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REVIEW

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Impact of antioxidant supplementations on cardio-renal protection in cardiac surgery: an updated and comprehensive meta-analysis and systematic review

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Summary

This systematic review with meta-analysis sought to determine the strength of evidence in terms of the impact of common antioxidant supplementations, such as N-acetylcysteine (NAC), vitamin C, and polyunsaturated fatty acids (PUFA) on perioperative outcomes after cardiac surgery with particular focus on the incidence of atrial fibrillation (AF) and acute kidney injury (AKI) with associated mortality. A total of 29 trials were identified that reported incidence of AF and 17 trials that reported incidence of AKI. Pooled analysis reported that NAC (OR=0.5; *P*=.001), vitamin C (OR=0.4; *P*=.001), and PUFA (OR=0.8; *P*=.01) administration were associated with significantly reduced incidence of AF. In terms of postoperative AKI, only NAC was shown to be a beneficial supplement that was able to significantly reduce the incidence of AKI (OR=0.7; *P*=.01), and NAC could also significantly decrease overall mortality (OR=0.3; *P*=.03) following cardiac surgery. The use of NAC in patients undergoing cardiac surgery should be strongly recommended due to its combined cardio-renal protective effects and reduced mortality. Also, PUFA and vitamin C might be able to significantly decrease the incidence of arrhythmia; however, reno-protective effects and impact on overall mortality of these supplements seem to be less impressive.

KEYWORDS

Acute renal injury, Atrial fibrillation, Cardiac surgery, N-acetylcysteine, Polyunsaturated fatty acids, Vitamin C

1 | INTRODUCTION

Atrial fibrillation (AF) is the most frequent type of arrhythmia after coronary artery bypass graft (CABG) surgery with the incidence ranging from 10% to 65% and imparts an increased risk for morbidity and mortality.[1] Nevertheless, prompt pharmacological or electrical cardioversion as well as surgical procedures, such as posterior pericardiotomy, may induce or support successful conversion of AF to a sinus rhythm without major clinical complications.[2,3]

Acute kidney injury (AKI) is another serious complication of CABG surgery with the incidence described in the literature of 5%–30% and is associated with significant morbidity and mortality, prolonged hospitalization, and need for hemodialysis.[4] Thus, despite advanced therapy of

these complications, safe and reliable prophylactic approaches to prevent Postoperative atrial fibrillation (POAF) and AKI with the view to decreasing morbidity and mortality, and other following complications are paramount for managing these demanding patients. Reactive oxygen species (ROS) are involved in the structural and electrical remodeling of the myocardium. In particular, NADPH oxidase can be activated by well-known triggers of AF, such as angiotensin II and atrial stretch.[5,6] Cellular damage is mediated by an alteration in the antioxidant status, which increases the concentration of ROS in oxidative stress. Oxidative stress mediates a wide spectrum of renal impairments, from acute renal failure, obstructive nephropathy to chronic renal failure, and hemodialysis.[7] Previous investigations have reported on the role of oxidative stress in pathogenesis of both AF and AKI, whereas N-acetylcysteine (NAC), vitamin C, and polyunsaturated fatty acids (PUFA) have been identified as promising supplementations that may be able to reduce oxidative stress and its deleterious cardio-renal effects.[8–11]

This comprehensive systematic review with meta-analysis sought to determine the strength of evidence in terms of NAC, vitamin C, and PUFA on perioperative outcomes after cardiac surgery with particular focus on the incidence of AF and AKI.

2 | METHODS AND MATERIALS

2.1 | Literature search

A systematic and comprehensive literature search was conducted in electronic medical databases (Medline/Pubmed, Embase, Elsevier, Web of Science, and Google Scholar) from their inception through October 25, 2014, to identify randomized controlled trials (RCT) reporting on the effects of antioxidant supplementations NAC, vitamin C, and PUFA on the incidence of AF and AKI after cardiac surgery. Predefined search terms have been shown in Supplemental method and materials. No limitations were imposed on language, study period, or sample size. All retrieved references of the included RCTs, recent published meta-analyses, or review articles were also reviewed to determine additional studies not indexed in the common databases. Studies were included into the analysis when they met the following criteria: (1) RCT, (2) comparison of antioxidant supplementations NAC, vitamin C, or PUFA with placebo, and (3) reporting data on the primary clinical outcomes according to our review checklist. Not peer-reviewed manuscripts, abstracts of congress presentations, and gray literature were included.

2.2 | Data extraction and outcome measures

Four investigators (S.A-H-S, M.T, P.M, and A.K-B) extracted the data independently, and discrepancies were resolved via a consensus standardized abstraction checklist used for recording data in each study. Disagreements were resolved through discussion with other senior authors (A.F-P, S.J-M, and A-S). Author's name, mean age, gender, sample size, type of antioxidant supplementation (NAC, vitamin C, or PUFA), details of study regimens and control groups, and type of surgery (CABG, valve, or combined procedures) were consequently extracted. Primary outcomes were the incidence of POAF (all primary authors' definitions for POAF were accepted) and AKI (defined as an increase in creatinine ≥25% or ≥0.5 mg/dL from the baseline) during hospital stay or follow-up, and associated overall mortality. Secondary outcome variables were other perioperative outcome variables, such as the incidence of stroke, re-myocardial infarction (re-MI), need for hemodialysis, length of ventilation time, amount of blood loss, and length of intensive care unit (ICU) and hospital stay.

2.3 | Statistical analysis, publication bias, and quality assessment

Data were analyzed by STATA software version 12.0 (College Station, TX, USA) utilizing METAN and METABIAS modules. The effect sizes measured were odds ratio (OR) with 95% confidence interval (CI) for categorical variables and weighted mean difference (WMD) with 95% CI for noncategorical data, including differences in ventilation time, amount of blood loss, and length of ICU and hospital stay between intervention and control groups. OR<1 favored study groups, and OR>1 favored control groups. Randomized controlled trials with no events in the two arms were removed from the analysis. The presence of publication bias was evaluated using the Begg's test. Quality assessment of RCTs was performed using the Jadad score that was reported on elsewhere.[12] The Jadad score assesses three items including randomization (0–2 points), blinding of study (0–2 points), as well as withdrawals and dropouts (0–1 points). Higher scores indicate higher quality of assessment ("high" quality: 5; "good" quality: 3–4; "poor" quality: 0–2). P value <.1 for Q test, or I^2>50% indicated significant heterogeneity among the studies. Heterogeneity among trials was accounted for by applying the random effect model where indicated. Results were considered statistically significant at a P value <.05.

3 | RESULTS

3.1 | Literature search strategy and included trials

Details of therapeutic strategies (cardio-protective effects of antioxidants or reno-protective effects of antioxidants) in association with included, excluded, and finally enrolled studies for the meta-analysis are shown in Table S1. In brief, a total of 832 manuscripts were selected during the initial literature search. After excluding 786 manuscripts without events according to principal inclusion and exclusion criteria, 46 remaining manuscripts were enrolled in the present meta-analysis (29 for cardio pathway and 17 for renal pathway). All enrolled manuscripts reported on AF and AKI as primary outcomes.

3.2 | Study characteristics, effect measures, and clinical outcomes

3.2.1 | Cardio-protective effects of antioxidants

N-acetylcysteine

A total of 1026 patients were included from 10 RCTs reporting on the incidence of POAF (Table 1). The size of patient cohorts from the

RCTs ranged from 20 to 240 patients. Of 1026 patients, 513 were allocated to NAC group and 513 to control group. Overall incidence of POAF was 24.6% ranging from 5% to 61.7% with 20.4% in NAC group and 28.8% in control group (Table 2). Pooled effect analysis revealed that NAC therapy was associated with significantly lower incidence of POAF with an OR of 0.55 (95% CI: 0.40–0.77; *P*=.001) using the fixed effects model (Figure 1). There was no significant heterogeneity among the studies included (χ^2=10.5, I^2=15%). There was no statistical publication bias (Begg's test; *P*=.805). Four RCTs reported data on the incidence of re-MI. Overall incidence of re-MI was 7.1% accounting for 7.3% in NAC group and 6.8% in control group (Table 2). In fact, one of four comparative analyses did not present any re-MI in two comparative arms; therefore, the remaining three RCTs were used to perform the meta-analysis. Pooled analysis indicated that the incidence of re-MI was statistically similar comparing NAC therapy with placebo with an OR of 1.07 (95% CI: 0.50–2.3; *P*=.8) using the fixed effects model (χ^2=0.98, I^2=0%). Only five RCTs with a total of 248 patients reported data on the volume of blood loss. Mean volume for all trials was 616.1±273.2 mL with 619.6±273.6 for NAC group and 612.6±308.8 for control group. Pooled analysis applied the fixed effects model and revealed that NAC supplementation was not associated with reduced postoperative blood loss with a WMD of 21.9 (95% CI: −26.4 to 70.2; *P*=.3). Seven RCTs reported data on the incidence of stroke. Overall incidence of stroke was 1.5% accounting for 1.9% in NAC group and 1.1% in control group. In fact, two of seven analyses did not present any stroke in two comparative arms; therefore, the remaining five RCTs were used to perform the meta-analysis. Pooled analysis indicated that the incidence of stroke was statistically similar comparing NAC therapy to placebo with an OR of 1.6 (95% CI: 0.60–4.3; *P*=.3) using the fixed effects model (χ^2=1.43, I^2=0%). Length of hospital stay was reported on in five RCTs with the total of 523 patients, whereas ICU stay was analyzed in three RCTs with 308 patients. Mean duration of hospital stay for all trials was 7.72±2.59 days with 7.8±2.6 in NAC and 7.6±2.5 in control group. Mean length of ICU stay was 72.4±35.7 hours with 71.7±27.7 in NAC and 73.1±43.8 in control group. Pooled analysis applied revealed that NAC could not significantly decrease postoperative length of hospital stay with a WMD of 0.09 (95% CI: −0.12 to 0.31; *P*=.4, χ^2=1.85, I^2=0%) and ICU stay with a WMD of 0.59 (95% CI: −0.96 to 2.16; *P*=.4, χ^2=0.90, I^2=0%). Nine RCTs included data on mortality as secondary outcome. Overall cumulative mortality was 2.1% accounting for 1.01% in NAC group and 3.25% in control group. In fact, two of nine comparisons did not show any mortality in two comparative arms; therefore, the remaining seven RCTs were enrolled to perform the meta-analysis. Pooled treatment effect analysis revealed that NAC could significantly decrease associated mortality with an OR of 0.39 (95% CI: 0.16–0.93; *P*=.03) using the fixed effects model (χ^2=5.8, I^2=0%).

Polyunsaturated fatty acids

A total of 2992 cases were included from 12 RCTs. Patient populations of the RCTs ranged from 28 to 1516 cases (Table 1). Of 2992 patients, 1487 were allocated to PUFA group and 1507 to control group. Overall incidence of POAF was 31.48% ranging from 7.14% to 54.1% and accounting for 29.3% in PUFA group and 33.5% in control group (Table 2). Pooled treatment effect analysis indicated that PUFA supplementation could statistically decrease the incidence of POAF with an OR of 0.81 (95% CI: 0.69–0.95; *P*=.01) using the fixed effects model (Figure 2). There was no significant heterogeneity among the studies analyzed (χ^2=16.13, I^2=31.8%). There was no statistical publication bias (Begg's test; *P*=.681). Four RCTs also reported on the incidence of postoperative re-MI, whereas its incidence was 1.39% with 1.30% in PUFA group and 1.48% in control group (Table 2). Extracted Forest plot showed that the incidence of re-MI was not significantly different comparing PUFA and placebo group with an OR of 0.88 (95% CI: 0.43–1.7; *P*=.7, χ^2=1.93, I^2=0%). Only two RCTs (222 patients) reported on the extent of postoperative bleeding. Mean volume of blood loss was 1012±618.5 for PUFA and 1140±916 for control group. Pooled analysis revealed that the volume of bleeding was statistically similar in PUFA and placebo group with a WMD of −106.27 (95% CI: −315.12 to 102.57; *P*=.3). Five RCTs provided data on the incidence of stroke. Overall incidence of stroke was 1.25% with 0.83% in PUFA group and 1.6% in control group. Pooled analysis showed that PUFA could not significantly decrease the incidence of stroke with an OR of 0.51 (95% CI: 0.23–1.14; *P*=.1, χ^2=1.15, I^2=0%). Five RCTs (622 patients) reported on the length of hospitalization and three (261 patients) on the length of ICU stay. Mean length of hospital stay for all trials was 11.25±4.84 days with 10.96±4.18 for PUFA and 11.54±5.5 for control group. Mean length of ICU stay was 49.8±31.3 hours for PUFA and 64.5±71.6 hours for control group. Pooled analysis revealed that PUFA was associated with decreased postoperative length of hospital stay with a WMD of −0.55 (95% CI: −1.12 to −0.07; *P*=.02, χ^2=2.38, I^2=0%) without decreasing effect on ICU stay with a WMD of −8.5 (95% CI: −19.8 to 2.67; *P*=.1, χ^2=3.14, I^2=36.3%). Eight RCTs reported on mortality that accounted for 1.37% with 1.1% in PUFA group and 1.6% in control group. In fact, three of eight comparisons did not present any mortality in two comparative arms; therefore, the remaining five RCTs were used to perform the analysis. Pooled analysis revealed that PUFA could not significantly decrease the incidence of mortality with an OR of 0.66 (95% CI: 0.33–1.31; *P*=.2) using the fixed effects model (χ^2=2.04, I^2=0%).

Vitamin C

A total of 785 patients were included from seven RCTs. Patient populations ranged from 24 to 185 cases (Table 1). From 785 patients, 390 were allocated to vitamin C group and 395 to control group. Overall incidence of POAF was 29.9% ranging from 15% to 52.9% and accounting for 22.5% in vitamin C group and 37.2% in control group (Table 2). Pooled treatment effect analysis revealed that vitamin C therapy could significantly decrease the incidence of POAF with an OR of 0.40 (95% CI: 0.23–0.68; *P*=.001) using the random effect model (Figure 3). However, there was significant heterogeneity among the studies (χ^2=12.44, I^2=51.8%). There was no statistical publication bias (Begg's test; *P*=.176). Three RCTs reported data on the incidence of stroke. Overall incidence of stroke was 1.8% with 1.05% in vitamin C group and 2.55% in control group. Pooled analysis indicated that the incidence of stroke was similar using vitamin C therapy compared to

TABLE 1 Demographic data of included studies

	Number of patients		Mean age		Male [%]					
Author	AO	Control	AO	Control	AO	Control	Surgery	Type of AO	Regimen	Jadad
Berger[13]	14	14	64.7	66.3	100	78.5	CABG and/or valve	PUFA	Three infusions of 0.2 g/kg FO emulsion or saline (control) 12 and 2 h before and immediately after surgery	5
Calo[14]	79	81	66.2	64.9	86	84	CABG only	PUFA	2 g PUFA daily for at least 5 d before surgery until hospital discharge	3
Farquharson[15]	97	97	64	64	82	64	CABG and/or valve	PUFA	4.6 g daily of long-chain omega-3 fatty acid starting 3 wk before CABG	5
Heidarsdottir[16]	83	85	67	67	81.9	76.9	CABG only	PUFA	Capsules of PUFA for 5–7 d before CABG until hospital discharge	4
Heidt[17]	52	52	67.8	68.6	73	64	CABG only	PUFA	Dosage of 100 mg fish oil/kg body weight/d	3
Lomivorotov[18]	18	21	61	58	94.5	95.3	CABG only	PUFA	Polyunsaturated fatty acids (200 mg/kg/d starting before anesthesia induction for 24 h followed by 100 mg/kg/d for 7 d)	5
Mozaffarian[19]	758	758	63.8	63.6	72.7	71.6	CABG and/or valve	PUFA	1 g capsules containing ≥840 mg PUFA, with preoperative loading of 10 g over 3–5 d followed by 2 g until hospital discharge or day 10 after CABG and/or valve surgery	5
Sandersa[20]	120	123	63.4	62	78	83	CABG and/or valve	PUFA	PUFA 2 g orally twice daily for 72 h after surgery	4
Sarvanan[21]	52	51	64	68	77	82	CABG only	PUFA	2 g PUFA daily for at least 5 d after surgery	5
Wilbring[22]	99	100	67.6	67.5	87.9	82.7	CABG only	PUFA	Daily dose of 2 g omega-3 PUFA, initiated 5 d before surgery	3
Stanger[23]	19	20	65	65	100	85	CABG and/or valve	PUFA	n-3 PUFAs—EPA and DHA ~ 0.15 g fish oil/kg body weight at 42 and 18 h before surgery, and the third infusion was given as a single dose of 50 mL (=5 g fish oil) 42 h after surgery	3
Sorice[24]	96	105	63.5	63	79.1	83.8	CABG only	PUFA	2 g PUFA daily for at least 5 d after CABG	2
El-Hamamsy[25]	50	50	59.8	61.3	86	92	CABG only	NAC	600 mg orally the day before surgery and the morning of CABG and 150 mg/kg intravenous before incision of skin, then 12.5 mg/kg/h IV for 1 d	3
Eren[26]	10	10	61.1	60.5	80	70	CABG only	NAC	100 mg/kg intravenous before cardiopulmonary bypass and 40 mg/kg/d for 1 d after cardiopulmonary bypass	3
Hasse[27]	30	30	68.9	68.3	77	70	CABG and/or valve	NAC	150 mg/kg intravenous bolus after induction of anesthesia, then 50 mg/kg intravenous over 4 h, and then, 100 mg/kg intravenous over 20 h	5
Kazemi[28]	120	120	61.3	58.2	75.8	73.3	CABG and/or valve	NAC	1200 mg oral NAC twice daily, starting 48 h before and up to 2 d after CABG	4
Kim[29]	24	24	60.8	65.3	87.5	91.7	CABG only	NAC	100 mg/kg intravenous bolus over 15 min after induction of anesthesia, then IV infusion at 40 mg/kg/d for 24 h	4
Orhan[30]	10	10	59.6	61.8	70	60	CABG only	NAC	50 mg/kg intravenous at starting of anesthesia induction for 30 min	3

(Continues)

TABLE 1 (Continued)

Author	Number of patients		Mean age		Male [%]		Surgery	Type of AO	Regimen	Jadad
	AO	Control	AO	Control	AO	Control				
Ozaydin[31]	104	104	63	62	77.9	73.1	CABG and/or valve	NAC	50 mg/kg IV 1 h before surgery and 50 mg/kg/d for 2 d after operation. All patients received carvedilol 6.25 mg twice daily in study and control groups	5
Ozaydin[32]	58	57	57	59	81	77.2	CABG and/or valve	NAC	50 mg/kg IV before surgery and 50 mg/kg/d for 2 d after CABG	4
Wijeysundera[33]	88	87	74	73	60	59	CABG and/or valve	NAC	100 mg/kg intravenous after anesthetic induction over 30 min and 20 mg/kg/h intravenous after cardiopulmonary bypass for 4 h	5
Peker[34]	19	21	60	57.6	89.5	85.7	CABG only	NAC	50 mg/kg intravenous NAC for 1 h before operation and 50 mg/kg/d intravenous for 2 d after surgery	4
Bjordahl[35]	89	96	63	63	68.5	65.6	CABG only	Vitamin C	Two 1-g capsules of ascorbic acid orally the evening preoperation and 1 g two times per day orally for 5 d after CABG	5
Carnes[36]	43	43	61.6	61.8	83.7	83.8	CABG only	Vitamin C	2 g ascorbic acid the night preoperation followed by 500 mg doses two times per day for 5 d after CABG	2
Colby[37]	13	11	68.4	62.1	69	91	CABG and/or valve	Vitamin C	2 g ascorbic acid the night before surgery. From the day of operation and for 4 d after operation, 500 mg of oral ascorbic acid two times per day	4
Eslami[38]	50	50	60.7	59.6	72	62	CABG only	Vitamin C	2 g ascorbic acid on the night preoperation and 1 g twice daily for 5 d after CABG.	1
Papoulidis[39]	85	85	73.1	71.3	67	74.1	CABG only	Vitamin C	2 g ascorbic acid 3 d prior the start of cardiopulmonary bypass and afterward 500 mg twice daily from the day of surgery and for the next 5 d	2
Samadikhah[40]	60	60	N.D	N.D	N.D	N.D	CABG only	Vitamin C	Tablet of atorvastatin 40 mg (daily) with oral Vitamin C (2 g in operation day and 1 g from second day until 5 d)	2
Dehghani[41]	50	50	60.5	62.1	76	72	CABG only	Vitamin C	2 g of oral vitamin C before and 500 mg twice daily lasting for 5 d after surgery	3

CABG, coronary artery bypass graft; PUFA, polyunsaturated fatty acid; AO, antioxidant; NAC, n-acetylcysteine; IV, intravenously.

References 8–56 have been shown in Supporting information.

TABLE 2 Clinical outcomes of included studies (antioxidant supplementation on cardio-protection)

	POAF [n]		Re-MI [n]		Stroke [n]		Blood loss [mL] (Mean±SD)		ICU stay [h] (Mean±SD)		Hospital stay [d] (Mean±SD)		Mortality [n]	
Author	**AO**	**C**	**AO**	**C**	**AO**	**C**	**AO**	**C**	**AO**	**C**	**AO**	**C**	**AO**	**C**
PUFA														
Berger[13]	1	1	N.D	N.D	N.D	N.D	873±450	1030±1032	34.5±18	50.7±32.9	12.7±4.2	12.2±4.3	0	0
Calo[14]	12	27	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	7.3±2.1	8.2±2.6	1	2
Farquharson[15]	36	47	0	3	1	2	1151±787	1250±800	67±52	95±158	8.6±7.1	9.9±10.2	2	1
Heidarsdottir[16]	45	46	N.D	N.D	1	3	N.D	N.D	N.D	N.D	N.D	N.D	2	1
Heidt[17]	9	15	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D
Lomivorotov[18]	5	4	N.D	N.D	0	2	N.D	N.D	48±24	48±24	18±5	19±7	0	0
Mozaffarian[19]	224	231	10	10	4	8	N.D	N.D	N.D	N.D	N.D	N.D	8	15
Sandersa[20]	36	40	1	1	3	3	N.D	N.D	N.D	N.D	N.D	N.D	0	0
Sarvanan[21]	22	18	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D
Wilbring[22]	31	47	3	2	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	1	2
Stanger[23]	4	6	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D
Sorice[24]	11	24	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	8.2±2.5	8.4±3.4	N.D	N.D
NAC														
El-Hamamsy[25]	4	6	3	1	0	0	419±240	341±171	N.D	N.D	5.4±2.3	5.3±2.5	3	0
Eren[26]	2	1	0	0	0	0	667±89	622±98	N.D	N.D	N.D	N.D	0	0
Hasse[27]	19	16	N.D	N.D	N.D	N.D	610±430	625±510	N.D	N.D	N.D	N.D	0	1
Kazemi[28]	14	19	10	11	1	1	N.D	N.D	120±45.6	115.2±79.2	7.4±1.3	7.2±0.9	1	2
Kim[29]	4	8	2	2	1	0	614±341	598±630	72±36	81.6±50.4	11.3±6.3	10.5±4.5	0	2
Orhan[30]	0	1	N.D	N.D	N.D	N.D	788±88	877±135	23.2±1.7	22.6±1.8	7.2±0.42	7.3±0.48	0	0
Ozaydin[31]	9	25	N.D	N.D	2	0	N.D	N.D	N.D	N.D	N.D	N.D	1	2
Ozaydin[32]	3	12	N.D	N.D	1	0	N.D	N.D	N.D	N.D	7.7±3	7.9±4.2	0	2
Wijeysundera[33]	50	58	N.D	N.D	4	4	N.D	N.D	N.D	N.D	N.D	N.D	0	7
Peker[34]	0	2	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D
Vitamin C														
Bjordahl[35]	27	29	N.D	N.D	0	2	N.D	N.D	88.8±52.8	103.2±69.6	10.4±4	11.7±7.1	2	4
Carnes[36]	7	17	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D
Colby[37]	4	5	N.D	N.D	N.D	N.D	N.D	N.D	106.4±24.9	48.9±43.2	14.6±17.6	10.2±4.9	N.D	N.D
Eslami[38]	2	13	N.D	N.D	2	2	N.D	N.D	55.2±38.4	62.4±35.5	6.54±3.24	7.08±3.45	N.D	N.D
Papoulidis[39]	38	52	N.D	N.D	N.D	N.D	N.D	N.D	38.4±21.6	50.4±26.4	7.9±2.2	9.8±3.6	N.D	N.D
Samadikhah[40]	6	15	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D
Dehghani[41]	4	16	N.D	N.D	0	1	N.D	N.D	42.9±7.44	50.4±16	5.32±0.59	5.74±1.3	N.D	N.D

PUFA, polyunsaturated fatty acid; AO, antioxidant; NAC, n-acetylcysteine; C, control; Re-MI, re-myocardial infarction; ICU, intensive care unit; N.D, No Data.

References 8–56 have been shown in Supporting information.

placebo with an OR of 0.50 (95% CI: 0.12–2.05; *P*=.3, χ^2=0.83, I^2=0%). Volume of blood loss and incidence of re-MI were not addressed in the enrolled studies, and only one study reported on mortality.

3.2.2 | Reno-protective effects of antioxidants

N-acetylcysteine

Of 1863 patients enrolled from 14 RCTs, 935 cases were allocated to NAC group and 928 to placebo group (Table 3). Overall incidence of AKI was 28.66% ranging from 0.8% to 61.6% with 26.3% in NAC group and 31.03% in placebo group (Table 3). Pooled analysis revealed that NAC supplementation could significantly decrease the incidence of postoperative AKI with an OR of 0.77 (95% CI: 0.62–0.95; *P*=.01) using the fixed effects model (Figure 4). There was no significant heterogeneity among the studies (χ^2=17.52, I^2=25.8%). There was no statistical publication bias (Begg's test; *P*=.807). From all included studies on NAC supplementation, 10 RCTs reported data on the incidence of the need for hemodialysis. In fact, 2 of 10 comparisons did not have any cases of hemodialysis in two comparative arms; therefore, the remaining eight RCTs were used to perform the meta-analysis. Pooled analysis indicated that the incidence of hemodialysis was similar in NAC and placebo group with an OR of 1.03 (95% CI: 0.55–1.9; *P*=.9, χ^2=4.80, I^2=0%). From all 14 studies on NAC supplementation, 12 RCTs reported data on overall mortality. Pooled treatment effects analysis indicated that NAC significantly decreased associated mortality with an OR of 0.54 (95% CI: 0.31–0.93; *P*=.03, χ^2=6.42, I^2=0%).

Polyunsaturated fatty acids

Of 571 patients enrolled from three RCTs, 282 cases were allocated to PUFA group and 289 to the placebo group (Table 3). Overall incidence of AKI was 2.8% ranging from 1.8% to 3.2%. The incidence of AKI was 2.83% in PUFA group and 2.76% in placebo group. Pooled

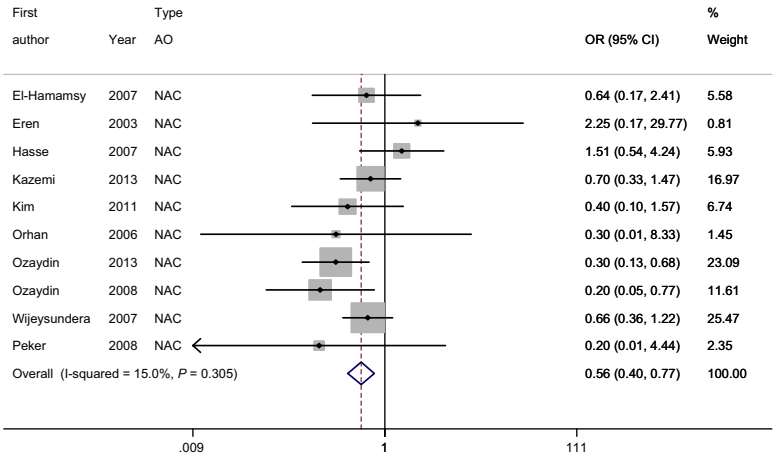

FIGURE 1 Forest plot of odds ratio (OR) for the effects of N-acetylcysteine (NAC) on incidence of POAF

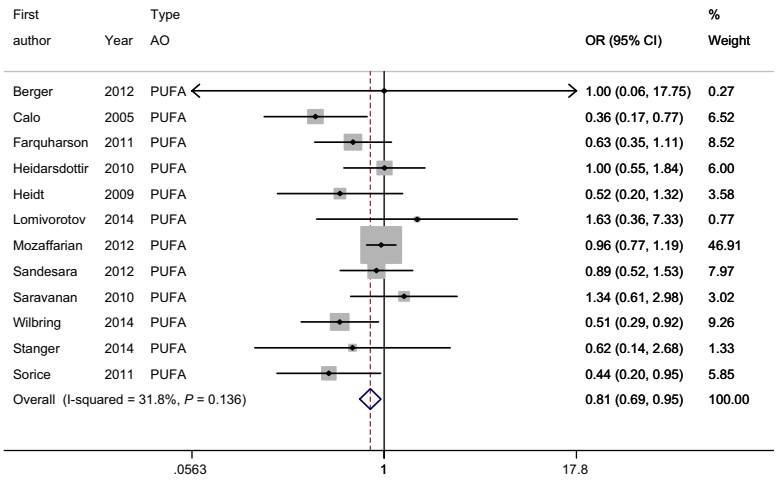

FIGURE 2 Forest plot of odds ratio (OR) for the effects of PUFA on incidence of POAF

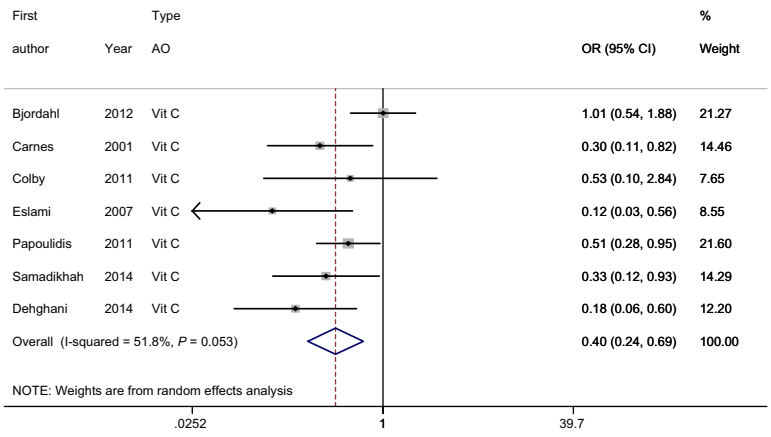

FIGURE 3 Forest plot of odds ratio OR) for the effects of vitamin C on ncidence of POAF

analysis revealed that PUFA supplementation did not have the ability to decrease the incidence of postoperative AKI with an OR of 1.02 (95% CI: 0.37–2.77; P=.9, χ^2=5.3, I^2=0%) (Figure 5). There was no statistical publication bias (Begg's test; P=.117). In fact, the three studies analyzed did not report on the incidence of need for hemodialysis. Also, one of three analyses did not present any mortality in two comparative arms; therefore, the remaining two RCTs were used to perform the meta-analysis. Pooled analysis indicated that the incidence of mortality was similar in PUFA and placebo group with an OR of 1.02 (95% CI: 0.20–5.14; P=.9, χ^2=0.65, I^2=0%).

4 | DISCUSSION

Atrial fibrillation is known as a one of the most frequent complications after cardiac surgery observed in roughly one-third of the

TABLE 3 Clinical outcomes of included studies (antioxidant supplementation on renal-protection)

Author	Number		Regimen	Surgery	AKI [n]		Need to dialysis [n]		Mortality [n]		Mean baseline creatinine	Jadad
	AO	C			AO	C	AO	C	AO	C		
PUFA												
Calo[14]	79	81	2 g PUFA daily for at least 5 d before surgery until hospital discharge	CABG only	1	2	N.D	N.D	1	2	N.D	3
Heidarsdottir[16]	83	85	Capsules of PUFA for 5–7 d before CABG until hospital discharge	CABG only	3	2	N.D	N.D	2	1	N.D	4
Sandersa[20]	120	123	PUFA 2 g orally twice daily for 72 h after surgery	CABG and/or valve	4	4	N.D	N.D	0	0	N.D	4
NAC												
Hasse[27]	30	30	150 mg/kg intravenous bolus after induction of anesthesia, then 50 mg/kg intravenous over 4 h, then 100 mg/kg intravenous over 20 h	CABG and/or valve	18	19	0	2	0	1	90 μmol/L	5
Kazemi[28]	120	120	1200 mg oral NAC twice daily, starting 48 h before and up to 2 d after CABG	CABG and/or valve	9	4	N.D	N.D	1	2	N.D	4
Kim[29]	24	24	100 mg/kg intravenous bolus over 15 min after induction of anesthesia, then IV infusion at 40 mg/kg/d for 24 h	CABG only	3	8	N.D	N.D	0	2	1.15 mg/dL	4
Ozaydin[32]	58	57	50 mg/kg IV before surgery and 50 mg/kg/d for 2 d after CABG	CABG and/or valve	1	0	N.D	N.D	0	2	N.D	4
Ozaydin[42]	100	101	NAC intravenously at a dose of 50 mg/kg for 1 h before surgery and at the same dose for 48 h after the procedure.	CABG and/or valve	21	39	0	0	1	2	1.03 mg/dL	5
Wijeysundera[33]	88	87	100 mg/kg intravenous after anesthetic induction over 30 min and 20 mg/kg/h intravenous after cardiopulmonary bypass for 4 h	CABG and/or valve	25	28	1	3	0	7	127 μmol/L	5
Adabag[43]	50	52	Packages containing 14 doses of liquid NAC (3 mL, 600 mg), three doses before surgery and 11 after the surgery or until discharge from the hospital	CABG and/or valve	22	19	3	2	2	3	1.9 mg/dL	5
Brar[44]	20	19	600 mg orally twice per day on preoperative day 1 and was given the morning of surgery ≥4 h preoperatively, and one dose was administered the night after surgery	CABG and/or valve	2	2	2	2	1	1	2.06 mg/dL	3
Burns[45]	148	147	600 mg NAC at four doses, The first two doses in the operating room immediately following induction of anesthesia. The third and fourth doses in the ICU, 12 and 24 h after administration of the first dose.	CABG and/or valve	44	42	1	3	5	4	1.15 mg/dL	5

(Continues)

TABLE 3 (Continued)

Author	Number		Regimen	Surgery	AKI [n]		Need to dialysis [n]		Mortality [n]		Mean baseline creatinine	Jadad
	AO	C			AO	C	AO	C	AO	C		
Prasad[46]	35	35	Oral NAC 600 mg twice a day on the preoperative day and intravenous NAC 600 mg prior to the induction of anesthesia on the day of surgery. This was followed by intravenous NAC 600 mg twice a day until the second postoperative day (total dose of NAC administered was 4.8 g).	CABG only	3	4	N.D	N.D	N.D	N.D	87 μmol/L	2
Ristikankare[47]	38	39	NAC was administered in saline 0.9% as a loading dose of 150 mg/kg in 15 min, followed by 50 mg/kg for the next 4 h, and thereafter, 100 mg/kg for 16 h.	CABG and/or valve	16	19	1	0	1	2	130.5 μmol/L	3
Santana-Santos[48]	35	35	NAC 150 mg/kg in 500 mL 0.9% IV saline in 2 h, started 2 h before surgery, followed by NAC 50 mg/kg in 500 mL 0.9% IV saline over 6 h	CABG only	10	20	0	0	2	4	N.D	4
Sisillo[49]	129	125	Intravenous bolus of 1200 mg of NAC immediately before induction of anesthesia, followed by three additional boluses administered at 12-h intervals in the ICU (total dose of NAC =4800 mg).	CABG and/or valve	52	65	10	6	5	4	1.2 mg/dL	4
Song[50]	60	57	150 mg/kg of NAC IV bolus at anesthetic induction followed by a continuous infusion at 150 mg/kg per day for 24 h.	CABG only	20	19	3	2	N.D	N.D	1.2 mg/dL	5

PUFA, polyunsaturated fatty acid; AO, antioxidant; NAC, n-acetylcysteine; C, control; AKI, acute kidney injury; N.D, No Data; IV, intravenously; CABG, coronary artery bypass graft.

References 8–56 have been shown in Supporting information.

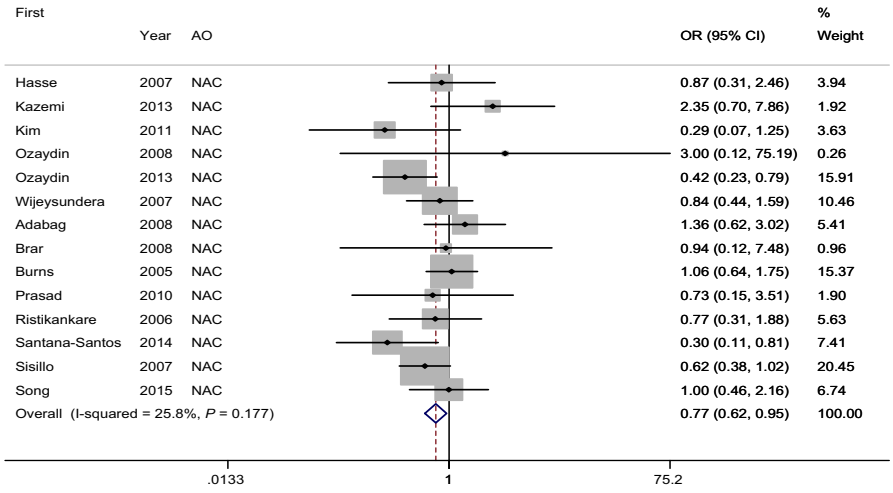

FIGURE 4 Forest plot of odds ratio (OR) for the effects of N-acetylcysteine (NAC) on incidence of acute kidney injury (AKI)

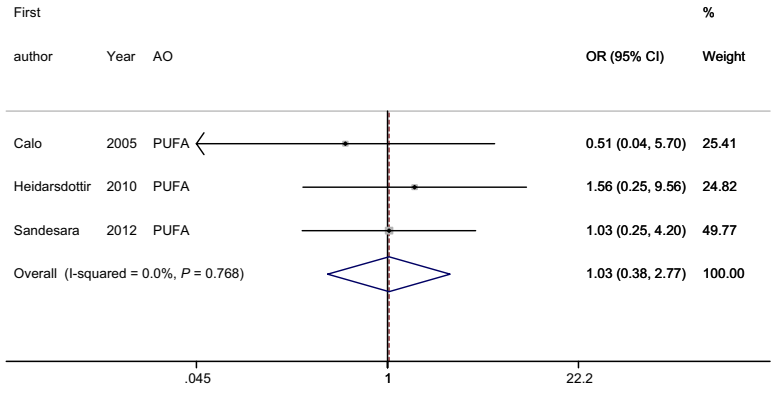

FIGURE 5 Forest plot of odds ratio (OR) for the effects of PUFA on incidence of acute kidney injury (AKI)

patients early after major cardiac surgical procedures and may influence morbidity and mortality.[1–3,55] Moreover, ischemia in combination with high cardiac rate occurring simultaneously might have additive effects, resulting in increased cardiac involvement.[56] Renal failure is another important and frequently observed area affected after cardiac surgery.[7] Postoperative AKI is a common complication which precipitates various complications including increased morbidity, the need for hemodialysis, longer hospital stay, and higher treatment costs. Oxidative stress was shown to be one of the leading mechanisms increasing the incidence of AF and AKI. Supplementations, such as NAC, vitamin C, and PUFA are well-known antioxidants with considerable ability of suppressing oxygen-free radicals.[9,10] The present study was split into two parts of meta-analysis. The first part examined cardio-protective effects of NAC, vitamin C, and PUFA supplementations with the main focus on the incidence of POAF and associated mortality, while other perioperative complications less frequently reported on in the RCTs mainly addressing POAF, such as stroke, re-MI, volume of bleeding, and length of hospital and ICU stay, were therefore addressed as secondary clinical outcomes. In the second part of our analysis, reno-protective effects of the supplementations were reviewed, whereas the incidence of AKI and associated mortality were taken as the primary clinical outcome. The results of our study indicated that NAC could significantly decrease POAF while having no considerable effect on the incidence of re-MI, stroke, volume of bleeding, and length of hospital and ICU stay. Moreover, it was striking to learn that NAC had notably decreased overall cumulative mortality. This statistically meaningful result with no heterogeneity in terms of lower mortality in NAC group might be explained by the fact that NAC may significantly reduce the incidence of AF and its associated complications that were not addressed in the RCTs included. In agreement with our analysis, Gu et al. in their systematic review and meta-analysis found out that NAC was associated with antiarrhythmic effects while having no significant effect on the length of hospital stay.[51] However, mortality was not particularly addressed in that study.

The results of the present study also revealed that NAC was associated with strong reno-protective effects in terms of significantly reduced incidence of postoperative AKI; however, NAC supplementation appeared to have no impact on the need for hemodialysis. This finding is supported by previous meta-analyses and enhances the fact that NAC may only be able to beneficially influence early stages of AKI or mild renal disturbances. Similarly, to the analysis of cardio-protective effects, the analysis of reno-protective effects of antioxidants also resulted in decreased mortality when NAC was administered. Interestingly, previous meta-analyses reported that NAC was not able to decrease the incidence of AKI.[52,53] Also, Baker et al. found that NAC could decrease postoperative AF, however

without significant effect on AKI, need for hemodialysis, stroke, re-MI, and mortality.[52]

The present study reported that PUFA could significantly decrease the incidence of POAF and the length of hospital stay, while it had no effect on the incidence of re-MI, stroke, mortality, volume of bleeding, and length of ICU stay. As these variables addressed in the present meta-analysis were similarly distributed between the treatment and control group, it might be assumed that decreased hospital stay in PUFA group might be attributed to the lower incidence of POAF. This theory might find support in the work by Aranki et al. who claimed that POAF could increase the length of hospital stay for approximately 5 days.[54] However, other hidden confounders that might also be responsible for longer hospitalization cannot be excluded. Our findings also showed that PUFA could not decrease the incidence of AKI and, therefore, despite its clearly beneficial cardio-protective effects, it failed protecting renal function.

Our meta-analysis indicated that vitamin C could strongly decrease the incidence of POAF while it was not associated with lower incidence of stroke. These findings are also supported by previous research.[6] Of all enrolled RCTs related to vitamin C, no study reported on the incidence of re-MI, AKI, need for hemodialysis, and volume of bleeding, whereas only one study reported on mortality. Therefore, there was no meta-analysis possible regarding the effects of vitamin C on above-mentioned outcome variables.

In general, our results found NAC to have significant cardio-renal protective effects in terms of its ability to decrease the incidence of POAF and AKI. However, PUFA and vitamin C are also both associated with cardio-protective effects and might be able to decrease the incidence of POAF, their reno-protective characteristics are insignificant or not appropriately addressed in previous RCTs. Also, compared to other supplements, NAC might be able to significantly decrease overall mortality following cardiac surgery due to its strong cardio-renal protection.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Mirhosseini SJ, Forouzannia SK, Sayegh AH, Sanatkar M. Effect of prophylactic low dose of methylprednisolone on postoperative new atrial fibrillation and early complications in patients with severe LV dysfunction undergoing elective off-pump coronary artery bypass surgery. *Acta Med Iran*. 2011;49:288–292.
2. Rostagno C. Atrial fibrillation in patients undergoing surgical revascularization: an update on pharmacologic prophylaxis. *Cardiovasc Hematol Agents Med Chem*. 2012;10:325–338.
3. Ali-Hassan-Sayegh S, Mirhosseini SJ, Liakopoulos O, et al. Posterior pericardiotomy in cardiac surgery: systematic review and meta-analysis. *Asian Cardiovasc Thorac Ann*. 2015;23:354–362.
4. Azzalini L, Spagnoli V, Ly HQ. Contrast-induced nephropathy: from pathophysiology to preventive strategies. *Can J Cardiol*. 2016;32:247–255.
5. Rodrigo R. Prevention of postoperative atrial fibrillation: novel and safe strategy based on the modulation of the antioxidant system. *Front Physiol*. 2012;3:93.
6. Ali-Hassan-Sayegh S, Mirhosseini SJ, Rezaeisadrabadi M, et al. Antioxidant supplementations for prevention of atrial fibrillation after cardiac surgery: an updated comprehensive systematic review and meta-analysis of 23 randomized controlled trials. *Interact Cardiovasc Thorac Surg*. 2014;18:646–654.
7. Singh D, Kaur R, Chander V, Chopra K. Antioxidants in the prevention of renal disease. *J Med Food*. 2006;9:443–450.

References 8–56 have been shown in Supporting information.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.