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REVIEW ARTICLE

New-onset atrial fibrillation: an update

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Abstract
New-onset atrial fibrillation (NOAF) is the most common perioperative complication of heart surgery, typically occurring in the perioperative period. NOAF commonly occurs in patients who are elderly, or have left atrial enlargement, or left ventricular hypertrophy. Various factors have been identified as being involved in the development of NOAF, and numerous approaches have been proposed for its prevention and treatment. Risk factors include diabetes, obesity, and metabolic syndrome. For prevention of NOAF, β-blockers and amiodarone are particularly effective and are recommended by guidelines. NOAF can be treated by rhythm/rate control, and antithrombotic therapy. Treatment is required in patients with decreased cardiac function, a heart rate exceeding 130 beats/min, or persistent NOAF lasting for ≥ 48 h. It is anticipated that anticoagulant therapies, as well as hemodynamic management, will also play a major role in the management of NOAF. When using warfarin as an anticoagulant, its dose should be adjusted based on PT-INR. PT-INR should be controlled between 2.0 and 3.0 in patients aged < 70 years and between 1.6 and 2.6 in those aged ≥ 70 years. Rate control combined with antithrombotic therapies for NOAF is expected to contribute to further advances in treatment and improvement of survival.

Keywords Anticoagulant therapy · Rhythm control · Rate control · Hemodynamic management · Perioperative atrial fibrillation

Introduction

New-onset atrial fibrillation (NOAF) is the most common perioperative complication of heart surgery (Table 1) [1, 2]. Despite the proposal and subsequent clinical application of various minimally invasive techniques, such as transcatheter aortic valve replacement (TAVR) and off-pump coronary artery bypass (OPCAB) surgery, as well as advances in perioperative management, the complete prevention of NOAF has not yet been achieved. It was previously believed that, while the development of chronic atrial fibrillation (AF) doubles the risk of cardiovascular complications, such as cerebral infarction and heart failure, the development of NOAF only slightly prolongs hospital stay and has little impact on patients' prognoses [3, 4]. However, emerging evidence suggests an association of NOAF with cardiovascular and various other complications, such as kidney failure, infections, and cerebral infarction. As various factors have been identified as being involved in the development of NOAF, different approaches have been proposed for the prevention and treatment of this condition. This review outlines the current knowledge, characteristics, and causes of NOAF, as well as approaches for the prevention and treatment of this condition.

Characteristics of NOAF

As mentioned above, NOAF commonly occurs in the perioperative period in patients undergoing heart surgery. In particular, it occurs in 30–40% of patients undergoing valve replacement and in 40–60% of patients undergoing combined procedures, such as simultaneous coronary artery surgery and valve replacement [5]. The development of NOAF has also been reported in patients undergoing noncardiac surgeries, including lung lobectomy, with an incidence of 10–20%, and total pneumonectomy, with an incidence of as high as 40% [1]. It most commonly occurs 2 days after

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Table 1 Postoperative complications after coronary artery bypass grafting

	(%)
Re-thoracotomy	2
Renal failure	5
Cerebral infarction	2.5
Respiratory failure	6
Gastrointestinal failure	2
Atrial fibrillation	30

surgery, but can also occur up to 7 days after surgery, and it subsequently recurs in 40% of patients.

It was previously believed that NOAF, unlike chronic atrial fibrillation (AF), would not affect patient survival. However, recent studies have shown that NOAF in patients undergoing coronary artery bypass graft (CABG) surgery is associated with a twofold or greater risk of developing cerebral infarction (2.4 vs. 5.3% in patients without and with NOAF, respectively; $p < 0.001$), prolonged stay in the intensive care unit (2.0 vs. 3.6 days; $p < 0.001$), and prolonged hospital stay (7 vs. 10 days; $p < 0.001$) [4]. NOAF has also been identified as an independent risk factor that determines patients' long-term prognosis [5]. These emerging findings suggest that NOAF affects not only the perioperative, but also the mid- to long-term outcome of operated patients.

Table 2 Risk factors for new-onset atrial fibrillation

Preoperative risk factors
Old age
Enlargement of the left atrium
Left ventricular hypertrophy
Hypertension
Genetics predisposition
Diabetes
Obesity
Metabolic syndrome
Intraoperative risk factors
Damage to the atrium
Myocardial ischemia
Insertion of vent tube
Venous cannulation
Acute volume change
Postoperative risk factors
Volume overload
Increased afterload
Hypotension
Inflammation
Atrial extrasystole
Imbalance of automatic nerve system
Electrolyte imbalance

Causes of NOAF

In most cases of chronic AF, AF is triggered by focal excitement originating from the pulmonary vein ostia and can be resolved by targeted electric stimulation of this origin, as reported by Haïssaguerre et al. [6]. Kiaii et al. performed simultaneous pulmonary vein isolation in patients undergoing CABG surgery and evaluated its protective effect against NOAF [7]. The incidence of NOAF was similar between those undergoing simultaneous CABG and pulmonary vein isolation and those undergoing CABG alone (37.1 vs. 36.1%; $p = 0.887$) [7].

Given these findings, the causes of NOAF have yet to be fully elucidated, although several possible mechanisms have been proposed. Advanced age, enlarged left atrium, and atrial structural remodeling after surgical intervention to the left atrium are predisposing factors for re-entry [1]. At the same time, factors such as sympathetic nervous system instability in the perioperative period, and inflammation and oxidative stress can promote atrial electrical remodeling, causing a shortened atrial refractory period and delayed atrial conduction. Consequently, NOAF is induced by triggers, such as premature atrial contractions (PACs) and electrolyte abnormalities [8, 9].

Table 2 lists the preoperative risk factors for NOAF. NOAF commonly occurs in the elderly, particularly those aged ≥ 70 years [10, 11]. In addition to traditional risk factors for NOAF, such as left atrial enlargement and left ventricular hypertrophy, several emerging risk factors have been identified, such as diabetes, obesity, and metabolic syndrome [12]. Obese patients aged ≥ 50 years are considered to be at particularly high risk of developing NOAF [13, 14].

Table 2 also lists intraoperative risk factors for NOAF. These include atrial injury, atrial ischemia, catheter insertion, and rapid change in circulating blood volume. Heart surgeries impose significant stress on the patient's system and often cause excessive inflammatory reactions, which may play a major role in the development of NOAF [1, 10–12, 15–17]. Table 2 also lists postoperative risk factors for NOAF, including volume overload, electrolyte abnormalities, PAC, and an overactive sympathetic nervous system [1, 14]. Based on the concept that elimination of these risk factors could prevent NOAF, various prophylactic methods have been proposed and implemented.

Prevention of NOAF

Table 3 lists the methods reported for preventing NOAF. Traditional prophylactics for NOAF include non-dihydropyridine calcium antagonists and digitalis preparations [18, 19]. The former agents are effective for preventing

Table 3 Prevention of postoperative atrial fibrillation

β-blockers	Amiodarone
Statins	Corticosteroids
Non-steroidal anti-inflammatory drugs	Colchicine
Angiotensin converting enzyme inhibitors	Vitamin C
N-Acetylcysteine	Magnesium
Off-pump coronary artery bypass grafting	Atrial pacing
Transcatheter aortic valve replacement	Posterior pericardiotomy

supraventricular tachycardia [20], but often cause adverse reactions, such as atrioventricular block and heart failure [21]. These agents are therefore not preferred first-line prophylactic treatments. A meta-analysis has shown that digitalis preparations are ineffective for preventing NOAF [22]. While these agents suppress the ventricular heartbeat by acting on the parasympathetic nervous system, NOAF is considered, at least partially, to be caused by overactivation of the sympathetic nervous system [23].

Beta-blockers

Beta-blockers act directly on the impulse conduction system and myocardial cells, and are classified as Vaughan-Williams class II agents. They are particularly effective in treating tachyarrhythmia [24]. The perioperative prophylactic use of beta-blockers has been shown to reduce cardiovascular complications [25–32]. Coleman et al. reported that the postoperative use of beta-blockers significantly reduced the perioperative incidence of NOAF (23.5 vs. 28.4%) in patients undergoing cardiothoracic surgery, who were treated with a beta-blocker or placebo, respectively ($p=0.02$) and hospitalization period (10.22 ± 11.38 vs. 12.40 ± 15.67 days; $p=0.001$) [33]. Similarly, a meta-analysis conducted by Crystal et al. showed that prophylactic treatment with beta-blockers substantially reduced NOAF [odds ratio (OR) 0.35; 95% confidence interval (CI) 0.26–0.49] in patients undergoing post-coronary artery bypass grafting or combined CABG and valvular surgery [34]. Recently, the perioperative use of landiolol, an ultrashort-acting beta1-selective adrenoceptor antagonist, has been shown to reduce the incidence of NOAF in patients undergoing cardiac surgery, especially following its frequent use in Japan [35–38]. A meta-analysis conducted by Tamura et al. also showed that the use of landiolol substantially reduced NOAF (OR 0.27; 95% CI 0.18–0.42, $p<0.001$) in patients undergoing cardiac surgery [39]. Lindenauer et al. reported that perioperative beta-blockers were effective in improving the survival outcome of high-risk patients after noncardiac surgery, such as those with prior heart failure or current cerebral infarction, but worsened the survival outcome of low-risk patients [40]. Moreover, in the Perioperative Ischemia Study Evaluation (POISE) trial [41], a multi-center study involving noncardiac surgery patients, treatment with a beta-blocker, metoprolol, reduced the incidence of perioperative cardiovascular complications (5.8 vs. 6.9% in the metoprolol group and placebo group, respectively; hazard ratio [HR] 0.84, 95% CI 0.70–0.99, $p=0.04$). However, it significantly increased the incidence of cerebral infarction (1.0 vs. 1.5%, HR 2.17, 95% CI 1.26–3.74, $p=0.005$) and mortality rate (3.1 vs. 2.3%; HR 1.33, 95% CI 1.03–1.74, $p=0.03$). The possible causes of the increased rates of cerebral infarction and mortality included hypotension/bradycardia caused by high-dose beta-blocker therapy. Sepsis or infection was a more frequent cause of death in patients in the metoprolol group than in patients in the placebo group. The bradycardia induced by beta-blockers could delay the diagnosis of sepsis and infection, thereby delaying treatment and increasing the risk of death in these patients. A meta-analysis of 33 multi-center studies, including the POISE trial, also showed that treatment with perioperative beta-blockers reduced cardiovascular complications after noncardiac surgery, but increased cerebral infarction, cautioning against uniformly providing high-dose beta-blocker therapy to all patients [42]. For patients undergoing heart surgery, many of whom have other concomitant disorders, the benefits of prophylactic beta-blocker therapy outweigh its disadvantages. For the prophylactic use of beta-blockers in low-risk patients, physicians should ascertain the optimal dose for each patient prior to surgery.

Amiodarone

Amiodarone, a Vaughan-Williams class III agent, is a multichannel blocker that acts not only on potassium channels, but also on sodium and calcium channels and even on alpha and beta receptors. This agent has been used for both the prevention and treatment of NOAF. A reduction in the incidence of NOAF has been achieved by 1-week preoperative treatment with amiodarone (25 vs. 53% in the amiodarone group and placebo group, respectively; $p=0.003$) in patients undergoing elective cardiac surgery [43], who received postoperative intravenous infusion of amiodarone (35 vs. 47%; $p=0.01$) [44], and perioperative treatment with amiodarone (16 vs. 25%; $p=0.001$) [45]. Based on these results, the American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) Guideline for the Management of Patients with Atrial Fibrillation recommends the use of amiodarone for prophylactic purposes in high-risk patients (Class IIa, level of evidence; LOE A) [46].

Nevertheless, an increased dose of amiodarone has been associated with escalation of the incidence of adverse reactions, such as bradycardia and hypotension [47]. Precautions are therefore needed when using this agent, such as setting the maximum dose to 1 g [47]. Similar to beta-blockers, amiodarone should preferably be avoided in low-risk patients.

Statins

Statins have various pharmacological actions, including reducing and stabilizing plaques, and improving vascular endothelial function and anti-inflammatory actions, and thus have been considered to be a potential prophylactic agent for NOAF. Mariscalco et al. reported that, in patients undergoing isolated CABG surgery, NOAF occurred in 29.5% of patients taking statins, as compared to 40.9% of patients not taking statins ($p = 0.021$) [48]. A meta-analysis also showed that statins significantly reduced perioperative myocardial infarction [risk ratio (RR) 0.57, 95% CI 0.46–0.70, $p < 0.0001$] and NOAF (RR 0.54, 95% CI 0.43–0.68, $p < 0.0001$) in patients undergoing percutaneous coronary intervention, CABG, and noncardiac surgery [49]. These findings supported the notion that statins, which have few side effects, should also be actively administered in the perioperative period.

However, a recent large-scale randomized controlled trial (RCT) questioned the preventative effect of statins on NOAF in patients who were scheduled for elective cardiac surgery (21.1% and 20.5% in the rosuvastatin and placebo groups, respectively; odds ratio [OR] 1.04; 95% CI 0.84–1.30; $p = 0.72$) [50]. A subsequent meta-analysis also showed that statins did not reduce perioperative cardiovascular complications, including NOAF (OR 1.26; 95% CI 0.90–1.30; $p = 0.40$), but rather increased the risk of kidney complications (OR 1.26; 95% CI 1.05–1.52; $p = 0.01$) [51]. These findings suggest the need for reconsideration of the active and ubiquitous use of statins in the perioperative period.

Corticosteroids

Systemic inflammatory reactions caused by cardiovascular surgeries are believed to be a cause of NOAF. In fact, patients with NOAF have been shown to have significantly higher levels of C-reactive protein (CRP), leukocyte counts, and inflammatory cytokine levels, as compared to those without NOAF, providing evidence for a role of inflammation in the development of NOAF [52, 53]. While several studies have reported that corticosteroids significantly reduced postoperative CRP levels [54], Halonen et al. reported that the administration of 100 mg of hydrocortisone before elective cardiac surgery significantly reduced the incidence of NOAF as compared to placebo (30 vs. 48% in the hydrocortisone group and placebo group, respectively; $p = 0.004$) [55].

However, several recent studies suggest that corticosteroids do not reduce perioperative complications, including NOAF, in patients undergoing cardiac surgery with cardiopulmonary bypass [56, 57]. The current American College of Cardiology Foundation (ACCF)/AHA Guideline for Coronary Artery Bypass Graft Surgery also recommends against the routine use of corticosteroids after CABG [58].

Non-steroidal anti-inflammatory drugs

Similar to corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) have also been expected to suppress NOAF through their anti-inflammatory actions. Cheruku et al. reported the efficacy of NSAIDs in preventing NOAF after CABG surgery (9.8 vs. 28.6% in the NSAID group and placebo group, respectively, $p = 0.017$) [59], whereas Horbach et al. could not demonstrate a protective effect of prophylactic treatment with naproxen, an NSAID, against NOAF in patients undergoing CABG surgery (7.3 vs. 15.2% in the naproxen group and placebo group, respectively, $p = 0.11$) [60]. Given the inconsistent study results and potential associated risks, such as kidney function impairment [61], the use of NSAIDs for this indication may be limited to certain patient populations.

Angiotensin converting enzyme inhibitors

During the recovery period after heart surgery, atrial enlargement occurs due to intravascular volume change and stimulates angiotensin II receptors, and the subsequent increase in angiotensin converting enzyme (ACE) concentration causes fibrosis of the atrial tissue [62]. Electrical/structural remodeling induced by angiotensin II and ACEs plays a major role in the development and persistence of AF [62]. This has led to the notion that ACE inhibitors may be protective against NOAF. An observational study involving 4657 patients who underwent CABG surgery reported that ACE inhibitors suppressed the development of NOAF (OR 0.62, 95% CI 0.48–0.69, $p < 0.001$) [11], whereas a retrospective observational study involving 10,023 patients who underwent isolated CABG surgery reported that the use of ACE inhibitors rather increased the risk of NOAF development (OR 1.34, 95% CI 1.18–1.51, $p < 0.00001$) [63]. A meta-analysis of 11 studies including 40,112 patients who underwent CABG surgery and CABG plus valve surgery also showed an increased risk of NOAF with the use of ACE inhibitors (OR 1.2, 95% CI 1.11–1.29, $p < 0.00001$) [15].

The ACCF/AHA Guidelines for Coronary Artery Bypass Graft Surgery recommends that patients who used ACE inhibitors before surgery should resume the therapy early after surgery, as soon as hemodynamic stabilization has been achieved (Class I, LOE B) [58]. For patients with impaired heart function, hypertension, diabetes or impaired kidney function, the use of ACE inhibitors is recommended, but the de novo use of these agents may be harmful due to the high risk of causing hypotension.

Colchicine

Colchicine, a treatment for gout, also has an anti-inflammatory activity [64]. This agent exerts an anti-inflammatory effect by acting on microtubules, inhibiting changes in mitochondrial spatial arrangement, thereby inhibiting the formation of NLRP3 inflammasomes [64]. With this effect, colchicine has also been tested in RCTs, which showed that treatment of patients with heart disease using colchicine reduced cardiovascular events by 60% (RR 0.44, 95% CI 0.28–0.69, $p=0.0004$) [62]. Colchicine has also been shown to reduce the incidence of postoperative complications of heart surgery, such as postpericardiotomy syndrome, pericarditis, myocardial disorders, and postoperative AF (RR 0.65, 95% CI 0.51–0.82, $p=0.0003$) [65].

Nevertheless, in an RCT involving patients undergoing heart surgery, the incidence of postoperative AF was similar between those treated with colchicine and those treated with placebo (14.5 vs. 20.5% in the colchicine group and no-colchicine group, respectively, $p=0.14$) [64]. Diarrhea, a known adverse reaction to colchicine, occurred in more than 24.6% of colchicine-treated patients. Reports showing the efficacy of colchicine in preventing postoperative AF also emphasized the need for caution when using this agent, as many patients had to discontinue colchicine due to gastrointestinal events [66].

Vitamin C

Vitamin C is known to have antioxidant, free radical-scavenging, and anti-inflammatory activities [67]. Given the major roles of oxidative stress and inflammation in NOAF development [8, 9], the protective effect of vitamin C against NOAF has been explored. After Carnes et al. reported the efficacy of vitamin C in preventing NOAF in patients undergoing CABG surgery (16.3 vs. 34.9%, in the ascorbate group and control group, respectively, $p=0.048$) [68], an RCT also demonstrated that treatment with vitamin C suppressed the development of NOAF (OR 0.12, 95% CI 0.025–0.558, $p<0.002$) [69]. A recent meta-analysis also suggested the AF-preventing effect of vitamin C in patients undergoing cardiac surgery (OR 0.50, 95% CI 0.27–0.91, $p=0.02$) [70]. A large-scale RCT should be conducted to evaluate the protective effect of vitamin C against NOAF.

N-Acetylcysteine

N-Acetylcysteine also has antioxidant free radical-scavenging and anti-inflammatory activities [71–73]. A meta-analysis has shown that prophylactic *N*-acetylcysteine treatment reduces the incidence of NOAF (OR 0.56, 95% CI 0.40–0.77; $p<0.001$), and all-cause mortality (OR 0.40, 95% CI 0.17–0.93; $p=0.03$) after cardiac surgery [74]. However, the meta-analysis included a small number of patients, and the design varied among the different studies, which limited the interpretation of the results. In future, larger RCTs evaluating these and other postoperative complication endpoints are needed.

Magnesium

Previous studies have suggested a strong correlation between decreased blood magnesium concentration and NOAF after cardiac surgery [75]. A meta-analysis has also shown that active magnesium replacement reduces the incidence of NOAF in patients undergoing cardiac surgery (OR 0.54, 95% CI 0.38–0.75, $p<0.05$) [76]. Another meta-analysis of 22 studies, including 2896 patients, also showed a significant decrease in the incidence of NOAF after administration of magnesium (OR 0.57, 95% CI 0.42–0.77) [31], although many of the studies included had small sample sizes, varied protocols, and inconsistent results. Further studies are also needed to evaluate the protective effect of magnesium against NOAF.

Off-pump coronary artery bypass grafting

Off-pump coronary artery bypass grafting (OPCAB) does not require extracorporeal circulation and thus can avoid complications associated with the use of extracorporeal circulation. OPCAB has been associated with a lower incidence of NOAF than on-pump CABG (OR 0.78, 95% CI 0.74–0.82, $p<0.0001$) [77], although a recent RCT showed no significant difference in the incidence of cardiovascular complications, including NOAF, between OPCAB and on-pump CABG [78]. Moller et al. also reported no significant difference in the corresponding incidence among severely ill patients [79]. Thus, whether OPCAB is protective against NOAF remains controversial.

Transcatheter aortic valve replacement

Transcatheter aortic valve replacement (TAVR) does not require extracorporeal circulation and can be completed without mini-thoracotomy or other thoracotomy procedures. NOAF occurring after TAVR has also been shown to affect patient survival (HR 3.4, 95% CI 1.25–9.5, $p=0.017$) [80]. Compared to conventional aortic valve replacement (AVR), TAVR was associated with a significantly lower incidence of NOAF in a study involving 699 severely ill patients from 25 centers (8.6 vs. 16.0%, $p=0.006$) and in another study involving 1660 moderate-risk patients from 87 centers (9.1 vs. 26.4%, $p<0.001$) [81, 82]. A meta-analysis of four RCTs including 3806 patients, also showed a significantly lower incidence of NOAF with TAVR than with AVR (HR 0.46, 95% CI 0.34–0.63, $p<0.001$) [83]. Another meta-analysis

of five RCTs and 31 observational studies, including a total of 16,638 patients, also showed a significantly lower incidence of NOAF with TAVR (OR 0.24, 95% CI 0.15–0.40, $p = 0.001$) [84]. Although many studies have shown that TAVR is significantly more protective against NOAF than AVR, further case reports should be accumulated because of the limited surgical indications to date.

Atrial pacing

Atrial pacing is considered to be effective in maintaining interatrial conduction and the atrial refractory period [85]. One possible underlying mechanism is that 2 factors, i.e., suppressed dispersion of atrial repolarization due to bradycardia and overdrive suppression, protect against AF [14]. Several meta-analyses have also provided evidence for NOAF prevention by either single atrial or bi-atrial pacing [86, 87]. Fan et al. reported a higher efficacy of bi-atrial than single atrial pacing in preventing NOAF after CABG surgery (bi-atrial pacing vs. left atrial pacing vs. right atrial pacing, 12.5 vs. 36.4% vs. 33.3%, $p < 0.05$) [88].

However, prophylactic atrial pacing poses the risk of arrhythmia in the event of abnormal sensing, dislodgement of a pacing lead, or other accidents. Moreover, bi-atrial pacing is technically complicated in the first place, which often precludes its use in clinical practice. Continued investigations on NOAF prevention by atrial pacing are needed, as many of the relevant studies had small sample sizes and varied protocols.

Posterior pericardiotomy

Pericardial effusion causes constant atrial stimulation and thus can be a major risk factor for NOAF. Several studies have shown that NOAF could be prevented by making a small incision on the posterior pericardium, thereby preventing pericardial effusion [89–91]. A meta-analysis of 6 RCTs, including 763 patients undergoing CABG, also showed a substantial protective effect of posterior pericardiotomy against NOAF (10.8 vs. 28.1%, OR 0.33, 95% CI 0.16–0.69, $p = 0.003$) [92].

Treatments for NOAF

NOAF is typically transient in nature and often requires no treatment. However, it requires treatment in patients with decreased cardiac function, a heart rate exceeding 130 beats/min, or persistent NOAF lasting for ≥ 48 h, or those at high risk of developing central nervous system (CNS) complications [93]. Treatments for NOAF are similar to those for chronic AF, including therapies aimed at maintaining the sinus rhythm or heart rate and antithrombotic therapies.

Rhythm/rate control therapies

Postoperative AF leads to a 20–30% decrease in cardiac output due to loss of the atrial kick [1, 94–96]. The atrial kick plays an important role in patients with diastolic dysfunction, as their cardiac output relies more on atrial contraction. Therefore, rhythm control therapies are considered to be effective and are recommended for patients with hemodynamic instability, a somewhat common postoperative complication of heart surgery [1, 94–96]. Flecainide and propafenone have been shown to be effective for restoring sinus rhythm. In cases unresponsive to these treatments, the use of direct-current defibrillation should be considered (Class IIa, LOE B) [46]. Cases have been reported in which sinus rhythm cannot be restored by these treatments. The AFFIRM study, which compared the efficacy of different treatments for chronic AF, demonstrated the superiority of rate control therapies to rhythm control therapies [97]. This was because the adverse effects of the antiarrhythmics used for maintaining sinus rhythm, particularly cardiac depression. Since the repeated use of antiarrhythmics for treating postoperative AF may further worsen the patient's hemodynamics, efforts should be made to maintain the heart rate in patients whose sinus rhythm cannot be maintained [1, 94–96].

For patients with stable hemodynamics and those with refractory NOAF, rate control therapies are recommended (Class IIa, LOE C) [46]. These therapies include beta-blockers, calcium antagonists, and amiodarone. The AHA/ACC/HRS Guidelines for the Management of Patients With Atrial Fibrillation recommend controlling the resting heart rate below 80 beats/min (Class IIa, LOE B) [46]. However, some reports have shown no significant difference in the outcome of patients whose heart rate during AF was strictly controlled below 80 beats/min, as compared to around 100 beats/min, suggesting that the perioperative heart rate should also be maintained around 100 beats/min [98]. Thus, the AHA/ACC/HRS Guidelines for the Management of Patients With Atrial Fibrillation allow a resting heart rate below 110 beats/min when patients remain asymptomatic and LV systolic function is preserved (Class IIb, LOE B) [46].

A recent RCT comparing rhythm versus rate control therapies for the management of postoperative NOAF in 2109 patients who underwent heart surgery at 23 centers reported no significant difference in the incidence of significant complications between these therapies up to 60 days after surgery (24.8 vs. 26.4 per 100 patient-months in the rate-control and the rhythm-control group, respectively, $p = 0.61$) [99]. This report has substantial impact, given the traditional belief that the development of NOAF itself affects patient survival. Data are awaited on the mid- to long-term outcome of patients receiving rhythm versus rate control therapies for the management of NOAF. In this trial, the

same antithrombotic therapies as for chronic AF were used in both therapy groups, except for patients ineligible for these therapies. It is anticipated that anticoagulant therapies, as well as hemodynamic management, will play a major role in the management of NOAF.

Antithrombotic therapy

Anticoagulants used for AF management have been shown to have a much greater protective effect against cerebral infarction than antiplatelets [100]. Antiplatelet therapies appear to be protective only against minor infarctions associated with lacunar infarction and atherothrombotic cerebral infarction, but not against major infarction in either paroxysmal or persistent AF cases. Therefore, these agents should not be used as first-line treatment, but should be considered only in patients not tolerating anticoagulants [46]. Thus, for patients with NOAF lasting for more than 48 h and those at risk of developing CNS complications, anticoagulant therapy should be used in combination with rhythm or rate control therapy (Class IIa, LOE C) [46]. Caution should be exercised when initiating anticoagulant therapy in the perioperative period of heart surgery, taking into account the risk of hemorrhage and cardiac tamponade [101].

Patients should be screened for the risk of CNS complications using the CHADS2 or CHA2DS2-VASc score [102–106]. The CHADS2 score is calculated as the sum of the scores for heart failure (1), hypertension (1), elderly aged ≥ 75 years (1), diabetes (1), and history of cerebral infarction or transient ischemic attack (2) [95]. The CHA2DS2-VASc score is calculated as the sum of the CHADS2 score and additional variables, including age ≥ 65 years but ≤ 74 years (1), concomitant vascular disease (1), and female (1), to allow for more detailed assessment [105, 106]. In patients with non-valvular AF, the decision on whether to initiate anticoagulant therapy should be made based on the calculated CHA2DS2-VASc score (Class I, LOE B) [46]. Early initiation of anticoagulant therapy is particularly recommended for patients with a prior history of cerebral infarction and a CHA2DS2-VASc score ≥ 2 (Class I, LOE A) [46].

When using warfarin as an anticoagulant, its dose should be adjusted based on PT-INR. PT-INR should be controlled between 2.0 and 3.0 in patients aged < 70 years and between 1.6 and 2.6 in those aged ≥ 70 years [107, 108]. Anticoagulant therapy should be continued for 30–60 days after restoration of sinus rhythm, due to possible atrial stunning, even after rhythm restoration [99]. Antithrombotic therapy with direct oral anticoagulants has been included in the AF treatment guidelines and has become increasingly popular, but has rarely been used for NOAF management [109]. Although the same treatments as used for chronic AF are currently used for NOAF, it would be preferable to establish antithrombotic therapy regimens focused on treating NOAF.

Conclusion

Following the publication of evidence regarding the impact of NOAF on patient survival, various findings on postoperative AF have been obtained and applied to the development of prevention and treatment strategies for NOAF. While it has been believed that the development of NOAF itself affects patient survival, recent evidence suggests that better survival can be achieved not by prophylaxis protocols, but by treatment of NOAF, including rhythm and rate control therapies, in particular. These treatments, combined with antithrombotic therapies, another major treatment approach for NOAF, are expected to contribute to further advances in treatment and improvement of survival.

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Compliance with ethical standards

Conflict of interest The authors have no competing interests to declare.

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