardiac surgery (HR 2.00; 95%CI 1.70–2.35) than in patients undergoing cardiac surgery (HR 1.20; 95%CI 1.07–1.34)
Bhave et al., 2012[42]	Retrospective observational study	370 447	Major non-cardiac surgery	Patients with POAF had higher mortality (adjusted odds ratio [OR] 1.72, 95%CI 1.59–1.86; $P < 0.001$), longer length of stay (adjusted relative difference, + 24.0%, 95%CI +21.5% to +26.5%; $P < 0.001$), and higher costs (adjusted difference, +$4,177, 95%CI +$3764 to + $4590; $P < 0.001$) compared to patients without POAF.

CI, confidence interval; HR, hazard ratio; IRR, incidence rate ratio; MI, myocardial infarction; OR, odds ratio; POAF, postoperative atrial fibrillation.

Amiodarone utilization is limited by risks of bradyarrhythmia, acute lung injury, and infusion-related hypotension.[93] Acute lung injury, while rare, is more likely to occur under high oxygen tensions, common in ventilated patients post-cardiac surgery.[94,95]

Sotalol

In a meta-analysis of 14 RCTs (5205 patients), sotalol significantly reduced the incidence of POAF following cardiac surgery compared with placebo (OR 0.37, 95%CI 0.29–0.48) and beta-blockers

(OR 0.42, 95%CI 0.26–0.65).[96] In the REDUCE trial, no significant differences in the risk of POAF was found among 160 cardiac surgical patients randomized to receive amiodarone or sotalol (17% vs. 25%, $P = 0.21$).[97] Sotalol is renally cleared and may lead to QT prolongation, which make its use complex in cardiac surgery patients.[20]

Other antiarrhythmic drugs

Limited data are available on the use of other antiarrhythmic drugs for POAF prophylaxis.

The evidence supporting the use of calcium-channel blockers is weak.[20,98] In a meta-analysis of 41 studies (3327 patients), calcium-channel blockers had no significant effect on the occurrence of postoperative supraventricular tachycardia in patients undergoing cardiac surgery (OR 0.73, 95%CI 0.48–1.12); at subgroup analysis non-dihydropyridine agents reduced the incidence of the arrhythmias (OR 0.62, 95%CI 0.41–0.93), whereas dihydropyridine agents increased it (OR 2.69, 95%CI 0.57–12.64).[98]

Very limited evidence is available on the use of class Ia, class Ic, or class III antiarrhythmic drugs (e.g.: procainamide, propafenone, and dofetilide). It is generally considered that antiarrhythmic drugs should be used with caution in the postoperative period, as their proarrhythmic adverse effects could be worsened in the setting of myocardial ischemia, concomitant inotropes administration, electrolyte disorders, hemodynamic instability, and abnormal liver and/or renal function.[20]

Magnesium

Conflicting data exist on the efficacy of intravenous magnesium for POAF prophylaxis.[99,100] In an RCT of 389 cardiac surgery patients randomized to receive magnesium as a 50 mg/kg bolus immediately after induction of anesthesia followed by another 50 mg/kg infusion over 3 h magnesium did not reduce the incidence of POAF compared with placebo.[101] In a meta-analysis of 20 small to medium-sized RCTs (2490 patients), magnesium administration was associated with a lower incidence of POAF (OR 0.54, 95%CI 0.38–0.75), with no effects on in-hospital length of stay or mortality.[102] Similar results were reported in a Cochrane meta-analysis of 22 small- and medium-sized RCTs.[86] However in a meta-analysis limited to five high-quality RCTs, magnesium administration was not associated with a significant reduction in POAF (OR 0.94, 95%CI 0.61–1.44; $P = 0.77$).[103]

Colchicine

Current evidence supporting the use of colchicine for POAF prophylaxis is mixed. In the END-AF (Effect of Low-dose ColchiciNe on the InciDence of Atrial Fibrillation in Open Heart Surgery Patients) trial,[104] low-dose colchicine did not prevent POAF in patients undergoing cardiac surgery (OR 0.85, 95%CI 0.37–1.99); the study was closed prematurely due to slow recruitment and had limited statistical power. However, in the Colchicine for the Prevention of the Post-Pericardiotomy Syndrome (COPPS) POAF substudy, 1-month colchicine reduced POAF incidence (12.0% vs. 22.0%; $P = 0.021$), in-hospital stay (9.4 ± 3.7 vs. 10.3 ± 4.3 days; $P = 0.040$) and rehabilitation stay (12.1 ± 6.1 vs. 13.9 ± 6.5 days; $P = 0.009$) after cardiac surgery.[48] The ongoing COP-AF (Colchicine For The Prevention Of Perioperative Atrial Fibrillation In Patients Undergoing Thoracic Surgery) trial (NCT03310125; *Table 2*) will provide important information on the role of colchicine for POAF prevention.

Statins, glucocorticoids, and polyunsaturated fatty acids

Statins, glucocorticoids, and polyunsaturated fatty acids (PUFA) have been proposed for POAF prevention based on their anti-inflammatory (statins, glucocorticoids) and electrophysiological (PUFA) effects. However, available data on their efficacy are limited and current guidelines do not support their routine use.[84]

Overdrive atrial pacing

Overdrive atrial pacing has been shown to prevent POAF in multiple RCTs.[105] In a Cochrane meta-analysis, Arsenault et al.[86] reported that the incidence of POAF across 21 trials (2933 participants) was reduced from 32.8% in the non-paced group to 18.7% in the paced group (OR 0.47, 95%CI 0.36–0.61). In a small RCT of 118 patients, bi-atrial overdrive pacing for 96 h reduced the occurrence of POAF vs. standard therapy (OR 0.38, 95%CI 0.15–0.93).[106] In a network meta-analysis of 14 RCTs (1727 patients) atrial pacing was associated with significantly lower incidence of POAF after CABG (OR 0.49, 95%CI 0.35–0.69) and bi-atrial pacing was associated with the largest risk reduction (OR 0.36, 95%CI 0.20–0.64 vs. OR 0.59, 95%CI 0.34–1.02 for left-atrial and OR 0.64, 95%CI 0.38–1.07 for right-atrial pacing).[107]

Overdrive atrial pacing is logistically difficult to implement in routine clinical practice and may interfere with patients' activities in the postoperative period; its adoption outside of dedicated studies has therefore been limited.

Left posterior pericardiotomy

Left posterior pericardiotomy is a surgical procedure that allows drainage of the pericardium into the left pleural space. Several RCTs have tested the role of posterior pericardiotomy in reducing POAF incidence, most of them reporting a significant effect; however, the methodologic quality of the RCTs was generally medium or low.[2] In a meta-analysis of 10 RCTs including a total of 1829 CABG patients, the incidence of POAF was significantly reduced in the posterior pericardiotomy group (RR 0.45, 95%CI 0.29–0.64; $P < 0.0001$).[108] The effects of posterior pericardiotomy were recently assessed in a well-powered, single-center RCT confirming that the intervention largely and significantly reduced the incidence of POAF (17% vs. 32%; $P < 0.001$; OR: 0.44, 95%CI 0.27–0.70; $P < 0.001$).[9]

Botulinum toxin injection, intraoperative epicardial fat removal, ganglionated plexi, and pulmonary vein ablation

Autonomic regulation and paracrine secretion of adipokines and cytokines mediated by peri-atrial fat play an important role in the modulation of atrial rhythm. However, current evidence suggests that anterior fat pad removal is not associated with decreased risk of POAF, as reported in a meta-analysis of seven RCTs including 991 CABG patients (RR 1.34, 95%CI 0.88–2.03; $P = 0.18$).[109]

Botulinum toxin injection for POAF prevention has shown promising results in animal models and in a small RCT including 60 CABG patients with a history of paroxysmal AF (POAF incidence: 7% vs. 30% in the intervention group vs. controls, respectively; $P = 0.024$).[110] The upcoming results of the NOVA trial (NCT03779841)[111] and of the ongoing

Table 2 Main ongoing randomized clinical trials on prevention and management of postoperative atrial fibrillation

Study name/Title	Design	*n*	Aim(s)	Population	Intervention(s)	Primary outcome(s)
CARDIAC SURGERY PATIENTS						
POAF prevention						
Assessment of IntraOperative Atrial Fibrillation Inducibility As a Screening Tool to Prevent PostOperative Atrial Fibrillation With Prophylaxis Amiodarone (NCT03868150)	Allocation: Randomized Intervention Model: Parallel Assignment Intervention Masking: None (Open Label)	600	To evaluate the effects of amiodarone on patients with inducible AF in reducing POAF incidence	Patients undergoing first time cardiac surgery	Use of prophylactic amiodarone vs. standard of care in patients with inducible AF (as screened by rapid atrial pacing prior to initiation of cardiopulmonary bypass)	Incidence of POAF
LANDI-POAF (Landiolol for Prevention of Postoperative Atrial Fibrillation in Patients Undergoing Cardiac Surgery) (NCT05084118)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	164	To evaluate whether postoperative low-dose landiolol reduces the incidence of POAF	Non-Asian patients undergoing cardiac surgery	Use of landiolol vs. placebo	Death from any reason or the occurrence of POAF
PREEMPTIVE (Preemptive Pharmacogenetic-guided Metoprolol Management for Postoperative Atrial Fibrillation in Cardiac Surgery) (NCT03943927)	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label)	400	To determine the genotype of CYP2D6 for patients undergoing cardiac surgery, provide an altered dosing recommendation for metoprolol, and report the relative effectiveness in managing POAF for each pharmacogenetic-guided dosing category	Patients undergoing cardiac surgery	Pharmacogenetic-guided metoprolol management	Incidence of POAF
STOP_AF (Transcutaneous [Tragus] Vagal Nerve Stimulation for Post-op Afib) (NCT04514757)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Outcomes Assessor)	266	To determine the value of transcutaneous (tragus) vagus nerve stimulation in reducing the burden of POAF and days of hospitalization after cardiac surgery.	Patients undergoing cardiac surgery	Active transcutaneous (tragus) vagus nerve stimulation vs. sham control	Incidence of POAF
COCS (COlchicine in Cardiac Surgery) (NCT04224545)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Investigator)	1000	To study the effectiveness of short-term administration of colchicine on POAF treatment	Patients undergoing cardiac surgery	Use of colchicine vs. placebo	Incidence of POAF
LANDIPROTEC (Prevention of Atrial Fibrillation by Low-dose Landiolol	Allocation: Randomized Intervention Model: Parallel Assignment	400	To evaluate whether landiolol postoperative infusion is associated with lower incidence of POAF without excess	Non-Asian patients	Use of landiolol vs. placebo	Incidence of POAF

Continued

Table 2 *Continued*

Study name/Title	Design	*n*	Aim(s)	Population	Intervention(s)	Primary outcome(s)
CARDIAC SURGERY PATIENTS						
POAF prevention						
Administration After Cardiac Surgery) (NCT04607122)	Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)		of adverse events as compared to standard of care	undergoing cardiac surgery		
BOTAF (Prevention Atrial Fibrillation by BOTulinum Toxin Injections) (NCT04075981)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Investigator)	220	To evaluate whether botulinum toxin injection may reduce POAF during the first postoperative month after cardiac surgery without any serious adverse events	Patients undergoing cardiac surgery	Botulinum toxin type A intraoperative injection vs. placebo	Incidence of POAF
Effects of Left Atrial Appendage Resection and Marshall Ligament Amputation on Clinical Outcome in Patients Undergoing Off-pump Coronary Artery Bypass (NCT04220047)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Investigator)	400	To investigate whether surgical occlusion of the left atrial appendage and Marshall ligament amputation during off-pump CABG is associated with reduced risks of POAF and stroke	Patients undergoing off-pump CABG	Left atrial appendage resection and Marshall Ligament amputation vs. no intervention	Incidence of POAF
Safety and Efficacy of Tocotrienols in Post-CABG Atrial Fibrillation (NCT03807037)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Investigator, Outcomes Assessor)	280	To evaluate the effects of supplementation with tocotrienols reducing the incidence of AF	Patients undergoing CABG	Use of tocotrienols vs. placebo	Incidence of POAF
TraP-AF (Tragus Stimulation to Prevent Atrial Fibrillation After Cardiac Surgery) (NCT03392649)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Single (Participant)	80	To determine whether tragus stimulation in subjects undergoing cardiac surgery leads to shorter occurrences, or even prevention, of POAF	Patients undergoing cardiac surgery	Tragus stimulation vs. sham control	Time to the first episode of AF >30 s Extended hospitalization of >5 days
Paravertebral Block to Reduce the Incidence of New Onset Atrial Fibrillation After Cardiac Surgery (NCT04472299)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label)	30	To determine if a perioperative infusion of ropivacaine via bilateral T3 paravertebral catheters can decrease the incidence of POAF	Patients undergoing cardiac surgery	Perioperative infusion of ropivacaine vs. no intervention	Incidence of POAF

Continued

Table 2 *Continued*

Study name/Title	Design	*n*	Aim(s)	Population	Intervention(s)	Primary outcome(s)
CARDIAC SURGERY PATIENTS						
POAF prevention						
PULVAB (Randomized Clinical Trial PULVAB -Prophylactic Pulmonary Veins Ablation) (NCT03857711)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label)	280	To compare different POAF prophylactic strategies: -Group I (conventional CABG) -Group II (CABG + pulmonary veins isolation) -Group III (CABG + pulmonary veins isolation + amiodarone) -Group IV (CABG + amiodarone)	Patients undergoing CABG	–Group I (conventional CABG) -Group II (CABG + pulmonary veins isolation). Concomitant CABG and epicardial bipolar radiofrequency pulmonary veins isolation. Group III (CABG + pulmonary veins isolation + amiodarone). Concomitant CABG and epicardial bipolar radiofrequency pulmonary veins ablation with administration of amiodarone in postoperative period. -Group IV (CABG + amiodarone). Conventional CABG with administration of amiodarone in postoperative period.	Incidence of POAF Major cardiovascular and cerebral events
POAF management						
PACES (Anticoagulation for New-Onset PostOperative Atrial Fibrillation After CABG) (NCT04045665)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label)	3200	To evaluate the effectiveness and safety of adding OAC to background antiplatelet therapy in patients with POAF	Patients undergoing isolated CABG	OAC in addition to concomitant antiplatelet therapy vs. no-OAC	Composite score of death, stroke, TIA, MI, systemic arterial thromboembolism or venous thromboembolism (deep venous thrombosis and/or pulmonary embolism). Any BARC (Bleeding Academic Research Consortium) type 3 or 5
TASK-POAF (Cost-effectiveness Analysis Between Two Anticoagulation Strategies for Atrial Fibrillation in the Postoperative Period of Coronary Artery Bypass Graft Surgery) (NCT05300555)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label)	50	To compare the cost-effectiveness related to the warfarin prescription strategy associated with bridge anticoagulation vs. the rivaroxaban prescription in patients with POAF with a minimum duration of 12 h or AF that requires intervention.	Patients undergoing CABG	Use of rivaroxaban vs. warfarin	Cost-effectiveness of the treatments in both therapeutic groups (rivaroxaban and warfarin)
NEW-AF (Rivaroxaban vs. Warfarin for Post-Cardiac Surgery Atrial Fibrillation) (NCT03702582)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Statisticians only	300	To compare the safety and financial benefits of arterial thromboembolism prophylaxis with warfarin vs. rivaroxaban in patients with POAF	Patients undergoing cardiac surgery	Use of rivaroxaban vs. warfarin	Postoperative length of stay

Continued

Table 2 Continued

Study name/Title	Design	*n*	Aim(s)	Population	Intervention(s)	Primary outcome(s)
CARDIAC SURGERY PATIENTS						
POAF prevention						
NON-CARDIAC SURGERY PATIENTS						
POAF prevention						
The Effect of IntraOperative Dexmedetomidine in Prevention of Early Postoperative Atrial Fibrillation in Patients Undergoing Thoracic Non-Cardiac Surgeries: a Randomized Controlled Trial (NCT05320705)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	350	To evaluate the efficacy of intraoperative dexmedetomidine in reducing the incidence of POAF	Patients undergoing thoracic non-cardiac surgery	Use of intraoperative dexmedetomidine vs. placebo	Incidence of POAF
COP-AF (Colchicine For The Prevention Of Perioperative Atrial Fibrillation In Patients Undergoing Thoracic Surgery) (NCT03310125)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Investigator, Outcomes Assessor)	2800	To assess whether the administration of oral colchicine reduces the incidence of POAF in patients undergoing major thoracic surgery	Patients undergoing thoracic surgery	Use of colchicine vs. placebo	Incidence of clinically important POAF
POAF management						
ASPIRE-AF (Anticoagulation for Stroke Prevention In Patients With Recent Episodes of Perioperative Atrial Fibrillation After Non-cardiac Surgery) (NCT03968393)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Single (Outcomes Assessor)	2800	To assess the effects of NOACs vs. no anticoagulation on the co-primary composite outcomes of (i) non-hemorrhagic stroke and systemic embolism, and (ii) vascular mortality, and non-fatal non-hemorrhagic stroke, MI, peripheral arterial thrombosis, amputation, and symptomatic venous thromboembolism 24 months after randomization.	Patients undergoing non-cardiac surgery	Use of NOAC vs. no anticoagulation	Incidence of non-hemorrhagic stroke or systemic embolism Incidence of vascular mortality, and non-fatal non-hemorrhagic stroke, MI, peripheral arterial thrombosis, amputation, and symptomatic venous thromboembolism

Source: Clinicaltrials.gov (accessed: 15 September 2022).
AF, atrial fibrillation; CABG, coronary artery bypass grafting; MI, myocardial infarction; NOAC, non-vitamin K oral anticoagulants; OAC, oral anticoagulant; POAF, postoperative atrial fibrillation; TIA, transient ischemic attack.

Table 3 Selected studies evaluating main strategies for prevention of postoperative atrial fibrillation

Study, year	Type of study	Number of patients	Setting	Tested interventions	Primary outcome	Follow-up	Main results
Kim et al., 2021[85]	Meta-analysis (five randomized and eight non-randomized studies)	25 496	Cardiac surgery	Beta-blockers vs. placebo	POAF incidence	In-hospital stay	Lower incidence of POAF in the beta-blocker group (OR 0.56, 95%CI 0.35–0.91 and OR 0.70, 95%CI 0.55–0.91 in randomized and non-randomized studies, respectively). Perioperative stroke and length of stay did not differ between the two groups.
Arsenault et al., 2013[86]	Cochrane meta-analysis (33 RCTs)	4698	Cardiac surgery	Beta-blockers vs. placebo	POAF or supraventricular tachycardia incidence	In-hospital stay	Lower incidence of POAF in the beta-blockers group (OR 0.33, 95%CI 0.26–0.43). No effects on length of stay, stroke rate or mortality.
Khan et al., 2013[87]	Meta-analysis (10 RCTs)	2556	Cardiac surgery	Beta-blockers vs. placebo	POAF incidence	In-hospital stay	Lower incidence of POAF in the beta-blockers group (20% vs. 32.8% in control subjects; $P < 0.001$). Carvedilol was the most effective beta-blocker for POAF prevention (55% RR reduction vs. metoprolol; $P < 0.001$).
POISE study, 2008[88]	RCT	8351	Non-cardiac surgery	Beta-blockers (extended-release metoprolol succinate) vs. placebo	Composite of cardiovascular death, non-fatal MI, and non-fatal cardiac arrest	30-day	Lower incidence of both the primary composite endpoint (5.8% vs. 6.9%; HR 0.84, 95%CI 0.70–0.99, $P = 0.04$) and of MI (4.2% vs. 5.7%; HR 0.73, 95%CI 0.60–0.89, $P = 0.001$) in the beta-blockers group. Higher rates of death (3.1% vs. 2.3%; HR 1.33, 95%CI 1.03–1.74, $P = 0.03$) and stroke (1.0% vs. 0.5%; HR 2.17, 95%CI 1.26–3.74, $P = 0.005$) were reported in the beta-blockers group.
PAPABEAR study, 2005[91]	RCT	601	Cardiac surgery	Amiodarone vs. placebo	Incidence of atrial tachyarrhythmias lasting 5 min or longer that prompted therapy by the sixth postoperative day.	1 year	Lower rates of postoperative atrial tachyarrhythmias in the amiodarone group (16.1% vs. 29.5%; HR 0.52; 95%CI 0.34–0.69; $P < 0.001$). No differences between the 2 groups were reported in serious postoperative complications, in-hospital mortality, or readmission to the hospital within 6 months of discharge or in 1-year mortality.
Arsenault et al., 2013[86]	Cochrane meta-analysis (33 RCTs)	5402	Cardiac surgery	Amiodarone vs. placebo	POAF or supraventricular tachycardia incidence	In-hospital stay	Lower incidence of POAF (OR 0.43, 95% CI 0.34–0.54) and length of hospital stay (−0.95 days, 95%CI −1.37 to −0.52 days) in the amiodarone group. No differences in stroke rate or mortality between the two groups.

Continued

Table 3 ***Continued***

Study, year	Type of study	Number of patients	Setting	Tested interventions	Primary outcome	Follow-up	Main results
Arsenault et al., 2013[86]	Cochrane meta-analysis (21 RCTs)	2933	Cardiac surgery	Overdrive atrial pacing vs. no pacing (no distinction between pacing sites)	POAF or supraventricular tachycardia incidence	In-hospital stay	Lower incidence of POAF in the pacing group (32.8% in the nopacing group vs. 18.7% in the paced group (OR 0.47, 95%CI 0.36–0.61).
Ruan et al., 2020[107]	Pairwise and network meta-analysis (14 RCTs)	1727	Cardiac surgery	Overdrive atrial pacing (bi-atrial, left-atrial, and right-atrial pacing) vs. no pacing	POAF incidence	In-hospital stay	Compared with no pacing, any form of atrial pacing was significantly associated with lower incidence of POAF (OR 0.49, 95%CI 0.35–0.69). Bi-atrial pacing was associated with the largest risk reduction (OR 0.36, 95%CI 0.20–0.64 vs. OR 0.59, 95%CI 0.34–1.02 for left-atrial and OR 0.64, 95%CI 0.38–1.07 for right-atrial pacing).
Xiong et al., 2021[108]	Meta-analysis (10 RCTs)	1829	Cardiac surgery	Left posterior pericardiotomy vs. no intervention	POAF incidence	In-hospital stay	Lower incidence of POAF in the posterior pericardiotomy group (risk ratio 0.45, 95%CI 0.29–0.64, $P < 0.0001$).
PALACS trial, 2021[9]	RCT	420	Cardiac surgery	Left posterior pericardiotomy vs. no intervention	POAF incidence	In-hospital stay	Lower incidence of POAF in the posterior pericardiotomy group (17% vs. 32%; $P < 0.001$; OR: 0.44, 95%CI 0.27–0.70, $P < 0.001$).

CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; OR, odds ratio; POAF, postoperative atrial fibrillation; RCT, randomized clinical trial.

Table 4 Summary of the recommendations for the management of postoperative atrial fibrillation from the current European Society of Cardiology (ESC) and American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guidelines[84,119,122]

Recommendation	Class of recommendation	Level of evidence
POAF PREVENTION		
EU 2020 ESC Guidelines		
Cardiac surgery: Perioperative amiodarone or beta-blocker therapy is recommended for the prevention of POAF.	I	A
Non-cardiac surgery: Beta-blockers should not be used routinely for the prevention of POAF.	III	B
US 2014 AHA/ACC/HRS Guidelines (updated 2019)		
Cardiac surgery: Preoperative administration of amiodarone reduces the incidence of AF and is reasonable as prophylactic therapy for patients at high risk for POAF.	IIa	A
Cardiac surgery: Prophylactic administration of sotalol may be considered for patients at risk of developing AF.	IIb	B
Cardiac surgery: Administration of colchicine may be considered for patients postoperatively to reduce AF.	IIb	B
POAF TREATMENT		
US 2014 AHA/ACC/HRS Guidelines (updated 2019)		
Cardiac surgery: Treating patients who develop AF with a beta blocker is recommended unless contraindicated.	I	A
A non-dihydropyridine calcium channel blocker is recommended when a beta blocker is inadequate to achieve rate control in patients with POAF.	I	B
It is reasonable to restore sinus rhythm pharmacologically with ibutilide or direct-current cardioversion in patients who develop POAF, as advised for non-surgical patients.	IIa	B
It is reasonable to administer antiarrhythmic medications in an attempt to maintain sinus rhythm in patients with recurrent or refractory POAF, as advised for other patients who develop AF.	IIa	B
It is reasonable to manage well-tolerated, new-onset POAF with rate control and anticoagulation with cardioversion if AF does not revert spontaneously to sinus rhythm during follow-up.	IIa	C
STROKE PREVENTION		
EU 2020 ESC Guidelines		
Non-cardiac surgery: Long-term OAC therapy to prevent thromboembolic events should be considered in patients at risk for stroke with POAF, considering the anticipated net clinical benefit of OAC therapy and informed patient preferences.	IIa	B
Cardiac surgery: Long-term OAC therapy to prevent thromboembolic events may be considered in patients at risk for stroke with POAF, considering the anticipated net clinical benefit of OAC therapy and informed patient preferences.	IIb	B
US 2014 AHA/ACC/HRS Guidelines (updated 2019)		
It is reasonable to administer antithrombotic medication in patients who develop POAF, as advised for non-surgical patients.	IIa	B

AF, atrial fibrillation; OAC, oral anticoagulant; POAF, postoperative atrial fibrillation.

BOTAF study (NCT04075981) are expected to shed more light on the role of this interesting strategy to prevent POAF (*Table 2*).

The effects of map-guided ablation of the ganglionated plexi have been tested in the Mapping and ablation of autonomic ganglia in prevention of POAF in coronary surgery trial, a pilot study that reported a 32% reduction in POAF incidence with mapping and ablation.[112] More recently, Wang et al.[73] reported a 63% reduction in POAF following $CaCl_2$ injection into the four major atrial ganglionated plexi ($P = 0.001$).

Current evidence suggests a little role for systematic pulmonary vein ablation for POAF prevention in cardiac surgical patients. In a study of 175 CABG patients randomized to undergo bilateral radiofrequency pulmonary vein ablation in addition to CABG or CABG alone (and in whom intraoperative pulmonary vein isolation was confirmed by the inability to pace the heart via the pulmonary veins after the ablation) no difference in POAF incidence was seen between the groups (37.1% vs. 36.1%; $P = 0.88$).[113] The ongoing PULVAB trial (NCT03857711) will provide more information on this strategy for POAF prophylaxis (*Table 2*).

Details of selected studies evaluating main strategies for POAF prevention are summarized in *Table 3*.[9,85–88,91,107,108]

POAF treatment

Rate vs. rhythm control

Treatment of POAF is highly variable, including the use of rate control, cardioversion, and antiarrhythmic medication.[114] When POAF

Table 5 Main gaps in current knowledge of postoperative atrial fibrillation

Gaps in knowledge
While POAF is generally defined as newly occurring AF immediately after surgery, there is no consensus on the details of its definition.
The mechanisms that initiate and sustain POAF are still not completely understood.
While traditional risk factors and altered atrial substrate predispose to all forms of AF, the degree to which acute factors and traditional risk factors contribute to the development of POAF is not entirely clear.
The nature of the relationship between POAF and subsequent adverse cardiovascular events remains unclear (causal relation or association?).
The use of oral anticoagulation to prevent stroke in patients with POAF is controversial; current evidence to support its use is mixed.

AF, atrial fibrillation; POAF, postoperative atrial fibrillation.

complicates cardiac surgery, patients with hemodynamic instability require immediate cardioversion and restoration of sinus rhythm. In hemodynamically stable patients, POAF can be treated with rate or rhythm control. Recommended drugs for rate control are beta-blockers, calcium-channel blockers, or digoxin in patients with preserved left ventricular ejection fraction (LVEF), and beta-blockers or digoxin in patients with reduced LVEF. When pharmacologic cardioversion is attempted, Class IC or III antiarrhythmic drugs should be preferred in patients with normal LVEF, while amiodarone should be used in those with reduced LVEF.[84]

Previously, evidence to support rate or rhythm control has been limited and predominantly originated from observational studies. A pilot trial published in 2003 suggested the potential for the reduced in-hospital length of stay with rhythm control.[115] However, an RCT comparing rate vs. rhythm control in 523 patients with POAF after cardiac surgery (CABG, valve surgery, or both) conducted by the Cardiothoracic Surgical Trials Network found no evidence for superiority with either a rate control only or a rhythm control approach.[116] In this RCT, rate control was predominantly achieved with beta-blockers (target heart rate: < 100 bpm) while rhythm control was performed with amiodarone (3 g load and 200 mg daily maintenance dose) and cardioversion, when necessary. At the end of the 60-day follow-up, there was no significant difference in in-hospital stay ($P = 0.76$), survival ($P = 0.64$), or serious adverse events ($P = 0.61$) between the two strategies. Notably, treatment deviation occurred in about 1 in 4 patients in both arms, highlighting the difficulties with these medications due to either ineffectiveness of rate control or adverse side effects with amiodarone. It is also important to note that the majority of patients were in sinus rhythm at discharge and at 60 days (94% in rate control and 98% in rhythm control), displaying the transient nature of POAF in most patients (acknowledging the high-rate of long-term recurrence). Thus, at present, managing hemodynamically stable POAF can be approached with either a rate or rhythm control strategy.

Stroke prevention

The use of systemic oral anticoagulation in ambulatory patients with established AF is supported by a wealth of data from RCTs.[117,118] In contrast, the use of oral anticoagulation to prevent stroke in patients with POAF is controversial and the evidence to support its use is mixed. According to current ESC guidelines, the use of long-term oral anticoagulation to prevent stroke is reasonable after POAF complicating non-cardiac surgery (Class of Recommendation IIa, Level of Evidence B) and cardiac surgery (Class of Recommendation IIb, Level of Evidence B), given informed patient preferences.[84]

Similarly, current US guidelines recommend anticoagulation in patients who develop POAF (Class of Recommendation IIa, Level of Evidence B).[119]

The argument for oral anticoagulation in patients with POAF after cardiac surgery is based upon observational data that identify significantly increased odds of stroke in patients with POAF.[83] Moreover, many patients with new-onset POAF will go on to develop established AF in follow-up. In one observational study, 50% of patients with POAF developed late AF, including 18% by 1 year.[6] Some observational data have shown lower rates of stroke in those treated with oral anticoagulation. In a study including more than 10 000 patients (2108 with POAF after cardiac surgery), oral anticoagulation was associated with a lower risk of stroke (adjusted HR 0.55, 95%CI 0.32–0.95; $P = 0.03$).[120] However, a more recent analysis of 38 936 patients with POAF in the Society of Thoracic Surgeons Adult Cardiac Surgery Database found an association between discharge anticoagulation and increased mortality (HR 1.16, 95%CI 1.06–1.26).[121] Furthermore, there was no apparent benefit with anticoagulation in those with CHA_2DS_2-VASc scores of 2–4 or ≥5.

Given these disparate data, it is unclear whether there is benefit or harm with oral anticoagulation after POAF. Data from ongoing large RCTS are awaited to provide clarity on this critically important question (NCT04045665; NCT03968393).

Current recommendations for the management of POAF from the European and US guidelines are summarized in *Table 4*.[84,119,122]

A summary of POAF epidemiology, pathophysiology, associated clinical events, prevention, and treatment strategies is provided in the *Graphical Abstract*.

Conclusions

Despite progress in prevention and treatment, POAF remains an important clinical problem for patients undergoing a variety of surgical procedures, and in particular cardiac surgery. Classic preventive measures (such as the use of beta-blockers or amiodarone) have been shown to be highly effective and must be considered standard of care. For others (such as sequential atrial pacing), the adoption by the surgical community has been low despite good efficacy, due to logistic considerations. Recent progresses in our understanding of the pathophysiology of POAF have led to the introduction of new treatment strategies, aimed at draining the pericardial cavity after surgery or at locally suppressing parasympathetic activation, that has shown high efficacy in initial studies and must be tested in large confirmatory RCTs (details of the main ongoing RCTs are summarized in *Table 2*).

Future directions for clinical research

The key gaps in current knowledge of POAF are summarized in *Table 5*. A key question that remains unanswered regards the nature of the association between POAF and subsequent adverse cardiovascular events. Future trials testing POAF prevention strategies should include a follow-up long enough to assess potential reductions in postoperative cardiovascular events associated with POAF reduction, as this is the ideal model to clarify if a casual association exists. Finally, it would be important to reach general consensus on a common definition of

POAF, to reduce heterogeneity and allow meaningful comparisons between studies.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Conflict of interest: Dr. Gaudino receives grant funding from the National Institutes of Health and the Canadian Institutes for Health and Research. Dr Di Franco has consulted for Servier, Novo Nordisk, and is an Advisory Board Member for Scharper. Michael Mack is a member of Steering Committee for AbbVie POAF Trial and Senior Vice President of CTSN Network. The other authors have no disclosures.

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