Antioxidant Drugs in the Prevention of Postoperative Atrial Fibrillation: A Literature Review

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Abstract

Background: Post-operative atrial fibrillation (POAF) is a prevalent complication after cardiac surgery, affecting 20-50% of patients and linked to increased morbidity and healthcare costs. Given the central role of oxidative stress in POAF pathogenesis, this review evaluates the efficacy and evidence base of antioxidant drugs for POAF prevention.

Methods: A narrative literature review was conducted. We searched PubMed, Scopus, and Web of Science up to April 2025 for studies on antioxidants and POAF prevention. The focus was on randomized controlled trials (RCTs), their meta-analyses, and key mechanistic studies.

Results: Twenty-eight relevant studies were included. Antioxidants, including N-acetylcysteine (NAC), ascorbic acid (vitamin C), L-carnitine, crocin, alpha-lipoic acid, coenzyme Q10, vitamin E, berberine, selenium and melatonin, were evaluated. NAC and vitamin C showed the most consistent benefit, with meta-analyses reporting significant reductions in POAF risk (e.g., pooled RR 0.69, 95% CI 0.52–0.91 for NAC; OR 0.44, 95% CI 0.32–0.61 for vitamin C). Evidence for other agents was less robust, often based on single-center trials or showing contradictory results (e.g., selenium, melatonin). Mechanisms involve ROS scavenging, anti-inflammatory effects, and improved mitochondrial function.

Conclusion: Current evidence supports a potential preventive role for specific antioxidants in POAF, particularly NAC and vitamin C. However, significant heterogeneity, contradictory findings for several agents, and a lack of large multicenter RCTs preclude firm clinical recommendations. Antioxidant therapy should currently be considered investigational. Future high-quality trials are needed to establish optimal agents and dosing for clinical practice.

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Introduction

Postoperative atrial fibrillation (POAF) is the most common significant cardiac rhythm disorder following cardiac surgery, occurring in 15 - 50% of patients and being associated with increased short-term and long-term mortality (1). POAF also increases the risk of long-term atrial fibrillation (AF), heart failure (HF), myocardial infarction, bleeding, prolonged hospital stays, thromboembolic events, acute renal failure, pneumonia, and higher hospital costs (2,3).

POAF can occur after both cardiac and non-cardiac surgeries, with a higher incidence observed in cardiac and

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thoracic procedures, particularly in patients undergoing combined surgeries (4). POAF is influenced by multiple risk factors, including age, thyroid disorders, a history of HF, race, chronic obstructive pulmonary disease (COPD), renal function, and underlying cardiac health. Intraoperative and postoperative factors, such as the use of certain medical devices, withdrawal of medications, and electrolyte imbalances, further increase the risk of POAF. POAF may lead to serious complications, including recurrent AF, thromboembolism, and hospitalizations due to HF (5).

The underlying mechanisms of POAF involve inflammation, oxidative stress, myocardial stretch, and electrical disturbances within the heart. Oxidative stress, which is exacerbated by postoperative injury, plays a central role, making antioxidant therapies a promising strategy for the prevention of POAF (6,7). During cardiac surgery, ischemia/reperfusion injury (IRI) and inflammation contribute to increased production of reactive oxygen species (ROS). Several injurious processes, including surgical trauma, myocardial ischemic cardioplegic arrest, and subsequent reperfusion, trigger an acute systemic inflammatory response (8). Inflammation also contributes to myocardial IRI (9). Hypoperfusion associated with IRI leads to excessive ROS generation, resulting in oxidative damage. Mitochondrial dysfunction — particularly due to anaerobic metabolism and impairment of the electron transport chain — further contributes to oxidative stress through activation of NADPH oxidase and xanthine oxidase systems (10). Additionally, under hypoxic conditions, activation of hypoxia-inducible factor-1α enhances NOX enzyme activity, further increasing ROS production and exacerbating cardiac injury (11).

Given the pivotal role of oxidative stress in POAF, this review focuses on its mechanistic contribution and the therapeutic potential of antioxidant agents for the suppression of POAF.

Methods

This narrative review synthesizes current evidence on antioxidant agents for the prevention of POAF. A focused literature search was conducted in April 2025 using PubMed, Scopus, and Web of Science. Key search terms included ("post-operative atrial fibrillation" OR "POAF") AND ("antioxidant" OR "oxidative stress") AND ("cardiac surgery" OR "CABG"). The search was supplemented by manual screening of references from retrieved articles and targeted searches for specific agents (e.g., N-acetylcysteine, vitamin C, and melatonin).

The primary emphasis was placed on randomized controlled trials (RCTs) and meta-analyses of RCTs evaluating the efficacy of antioxidants in adult patients undergoing cardiac surgery, as these represent the highest level of clinical evidence. Key preclinical studies elucidating underlying mechanistic pathways were also included to support biological plausibility. Given the heterogeneity in antioxidant interventions and outcome measures across studies, a formal meta-analysis was not performed. Instead, a narrative synthesis and critical appraisal of the literature were undertaken, with findings summarized by agent, dosing regimens highlighted, and study limitations and consistency of evidence discussed.

Results

A total of 240 articles relevant to the research topic were initially identified. After screening and eligibility assessment, 28 studies were selected for inclusion in the final analysis based on their focus on antioxidant mechanisms, dosing regimens, and POAF-related outcomes.

N-acetylcysteine (NAC)

We identified eight meta-analyses (Table 1) along with several supporting preclinical studies evaluating NAC for the prevention of POAF. N-acetylcysteine (NAC), a derivative of the amino acid cysteine, exhibits antioxidant properties primarily through free radical scavenging. It exerts both direct and indirect antioxidant effects, including acting as a precursor of cysteine for glutathione (GSH) synthesis, detoxifying hydroxyl (•OH), nitrogen dioxide ($•NO_2$), and carbonate ($CO_3•^-$) radicals, neutralizing semiquinone radicals, chelating transition and heavy metal ions, and reducing disulfide bonds while eliminating H_2O_2 and superoxide ($O_2•^-$). Through these mechanisms, NAC has demonstrated therapeutic potential in conditions associated with oxidative stress, including cardiovascular diseases (12). Given that oxidative stress is a key contributor to POAF, NAC has been proposed as a potential preventive strategy due to its antioxidant properties (13).

Several meta-analyses (Table 1) have evaluated the effectiveness of NAC in reducing the incidence of POAF. Three meta-analyses reported significant statistical heterogeneity ($I^2 = 92\%$, $P < 0.01$) (14) and ($I^2 = 86\%$, $P < 0.001$) (15), whereas the remaining five studies reported no significant heterogeneity. Effect measures varied across studies, with four meta-analyses reporting odds ratios (OR) (16-19) and four reporting risk ratios (RR) (14,15,20,21). Additional findings from these meta-analyses are summarized in Table 1. Furthermore, clinical studies have shown that NAC administration in patients undergoing on-pump coronary artery bypass grafting (CABG) can reduce myocardial oxidative stress (17). Given the established role of oxidative stress in POAF, NAC may have potential clinical utility in its prevention.

Table 1. Systematic reviews with meta-analysis regarding the efficacy of N-acetylcysteine in the prevention of Postoperative Atrial Fibrillation

N of RCTs (*Reference*)	N of patients	Was NAC effective?	Considerations
15 (***20***)	1875	Yes RR= 0.69; 95% CI: 0.52 to 0.91, P = 0.008	Incidence of POAF was not related to the NAC dose (P=0.439).
8 (***16***)	578	Yes OR= 0.62, 95% CI: 0.41 to 0.93, P = 0.021	Did not affect LOS.
11 (***17***)	648	Yes OR= 0.57; 95% CI: 0.33 to 0.97, P = 0.04	Shorter hospital LOS. No significant difference in all-cause mortality.
10 (***18***)	1026	Yes OR= 0.56; 95% CI: 0.40 to 0.77, P < 0.001	Could reduce the incidence of POAF and all-cause mortality in adult patients.
28 (***14***)	2174	Yes RR= 0.57, 95% CI: 0.30 to 1.06, P = 0.071	Intravenous administration of NAC can reduce the incidence of AKI and arrhythmia in patients after cardiac surgery. Oral NAC has no significant effect on the outcomes of patients after cardiac surgery.
25 (***15***)	2444	Yes RR = 0.74, 95% CI: 0.61 to 0.91, P = 0.004, I2 = 48%	Certainty of evidence was rated low for mortality, acute respiratory infection, acute cardiac injury, arrhythmia, and MI, and rated down to moderate for HLOS and ICULOS.
6 (***19***)	490	Yes Post-CTS AF: Chi2 (test odds ratio differs from 1) = 3.92, P = 0.048	Did not appear to significantly alter MI, stroke, AKI, RRT, mortality, LOS.
8 (***21***)	375	Yes RR= 0.775, 95% CI: 0.63 to 0.94, P = 0.013	

N: Number, AKI: Acute Kidney Injury, CABG: Coronary Artery Bypass Grafting, OR: Odds Ratio, CI: Confidence Interval, RR: Risk Ratio, ICULOS: Intensive Care Unit Length of Stay, LOS: Length of Stay, HLOS: Hospital Length of Stay, POAF: Postoperative Atrial Fibrillation, NAC: N-acetylcysteine, MI: Myocardial Infarction.

Vitamin C

Vitamin C (ascorbic acid) was evaluated in seven meta-analyses (Table 2). Vitamin C is a water-soluble antioxidant with diverse physiological functions. Studies have demonstrated its efficacy in reducing oxidative stress and preventing organ dysfunction, making it one of the most widely recognized antioxidants. Its antioxidant potential stems from its ability to regulate intracellular redox balance through interactions with GSH and to directly scavenge ROS, including singlet oxygen (O = O), superoxide anions (O_2•-), and hydroxyl radicals (OH•). Ascorbate donates one electron to O_2•-, forming the ascorbate radical (ASC•-), or loses a second electron to generate its oxidized form, DHA (22).

Table 2 summarizes meta-analyses assessing the antioxidant effects of ascorbic acid in POAF prophylaxis (21,23–28). Across all available meta-analyses, vitamin C demonstrated effectiveness in preventing POAF. Evidence was derived from multiple pooled analyses, including meta-analyses of: 4 RCTs (n = 541; RR = 0.716; 95% CI: 0.56 - 0.90; P = 0.005) (21), 11 RCTs (n = 1390; OR = 0.44; 95% CI: 0.32 - 0.61; I^2 = 25%) (23), 8 RCTs (n = 1060; OR = 0.46; 95% CI: 0.30 - 0.69; I^2 = 44%; P = 0.09) (24), 13 RCTs (n = 1956; RR = 0.68; 95% CI: 0.54 - 0.87; P = 0.002) (25), 28 RCTs (n = 3598; RR = 0.64; 95% CI: 0.52 - 0.78; P < 0.0001) (26), 5 RCTs (n = 565; OR = 0.50; 95% CI: 0.27 - 0.91; P = 0.02) (27), and 15 RCTs (n = 2050; RR = 0.56; 95% CI: 0.47 - 0.67) (28).

Table 2. Meta-analysis regarding the efficacy of ascorbic acid in the prevention of Postoperative Atrial Fibrillation

N of RCTs (*Reference*)	N of Patients	Was vitamin C effective?	Considerations
4 ***(21)***	541	Yes RR= 0.716, 95% CI: 0.56 to 0.90, P = 0.005	Fixed effects: RR= 0.716; 95% CI= 0.56 to 0.90; P = 0.005; random effects: RR= 0.641; 95% CI= 0.41 to 0.99; P = 0.04.
11 ***(23)***	1390	Yes OR= 0.44, 95% CI: 0.32 to 0.61, I^2 = 25% Cochran Q: P = 0.206	Reduced frequency of POAF and a shorter ICU LOS and total hospital LOS. No significant publication bias was noted (Egger's P = 0.13).
8 ***(24)***	1060	Yes I^2 44%, P = 0.09; OR= 0.46; 95% CI: 0.30 to 0.69	No evidence of publication bias (Egger test, P = 0.821; Begg test, P = 0.902).
13 ***(25)***	1956	Yes RR= 0.68, 95% CI: 0.54 to 0.87, P=0.002	Could significantly decrease ICULOS, HLOS, and risk of adverse events.
28 ***(26)***	3598	Yes RR= 0.64, 95% CI: 0.52–0.78, P < 0.0001	Associated with a reduction in POAF, ICU stay, and hospital stay, but, no differences in postoperative mortality, acute kidney injury, stroke, and ventricular arrhythmia were found.
5 ***(27)***	565	Yes OR= 0.50, 95% CI= 0.27 to 0.91, P = 0.02	
15 ***(28)***	2050	Yes 95% CI: 35 to 54%, P < 0.0001 RR=0.56, 95% CI: 0.47 to 0.67	Trials in less wealthy countries should be carried out to optimize the protocol for vitamin C administration and to determine which patient groups get the most benefit.

N: Number, OR: Odds Ratio, CI: Confidence Interval, RR: Risk Ratio, LOS: Length of Stay, ICULOS: Intensive Care Unit Length of Stay, HLOS: Hospital Length of Stay, POAF: Postoperative Atrial Fibrillation.

Carnitine

Three clinical studies and several supporting metabolic studies were reviewed (Table 3). Carnitine, a naturally occurring amino acid derivative, plays a critical role in fatty acid β-oxidation and adenosine triphosphate (ATP) production. Carnitine deficiency disrupts intermediary metabolism by leading to the accumulation of excess acetyl-CoA esters (29). During coronary artery bypass grafting (CABG), the myocardium has increased energy demands, which are primarily met through fatty acid metabolism (30). Preoperative carnitine therapy has been associated with enhanced myocardial ATP production and may attenuate perioperative lipotoxicity by improving fatty acid oxidation (31).

A meta-analysis reported that L-carnitine administration reduced arrhythmias by 65%, all-cause mortality by 27%, and anginal symptoms by 40% following myocardial infarction (32). Another meta-analysis demonstrated that carnitine supplementation reduced levels of C-reactive protein, interleukin-6, tumor necrosis factor-α (TNF-α), and malondialdehyde, while increasing superoxide dismutase (SOD) levels (33). Several studies summarized in Table 3 indicate that perioperative L-carnitine administration is associated with a reduced risk of POAF.

Table 3. Clinical trials evaluating the effect of antioxidants on the prevention of Postoperative Atrial Fibrillation

Type of surgery (*Reference*)	Name of antioxidant	Type of study	Population	Regimen	Results
Aortic valve surgery (*36*)	L-carnitine	Randomized clinical trial	30 (15 control, 15 L-Carnitine)	1g 3 times a day from 2 days before surgery, 7 days after surgery.	A significantly lower rate of new onset POAF by L-carnitine vs placebo group (20% and 60%, respectively; P = 0.025).
CABG (*35*)	L-carnitine	Randomized clinical trial (double blind)	134 (67 control, 67 L-Carnitine)	1g 3 times a day from 2 days before the surgery to 2 days afterward.	A significantly lower rate of new onset POAF by L-carnitine vs placebo group (7.5% vs 19.4%, respectively; P = 0.043).
Esophageal cancer surgery (*34*)	L-carnitine	Preliminary single-group	15 (15 L-Carnitine)	1g 3 times a day, 2 days before and 3 days after surgery.	Incidence of POAF was 7.7% (95% CI: 0.2–36%).
CABG (*42*)	CoQ10	Randomized clinical trial	80 (40 control, 40 CoQ10)	150mg a day for 7 days before surgery.	The incidence of postoperative AF decreased from 45% in the control group to 20% in the intervention group (P = 0.030).
Aortic valve replacement (*43*)	Ubiquinol	Randomized clinical trial	46 (22 control, 24 ubiquinol)	400mg ubiquinol (CoQ10 reduced form) once daily from 7 days before to 5 days after surgery.	There was no significant difference between ubiquinol and the control group (P = 0.307).
CABG/valve surgery (*48*)	Crocin	Randomized clinical trial	100 (50 control, 50 crocin)	15 mg 3 days before and 3 days after surgery.	POAF developed in 7 patients in the treatment group versus 18 patients in the control group (P= 0.02).
CABG (*54*)	Berberine	Randomized clinical trial	200 (100 control, 100 berberine)	0.4g 3 times daily, 7 days before to 7 days after surgery.	The POAF incidence was reduced from 35% to 20% under berberine treatment (hazard ratio, 0.5 (95% CI= 0.29to0.78); P= 0.01)
CABG/valve surgery (*59*)	ALA	Randomized clinical trial	90 (45 control, 45 ALA)	600mg twice daily ALA was given 5-10 days before surgery and continued till the day of discharge.	The incidence of POAF was significantly decreased in the ALA group (11%) compared to in control group (33%) (Log-rank test P= 0.01).
CABG (*64*)	Melatonin	Randomized clinical trial	76 (38 control, 38 melatonin)	12mg sublingual melatonin in the evening before and 12 mg 1 hour before surgery.	The incidence of POAF was not statistically significant between the two groups (P=0.71), but melatonin supplementation led to a significantly lower duration of AF (P = 0.01).
CABG/valve surgery/mixed (*69*)	Vitamin E	Randomized clinical trial	203 (100 control, 103 antioxidant supplements)	vitamin C (1 g/day) plus vitamin E (400 IU/day) and n-3 PUFAs (2g/day) two days before surgery.	The incidence of POAF is significantly lower in the intervention group (10 of 103 patients in the supplemented group versus 32 of 100 patients in the placebo group, P < 0.001).
CABG (*70*)	Vitamin E	Randomized clinical trial	250 (125 control, 125 Tocovid)	200 mg Tocovid (consisting of α, δ, γ-Tocotrienol) twice daily at least two days before up to 6 weeks after surgery.	There was no significant difference between the two groups.
CABG (*72*)	Selenium	Randomized clinical trial	54 (27 control, 27 selenium)	200 micrograms of selenium and 15 mg of zinc once daily, a week before the CABG.	4 cases of the control group had atrial fibrillation, and there was no case of AF in the intervention group; the difference between the two groups was significant (P = 0.015).
CABG/ valve surgery /others (*73*)	Selenium	Randomized clinical trial	1394 patients (697 control, 697 selenium)	2000 µg/L of intravenous selenium, 30 minutes after induction of anesthesia and before initiation of CPB, then 2000 µg/L of intravenous selenium immediately on admission to the postoperative ICU, then daily 1000 µg/L of intravenous selenium while in ICU for a maximum of 10 days.	There was no difference in clinically significant atrial fibrillation between the selenium and placebo groups.

POAF: Postoperative Atrial Fibrillation, CABG: Coronary Bypass Graft Surgery, ICU: Intensive Care Unit, CPB: Cardiopulmonary Bypass, AF: Atrial Fibrillation, ALA: Alpha Lipoic Acid, n-3 PUFAs: Omega-3 Polyunsaturated Fatty Acid.

In a preliminary single-group interventional study involving patients undergoing esophageal cancer surgery, fifteen patients received 1 g of L-carnitine three times daily, starting 2 days before surgery and continuing for 3 days postoperatively. The incidence of POAF in this cohort was 7.7% (95% CI: 0.2–36%) (34). In another randomized controlled trial involving 134 patients undergoing CABG (67 in the control group and 67 in the L-carnitine group), participants received 1 g of L-carnitine three times daily from 2 days before surgery until 2 days after surgery. The L-carnitine group exhibited a significantly lower incidence of new-onset POAF compared with the placebo group (7.5% vs. 19.4%; P = 0.043) (35).

The efficacy of L-carnitine for POAF prevention was also evaluated in a small randomized controlled trial involving thirty patients (15 in the control group and 15 in the L-carnitine group) undergoing aortic valve surgery. Patients received 1 g of L-carnitine three times daily from 2 days before surgery until 7 days after surgery. The L-carnitine group again demonstrated a significantly lower incidence of POAF compared with the placebo group (20% vs. 60%; P = 0.025) (36).

These three studies varied in treatment duration, and two of them had notably small sample sizes (15 and 30 patients). In addition, the study populations differed with respect to the types of surgeries performed. The study conducted in patients undergoing esophageal cancer surgery was a single-group interventional study, which limits the strength of its clinical conclusions.

Coenzyme Q10

Two randomized controlled trials were evaluated (Table 3). Coenzyme Q10 (CoQ10), also known as ubiquinone in its oxidized form and ubiquinol in its reduced form, is a lipid-soluble molecule that plays an essential role in mitochondrial electron transport and ATP production. Nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$) donate high-energy electrons to complexes I and II, respectively, which subsequently transfer these electrons to ubiquinone. The electrons are then shuttled to complex III, regenerating ubiquinone and establishing a proton gradient across the mitochondrial membrane that drives ATP synthesis (37).

Excess superoxide anions can damage lipids, proteins, and DNA; however, CoQ10 facilitates their conversion into hydrogen peroxide (H_2O_2), thereby reducing ROS toxicity and enhancing cellular antioxidant defenses. In addition, CoQ10 stabilizes mitochondrial membrane potential, improves mitochondrial respiration, and enhances the activity of antioxidant enzymes, including superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) (38,39).

Clinical trials suggest that perioperative CoQ10 administration provides cardioprotective effects (40); however, limited studies have evaluated its role in preventing post-CABG atrial fibrillation. A meta-analysis by Fernando de Frutos reported that preoperative CoQ10 supplementation significantly reduced ventricular arrhythmias after cardiopulmonary bypass but did not significantly affect the incidence of AF (41). In contrast, a randomized clinical trial demonstrated a significant reduction in postoperative AF with CoQ10 supplementation, although it did not significantly influence the incidence of ventricular tachycardia. In this study, eighty patients (40 control and 40 CoQ10) who were candidates for CABG were randomized to receive either CoQ10 (150 mg/day for 7 days before surgery) or placebo. The incidence of postoperative AF decreased from 45% in the control group to 20% in the intervention group (P = 0.030) (42).

Additionally, another study (Table 3) evaluated the clinical and biochemical effects of ubiquinol in forty-two patients (22 control and 24 ubiquinol) undergoing aortic valve replacement. Patients who received 400 mg of ubiquinol once daily from 7 days before surgery until 5 days after surgery showed attenuation of postoperative CoQ10 decline and oxidative stress, along with reduced troponin I levels, suggesting a potential role in preventing adverse surgical outcomes (43). These two studies differed in both duration and dosing, and the optimal effective dose remains unclear.

Crocin

Crocin is a natural, water-soluble carotenoid and one of the main active constituents of saffron (*Crocus sativus*). Crocin acts as a scavenger of reactive oxygen species and free radicals, particularly superoxide anions (44,45).

Crocin exerts cardioprotective effects through its antioxidant and anti-inflammatory properties. It suppresses nuclear factor-kappa B (NF-κB) activation via nuclear factor erythroid 2-related factor 2 (Nrf2) signaling. Studies have demonstrated that crocin reduces creatine phosphokinase (CPK) activity and restores redox balance, thereby contributing to its cardioprotective effects (46).

A meta-analysis of randomized controlled trials suggested that crocin exerts cardioprotective effects by reducing levels of tumor necrosis factor-α (TNF-α), low-density lipoprotein, triglycerides, fasting blood glucose, malondialdehyde, and high-sensitivity C-reactive protein (47). In addition, a randomized controlled trial conducted by Hashemi demonstrated the prophylactic effect of crocin in preventing POAF (Table 3). In this study, 100 patients were enrolled (50 in the control group and 50 in the crocin group). Patients in the intervention group received 15 mg of crocin twice daily from three days before surgery until three days postoperatively and exhibited a significantly lower incidence of POAF (7 vs. 18 patients; P = 0.02), along with significantly reduced prooxidant–antioxidant balance levels (P < 0.001) (48). As this trial was conducted at a single

center, additional multicenter clinical studies are required to enable more robust and generalizable conclusions.

Berberine

One pivotal clinical trial (Table 3) and several mechanistic studies were reviewed. Berberine (BBR) is a natural alkaloid extracted from the roots, rhizomes, and stems of plants belonging to the Ranunculaceae family (49). Although BBR possesses antioxidant properties, including enhancement of superoxide dismutase (SOD) activity and inhibition of nitric oxide (NO) expression, its primary antiarrhythmic effects are attributed to modulation of cardiac ion channels and prolongation of action potential duration (50). The relationship between berberine's antioxidant properties (51) and its antiarrhythmic effects has been supported by studies demonstrating that excessive mitochondrial ROS production — driven by elevated intracellular NADH — reduces cardiac sodium current (I_Na), thereby increasing arrhythmic risk. By attenuating ROS production, berberine may help restore I_Na and improve cardiac conduction velocity (52,53).

Jian Zhang conducted a randomized, double-blind, placebo-controlled trial involving 200 patients who underwent isolated coronary artery bypass grafting. Participants were randomized to the berberine group (n = 100) or the placebo group (n = 100). Patients received the assigned treatment continuously from 7 days before surgery until hospital discharge or up to 7 postoperative days. The incidence of POAF decreased from 35% in the placebo group to 20% in the berberine group (hazard ratio, 0.5 [95% CI, 0.29–0.78]; P = 0.01). At 48 hours after surgery, levels of lipopolysaccharide, interleukin-6 (IL-6), and C-reactive protein were significantly lower in the berberine group (54). This single-center trial is currently the only study evaluating the efficacy of berberine for POAF prevention.

Alpha-Lipoic Acid (ALA)

One clinical study was reviewed (Table 3). Alpha-lipoic acid (ALA) is a naturally occurring compound present in all animal species and is known for its potent antioxidant properties (55). Preoperative administration of antioxidants such as ALA has been proposed as a strategy to reduce postperative complications by enhancing endogenous antioxidant defenses.

ALA exerts multiple antioxidant effects, including scavenging of reactive oxygen species, regeneration of endogenous antioxidants (e.g., glutathione, coenzyme Q10, and vitamins E and C), metal chelation, and prevention of lipid and protein peroxidation. It also serves as a cofactor for mitochondrial enzyme complexes involved in carbohydrate, lipid, and protein metabolism, thereby contributing to ATP production (56-58).

In a randomized controlled trial (Table 3) involving patients undergoing primary cardiac valve surgery or CABG, the effect of ALA on POAF incidence was evaluated. Ninety patients were randomized into two groups: a control group (n = 45) receiving placebo and an ALA group (n = 45) receiving 600 mg of ALA twice daily. ALA therapy was initiated 5 - 10 days before surgery and continued until hospital discharge. The incidence of POAF was significantly lower in the ALA group (11%) compared with the control group (33%) (log-rank test, P = 0.01) (59). Further clinical studies are needed to confirm the efficacy of ALA in POAF prophylaxis.

Melatonin

Melatonin, a hormone produced by the pineal gland, possesses potent antioxidant properties. It directly scavenges reactive oxygen species (ROS), reactive nitrogen species (RNS), and other free radicals. In addition, melatonin improves mitochondrial function by preserving the integrity of complexes I and III, preventing mitochondrial permeability transition, and inhibiting NADPH oxidase activity. It also enhances endogenous antioxidant defenses by increasing the activity of glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD) (60,61).

Several studies have reported the cardioprotective effects of melatonin in patients undergoing CABG, particularly through attenuation of myocardial ischemia/reperfusion injury and surgery-related cardiac damage. However, evidence supporting its antiarrhythmic effects in humans remains limited (62,63). In a single-center study by Saghar Barati evaluating the effects of melatonin on oxidative stress and AF duration following CABG (Table 3), 76 patients (38 control and 38 melatonin) were randomly assigned to receive 12 mg of sublingual melatonin the evening before surgery and 1 hour after surgery. The incidence of AF after CABG was not significantly different between the groups (14.3% in the control group vs. 8.6% in the melatonin group; P = 0.71). However, melatonin significantly reduced the duration of AF episodes (3.5 ± 0.4 hours in the melatonin group vs. 6.6 ± 0.8 hours in the control group; P = 0.01). Larger, multicenter trials are needed to confirm and generalize these findings (64).

Vitamin E

Two randomized controlled trials using different formulations were identified (Table 3). The vitamin E family comprises tocopherols and tocotrienols, with tocotrienols considered more potent antioxidants due to their unsaturated side chain, which enhances free radical scavenging and protection against lipid peroxidation (65). Tocotrienols exert antioxidant effects by inducing antioxidant enzymes, including superoxide dismutase (SOD), quinone oxidoreductase, and glutathione peroxidase (GPx), and by scavenging peroxyl radicals (66). In addition, tocotrienols

possess anti-inflammatory properties through inhibition of pathways involving nuclear factor-kappa B (NF-κB), signal transducer and activator of transcription 3 (STAT3), and cyclooxygenase-2 (COX-2) (67,68).

In a clinical trial conducted by Ramón Rodrigo involving 203 patients, supplementation with n-3 polyunsaturated fatty acids (2 g/day; eicosapentaenoic acid to docosahexaenoic acid ratio of 1:2), vitamin C (1 g/day), and vitamin E (400 IU/day) significantly reduced the incidence of postoperative AF ($P < 0.001$). Moreover, the activity of antioxidant enzymes in atrial tissue — including catalase (CAT), SOD, and GPx — was significantly higher in the supplemented group compared with the placebo group (69).

In another randomized controlled trial involving 250 patients, participants in the Tocovid group received 200 mg of Tocovid (a mixture of α-, δ-, and γ-tocotrienols) twice daily, starting two days before surgery and continuing for up to 6 weeks (Table 3). Although the Tocovid group experienced a significantly shorter stay in the cardiac intensive care unit (CICU), no significant reduction in POAF incidence was observed. The absence of effect may have been related to poor absorption of vitamin E when administered on an empty stomach, which was common among postoperative cardiac surgery patients (70). These two trials evaluated different formulations and dosages of vitamin E.

Selenium

Two RCTs with opposing results were analyzed (Table 3). Selenium, an essential trace element, plays an important role in anti-inflammatory and antioxidant processes. Selenium-containing proteins, known as selenoproteins, contribute to the elimination of reactive oxygen species and the regulation of redox balance. For example, glutathione peroxidase (GPx) reduces hydrogen peroxide and lipid hydroperoxides, while thioredoxin reductase plays a key role in redox regulation (71).

In a single-center clinical trial (Table 3), 54 patients undergoing CABG (27 in the control group and 27 in the selenium group) were randomized to receive either 200 µg of selenium plus 15 mg of zinc or placebo once daily for one week before surgery. The intervention group showed a significantly lower incidence of AF (0% vs. 14.8%, $P = 0.015$), along with improved cardiac ejection fraction and reduced bleeding volume and hospital stay duration (72).

In contrast, a large multicenter randomized trial involving 1394 patients (697 receiving selenium and 697 receiving placebo) found no significant difference in AF incidence between the selenium and placebo groups. In this study, the selenium regimen consisted of 2000 µg/L of intravenous selenium administered 30 minutes after induction of anesthesia and before initiation of cardiopulmonary bypass, followed by 2000 µg/L administered immediately upon admission to the postoperative intensive care unit, and then 1000 µg/L intravenously each day during ICU stay for a maximum of 10 days. The lack of benefit observed in this trial may be attributable to the timing of selenium administration, as its antioxidant effects may require a longer period to develop, and administration immediately before surgery may have been insufficient to confer protective effects (73).

Discussion

Four main pathophysiological pathways contribute to the occurrence of AF: structural remodeling, electrical remodeling, the autonomic nervous system, and Ca^{2+} handling abnormalities (74,75). As discussed below, oxidative stress affects three of these four AF-triggering mechanisms. Oxidative stress can be defined as a significant and uncontrolled generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) that overwhelms endogenous antioxidant defenses. ROS participate in cell signaling as mediators and regulators of vascular function, prostaglandin production pathways, mitochondrial respiration, and host defense. Damage to DNA, proteins, and lipids, along with tissue injury resulting from excessive ROS in myocardial tissue, contributes to structural and electrical remodeling of the heart, processes that are closely associated with cardiac arrhythmias (76-78). The primary sources of ROS in the heart include mitochondrial electron transport (79), xanthine oxidase (80), nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase (NOX) (81), and uncoupled endothelial nitric oxide synthase (eNOS) (82). Studies in animal models have shown that activation of NOX2 and NOX4 isoforms leads to the production of superoxide and H_2O_2, promoting myocyte apoptosis, fibrosis, and inflammation, and thereby facilitating the perpetuation of atrial fibrillation (83-87).

Two important mechanisms contributing to AF are focal activity and reentry (88). In addition, triggered activity generated by membrane depolarization following the upstroke phase of an action potential represents another critical mechanism. Early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs), as forms of triggered activity, play a role in initiating AF, particularly in the pulmonary veins. Prolongation of action potential duration increases the likelihood of EADs. Reactivation of voltage-gated sodium channels and L-type Ca^{2+} channels during membrane repolarization and recovery from their inactivated state is associated with EAD generation. Dysfunction of ryanodine receptor 2 (RyR2) and intracellular Ca^{2+} overload lead to spontaneous Ca^{2+} release from the sarcoplasmic reticulum, contributing to DAD formation. RyR2 dysfunction activates the sodium-calcium exchanger, resulting in the extrusion of one Ca^{2+} ion in exchange for the influx of three sodium ions. This inward sodium current facilitates the development of DADs (89).

One proposed mechanism by which ROS exert

proarrhythmic effects is through oxidation of calmodulin-dependent protein kinase II (CaMKII) (90). Oxidized CaMKII promotes phosphorylation of the ryanodine receptor 2 (RyR2), leading to intracellular calcium overload and the generation of multiple reentrant wavelets that can trigger the onset of AF (91). Therefore, oxidized CaMKII may function as a ROS-activated mediator and potential biomarker in the development of AF (92).

Excessive ROS have also been shown to directly affect ion channels and action potential propagation (76). Hydrogen peroxide enhances early and delayed afterdepolarizations (EADs and DADs) by inducing late sodium (Na^+) current. ROS can contribute to downregulation of total Na^+ current and facilitate the formation of reentry circuits. In addition to promoting reentry, ROS disrupt intracellular calcium homeostasis by directly increasing L-type Ca^{2+} current, thereby further enhancing the likelihood of EAD formation (76).

Reentry occurs as a result of both electrical and structural remodeling, which can shorten the refractory period and slow conduction velocity. Reduction of the refractory period occurs through increased outward potassium current (Ito) and decreased inward L-type calcium current (ICa,L), leading to accelerated membrane repolarization. Other factors, including downregulation of sodium current, gap junction uncoupling (93,94), atrial enlargement (95,96), and fibrosis (97,98), can further impair impulse conduction. NOX2-dependent oxidative stress under hypoxic conditions has been shown to reduce and remodel atrial connexin40 and connexin43. Connexins are gap junction proteins responsible for conducting action potentials between adjacent cells (99). Studies have demonstrated that NOX4 mediates atrial structural remodeling and increases AF vulnerability through enhanced transforming growth factor beta 1 (TGF-β1) responsiveness, increased NOX4 expression, and elevated NOX activity in atrial fibroblasts. It has also been revealed that the TGF-β–mediated HA/CD44/STAT3 pathway contributes to atrial fibrosis and the development of AF (9,100). The hypothetical pathophysiology of POAF, with particular emphasis on the relationship between ischemia-reperfusion injury (IRI) and inflammation leading to oxidative stress, is illustrated in Figure 1.

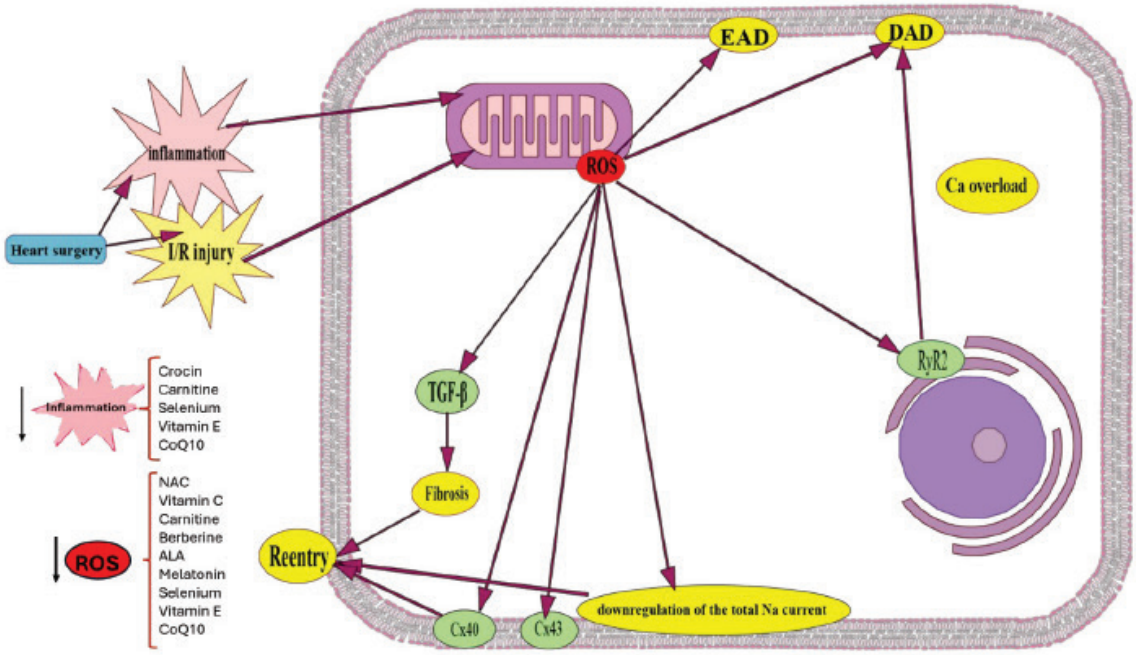

Figure 1. How can oxidation lead to POAF?

Heart surgery, through inflammation and I/R injury, can lead to overproduction of ROS. Oxidative stress can play a role in the pathophysiology of AF by altering electrical and structural remodeling. Two important mechanisms that contribute to AF are focal activity and reentry. Reentry occurs by electrical and structural remodeling. NOX4 mediates atrial structural remodeling and AF vulnerability due to increased TGF-β1 responsiveness, NOX4 expression, and NOX activity in atrial fibroblasts, and it has been shown that TGF-β-mediated HA/CD44/STAT3 pathway contributes to atrial fibrosis and AF development. the early after depolarizations (EADs) and delayed after depolarizations (DADs), as triggered activities, play a role in initiating AF in the pulmonary veins. Prolonged action potential duration (APD) enhances EADs. Hydrogen peroxide enhances EAD and DAD through inducing late Na+ current. And, it has been investigated that ROS has an effect on downregulation of the total Na+ current and accelerates the formation of reentry circuits. In addition to its effect on reentry formation, ROS can alter the intracellular calcium balance by directly upregulating the L-type Ca2+ current and promoting EADs. Reactivation of voltage-gated sodium and L-type Ca2+ channels during membrane repolarization and recovery from their inactive state is associated with EADs. RyR2 dysfunction and Ca2+ overload lead to spontaneous Ca2+ discharges from the sarcoplasmic reticulum (SR) contribute to DAD. RyR2 dysfunction activates the sodium-calcium exchanger (NCX), and then one Ca2+is extruded from the cell in exchange for three sodium ions entering the cell. This inward sodium current (ITi) facilitates DADs. NOX2-dependent oxidative stress in hypoxia can reduce and remodel atrial Connexin40 and Connexin43. Sodium current downregulation, gap junction uncoupling, fibrosis, and atrial enlargement.

Several antioxidant agents targeting POAF, particularly in the setting of cardiac surgery, have demonstrated potentially promising results; however, the available evidence remains preliminary. These agents — including vitamin C, NAC, crocin, carnitine, ALA, berberine, melatonin, selenium, CoQ10, and vitamin E — may contribute to the prevention of AF following cardiac surgery. Nevertheless, larger multicenter randomized trials are required to validate their efficacy.

Multiple strategies have been proposed for the prevention of POAF. The most common approaches include suppression of the renin–angiotensin–aldosterone system and reduction of oxidative stress and inflammation (101). However, due to insufficient evidence from large randomized controlled trials, the 2024 European Society of Cardiology (ESC) guidelines for the management of atrial fibrillation do not recommend these strategies. Instead, the guidelines recommend perioperative amiodarone therapy when pharmacological intervention is desired to prevent postoperative AF after cardiac surgery. β-blockers are also considered equally effective in reducing the incidence of postoperative atrial fibrillation (2). The 2023 American Heart Association (AHA) guidelines note that meta-analyses provide limited but consistent evidence supporting the efficacy of vitamin C in preventing POAF (102).

The efficacy of antioxidants in the prophylaxis of postoperative complications has been evaluated in numerous studies. In a review by Javier Toro-Pérez, postoperative liver failure, acute kidney injury, and POAF were discussed, with the suggestion that antioxidants may represent viable options for preventing these complications (103). In addition, a meta-analysis demonstrated that perioperative antioxidant treatment was associated with reduced mortality in patients undergoing surgery (104).

This review provides a comprehensive synthesis of current evidence on antioxidant therapies for POAF prevention, integrating both mechanistic insights and clinical outcomes. One of its key strengths is the breadth of antioxidants evaluated, ranging from well-established agents such as NAC and vitamin C to emerging candidates like crocin and berberine, thereby offering a balanced assessment of their therapeutic potential. By focusing on oxidative stress–related pathways—including ROS generation, mitochondrial dysfunction, and inflammatory cascades—the review establishes a strong pathophysiological rationale for the use of antioxidants in POAF. Furthermore, it highlights practical considerations such as dosing regimens and timing of administration, which may inform future clinical protocols.

However, several limitations should be acknowledged. The heterogeneity among included studies — particularly differences in POAF definitions, antioxidant administration protocols, and follow-up durations — limits direct comparisons and precludes definitive meta-analytic conclusions. Moreover, some compounds, such as berberine, exhibit pleiotropic effects beyond antioxidant activity, making it challenging to isolate their specific antiarrhythmic mechanisms. These limitations underscore the need for larger, well-designed, standardized clinical trials incorporating rigorous, biomarker-driven approaches to clarify the role of antioxidants in POAF prevention and to optimize their integration into perioperative care.

Our comprehensive literature review summarizes the available clinical evidence supporting the use of antioxidants for the prophylaxis of POAF. Some of these compounds also possess additional antiarrhythmic properties, which makes it difficult to distinguish their antioxidant effects from other electrophysiological mechanisms. For example, berberine modulates ion channels and action potential duration, while carnitine may influence QT interval dynamics. To optimize antioxidant efficacy, supplementation should ideally begin several days before surgery. However, absorption challenges — particularly for lipid-soluble agents during the postoperative period when patients are often restricted to liquid intake — represent an additional limitation.

Although several antioxidants demonstrate potential in reducing POAF risk, the overall evidence remains heterogeneous. Findings for agents such as selenium, melatonin, berberine, crocin, and CoQ10 are inconsistent, and most studies are small, single-center trials rather than large, multicenter randomized controlled trials or robust meta-analyses. Therefore, while current data are insufficient to definitively conclude that presurgical antioxidant therapy prevents POAF, a potential benefit cannot be excluded. Further research is needed to determine the most effective regimens that balance safety, tolerability, and clinical efficacy.

Conclusion

In conclusion, current evidence suggests that antioxidant therapy may have a potential role in the prevention of POAF, with the most consistent findings reported for NAC and vitamin C. These results support the relevance of oxidative stress in POAF pathophysiology. However, substantial heterogeneity across studies and inconsistent findings for several antioxidant agents limit the strength of these conclusions. The absence of large, adequately powered multicenter randomized controlled trials precludes firm clinical recommendations; therefore, antioxidant therapy should currently be regarded as investigational. Further high-quality trials with standardized methodologies and

optimized dosing strategies are required to clarify the clinical applicability of antioxidant interventions in POAF prevention.

Conflict of Interest
None declared.

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