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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Protective effects of anti-oxidant supplementations on contrast-induced nephropathy after coronary angiography: an updated and comprehensive meta-analysis and systematic review

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Abstract

Background and aim: This systematic review with meta-analysis sought to determine the strength of evidence for effects of antioxidants (AO) such as N-acetyl cysteine (NAC), vitamin C, vitamin E, and alpha-lipoic acid on the incidence of contrast-induced nephropathy (CIN), requirement for haemodialysis, level of serum creatinine, and mortality after coronary angiography.

Methods and results: After Medline, Embase, Elsevier, Sciences online database, and Google Scholar literature searches, studies with randomised controlled design were selected for the meta-analysis. The effect sizes measured were odds ratio (OR) for categorical variables and standard mean difference (SMD) with 95% confidence interval (CI) for calculating differences between mean changes of serum creatinine in intervention and control groups. A value of $p < 0.1$ for Q test or $I^2 > 50\%$ indicated significant heterogeneity between the studies. Literature search of all major databases retrieved 2350 studies. After screening, a total of 49 trials were identified that reported outcomes. Pooled treatment effect analysis revealed that NAC (OR of 0.79; 95% CI 0.69–0.9; $p = 0.000$), vitamin C (0.63; 95% CI 0.45–0.89; $p = 0.000$), and vitamin E (OR of 0.5; 95% CI 0.27–0.92; $p = 0.026$) could significantly reduce the incidence of CIN. NAC (SMD of –0.119; 95% CI –0.191 – –0.046; $p = 0.000$), but not vitamin C (SMD of –0.08; 95% CI –0.22–0.04; $p = 0.1$) and vitamin E (–0.25; 95% CI –0.46– –0.05; $p = 0.1$), could significantly reduce mean levels of serum creatinine. Nevertheless, AO could not reduce the incidence of mortality, with an OR of 0.94 (95% CI 0.69–1.28; $p = 0.7$).

Conclusions: Overall, antioxidants such as NAC, vitamin C, and vitamin E can reduce the incidence of CIN, while only NAC might be able to significantly lower serum creatinine levels. There is no impact of AO supplementation on mortality.

Key words: contrast-induced nephropathy, antioxidant, vitamin C, N-acetyl cysteine, vitamin E, alpha-lipoic, coronary angiography

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INTRODUCTION

Contrast-induced nephropathy (CIN) is a recognised complication after coronary angiography and percutaneous coronary intervention, which has been associated with morbidity, mortality, prolonged hospitalisation, and health care costs [1, 2]. CIN is the leading cause of hospital-acquired renal failure and requirement for haemodialysis in high-risk patients, such as those with history of chronic renal impairment, diabetic nephropathy, and heart failure, although the incidence of CIN is relatively low in the general population [3, 4]. CIN usually occurs during the first week and serum creatinine rises 24–48 h after exposure to radiocontrast agent [5]. Larger doses and intracoronary or intra-aortic injections of contrast agents can be associated with higher incidence of CIN [6]. The pathogenesis of CIN involves a combination of insults affecting renal tubular endothelial cells, such as intra-renal vasoconstriction and ischaemia, reperfusion injury, and toxicity of renal cells [7–10]. Reperfusion injury can increase production of oxygen free radicals that exacerbate hypoxia-induced injuries of renal cells [7–10]. Currently, the standard of care in the management of patients requiring coronary diagnostic imaging is sufficient hydration, minimisation of the volume of contrast agent, and careful use of nephrotoxic drugs [11]. Antioxidant (AO) supplementations such as N-acetyl cysteine (NAC), vitamin C, vitamin E, and alpha-lipoic acid are known as cytoprotective agents with scavenging action against oxygen free radicals that can also attenuate renal damage and inhibit pro-inflammatory markers, such as interlukin-10 and tumour necrosis factor-alpha [12]. This systematic review with meta-analysis sought to determine the strength of evidence for effects of anti-oxidants such as NAC, vitamin C, vitamin E, and alpha-lipoic acid on the incidence of CIN, requirement for haemodialysis, level of serum creatinine, and mortality after coronary angiography.

METHODS

Literature search

A comprehensive literature search was conducted in major electronic databases (Medline/Pubmed, Embase, Elsevier, Web of Knowledge, Sciences online database, and Google Scholar) from their inception through July 25, 2014 to identify randomised controlled trials (RCT) reporting on the effects of anti-oxidants on the incidence of CIN, requirement for haemodialysis, and level of serum creatinine. Predefined search terms included: "N-acetyl cysteine", "acetylcysteine", "NAC", "vitamin C", "ascorbic acid", "vitamin E", "tocopherol", "alpha-lipoic acid", and "contrast induced nephropathy", "CIN", "serum creatinine", "coronary angiography", "coronary imaging". No language restrictions were applied. All retrieved references of the included RCTs were also reviewed to determine additional studies not indexed in common databases. Studies were included into the analysis when they met the following criteria: 1) RCT, 2) comparison of AO supplementations with a control group, and 3) reporting data on the incidence of radiocontrast-induced complications according to our review-checklist. Congress presentations and abstracts without peer-review publications of manuscripts were not included in this review.

Data extraction and outcome measures

Three investigators (S.A.-H.-S., Z.G., and Z.S.) extracted the data independently, and discrepancies were resolved via a consensus standardised abstraction checklist used for recording data in each study. Data retrieved from the trials included: author's name, type of radiocontrast agent (low, iso, or high osmolality), type of anti-oxidant (NAC, vitamin C, vitamin E, and alpha-lipoic acid), details of dose and route of anti-oxidant regimens, details of hydration regimens, mean baseline serum creatinine, study design, sample size, mean age, and gender. The incidence of CIN, requirement for renal dialysis, mortality, and changes of creatinine serum levels were recorded for each group. For exploration of heterogeneity among the trials, a subgroup analysis of disparities in the patients' characteristics was performed for: 1) dose of anti-oxidants (for NAC: < 2400 mg, $= 2400$ mg and > 2400 mg), 2) type of administration (orally or intravenously), 3) radiocontrast agent type (low, iso, or high osmolality), and 4) type of angiography (elective, non-elective, both types, and no exact data).

Definitions

CIN was defined as $\geq 25\%$ or ≥ 0.5 mg/dL increase in creatinine from baseline, and renal failure was defined as new onset of haemodialysis.

Statistical analysis, publication bias, and quality assessment

Data were analysed by STATA version 11.0 utilising METAN and METABIAS modules. The effect sizes measured were odds ratio (OR) with 95% confidence interval (CI) for categorical variables. For non-categorical data the standard mean difference (SMD) with 95% CI was used for calculating differences in mean changes of serum creatinine between intervention and control groups. OR < 1 favoured supplementation, and OR > 1 favoured control. RCTs with no events in the two arms were discarded from pooled analysis. Forest plots were created for each outcome. A value of $p < 0.1$ for Q test or $I^2 > 50\%$ indicated significant heterogeneity among the studies. Heterogeneity among trials was accounted for by applying a random effect model when indicated. The presence of publication bias was evaluated using the Begg and Egger tests. Quality assessment of RCTs was performed using the Jadad score. The Jadad score [13] assesses three items including randomisation (0–2 points), blinding of study (0–2 points), and withdrawals and dropouts (0–1 points). Higher scores indicate better reporting ("high" quality: 5; "good" quality: 3–4; "poor" quality: 0–2). Results were considered statistically significant at p-values < 0.05.

RESULTS

Literature search strategy and included trials

The literature search retrieved 2350 studies from the screened databases, of which 1890 (80.4%) were excluded after initial review. Of the 460 primary included studies, 411 were excluded after detailed evaluation due to insufficient reporting of endpoints of interest. The final analysis included 49 RCTs.

Study characteristics and effect measures

Incidence of CIN. A total of 10,782 patients were included from 49 RCTs reporting data about all AO supplementations on incidence of CIN (Table 1) [14–62]. The patient population of RCTs ranged from 30 to 2308 patients. From the 10,782 patients, 5395 were allocated to the AO group and 5387 to the control group. The overall incidence of CIN was 12.16%, ranging from 4.9% to 27.7%. CIN occurred in 10.5% in the AO group and in 13.7% in the control group (Table 2) [14–62]. Pooled treatment effect analysis revealed that AO therapy significantly reduced the incidence of CIN with an OR of 0.75 (95% CI 0.67–0.85; p = 0.000) using a fixed model (Fig. 1). No significant heterogeneity was observed among the RCTs (χ^2 = 77.94, I^2 = 38.4%). A total of 8851 patients were included from 38 RCTs reporting data about NAC supplementation only on the incidence of CIN (Table 1). Pooled treatment effect analysis revealed that NAC therapy significantly reduced the incidence of CIN with an OR of 0.79 (95% CI 0.69–0.9; p = 0.000) using a fixed model (Suppl. Fig. 1). No significant heterogeneity was observed among the RCTs (χ^2 = 65.62, I^2 = 43.6%). A subgroup analysis showed that NAC had more preventing effects on CIN when administered orally compared to intravenous route, as well as dose ≤ 2400 mg NAC compared to > 2400 mg, and low-osmolality radiocontrast agents compared to iso or high osmolality agents (Table 3). A total of 1243 cases were included from seven RCTs reporting data about vitamin C supplementation only on the incidence of CIN. Pooled treatment effect analysis revealed that vitamin C therapy significantly reduced the incidence of CIN with an OR of 0.63 (95% CI 0.45–0.89; p = 0.000) using a fixed model (Suppl. Fig. 2). No significant heterogeneity was observed among the RCTs (χ^2 = 5.6, I^2 = 0%). Two RCTs for each of the other supplementations of vitamin E and alpha-lipoic acid were selected for the analysis (Table 1). Pooled treatment effect analysis revealed that vitamin E therapy could significantly reduce the incidence of CIN with an OR of 0.5 (95% CI 0.27–0.92; p = 0.026) (Suppl. Fig. 3). However, alpha-lipoic acid failed to decrease the incidence of CIN with an OR of 0.5 (95% CI 0.20–1.67; p = 0.3) (Suppl. Fig. 4). Begg and Egger tests for studies about all AO supplementations showed that there was no potential publication bias among the included RCTs (Begg test, p = 0.076; Egger test, p = 0.076).

Requirement of haemodialysis. A total of 7301 patients were included from 24 RCTs reporting data on requirement for haemodialysis (Table 1). After removing 13 RCTs with no events in two arms, and one RCT about vitamin C, a total of 5468 patients were included in the meta-analysis from 10 studies on NAC supplementation. From 5468 patients, 2766 were allocated to the NAC group and 2702 to the control group. The overall incidence of requirement for haemodialysis was 0.51%, ranging from 0.25% to 2%. Requirement for haemodialysis occurred in 0.57% of the cases in the NAC group and 0.44% in the control group (Table 2). Pooled treatment effect analysis revealed that NAC therapy could not reduce the incidence of requirement for haemodialysis after coronary angiography with an OR of 1.27 (95% CI 0.36–2.54; p = 0.4) using a fixed model (Fig. 2). No significant heterogeneity was observed among the RCTs (χ^2 = 4.34, I^2 = 0.0%).

Mortality

Fourteen RCTs reported data on death. Mortality occurred in 2.67% in the AO group and 2.84% in control group (Table 1). In fact, four out of 14 comparisons did not present any postoperative death event in two comparative arms; therefore, the remaining 10 RCTs (5658 patients) were used to perform the meta-analysis. The type of AO supplementation for 10 RCTs was NAC (Table 2). Pooled treatment effect analysis revealed that AO supplementation therapy could not reduce the incidence of mortality with an OR of 0.94 (95% CI 0.69–1.28; p = 0.7) using a fixed model (Fig. 3). No significant heterogeneity was observed among the RCTs (χ^2 = 4.06, I^2 = 0.0%).

Mean changes of serum creatinine

Mean changes of the level of serum creatinine for 30 trials were 0.08 ± 0.5 with 0.02 ± 0.51 for all AO and 0.13 ± 0.51 for the control group. From 4303 patients, 2133 were allocated to AO and 2170 to the control group (Tables 1, 2). Pooled treatment effect analysis revealed that AO therapy could significantly prevent the increase of serum creatinine after angiography compared with baseline creatinine levels before the procedure, with an SMD of –0.128 (95% CI –0.189 – –0.067; p = 0.000) using a random model. Significant heterogeneity was observed among the RCTs (χ^2 = 76.25, I^2 = 62%). A total of 2999 patients were included from 24 RCTs reporting data about NAC supplementation only on mean changes of level of serum creatinine (Tables 1, 2). Pooled treatment effect analysis revealed that NAC therapy significantly reduced mean level of serum creatinine with an SMD of –0.123 (95% CI –0.195 – –0.051; p = 0.001) using a random model. A subgroup analysis showed that NAC had more decreasing effect on mean level of serum creatinine when administered orally compared to intravenously, as well as > 2400 mg NAC compared to ≤ 2400 mg, and low-osmolality radiocontrast agent compared to iso or high osmolality agents (Table 3).

Table 1. Demographic data of included studies

Mean baseline sCr	Contrast media	AO regimen	AO type	Male (%)		Mean age [years]		N		Author
				C	AO	C	AO	C	AO	
1.2 mg/dL	Low, iso, and high osmolality	A dose of 1200 mg (two envelops) of NAC was administered orally every 12 h, for two doses before and two doses after the procedure	NAC	60.7	62	68.1	68	1136	1172	ACT trial [14]
1.29 mg/dL	Ioxaglate a low osmolality ionic contrast medium	NAC orally 600 mg twice daily for two days starting the evening before the procedure	NAC	81.8	71	59.8	62	66	62	Albabtain [15]
1.2 mg/dL	Iomeron low osmolality non-ionic contrast medium	NAC was administered twice a day in two dose of 600 mg from the day before until the day after procedure	NAC	67.7	66.6	65	64.2	158	138	Alessandri [16]
1.7 mg/dL	Low, iso, and high osmolality	NAC was orally administered at the doe of 600 mg twice a day, starting 24 h before the procedure (two doses before and two doses after the procedure)	NAC	75.5	44.4	65	63.2	45	45	Amini [17]
1.8 mg/dL	Isotonic, non-ionic contrast medium iodixanol	NAC was administered IV a dose of 150 mg/kg in 500 mL saline over 30 min immediately before contrast exposure, and followed by 50 mg/kg in 500 mL saline over the subsequent 4 h	NAC	84.6	90.2	70.9	67.4	39	41	Baker [18]
1.3 mg/dL	Non-ionic, low osmolality contrast medium	NAC (600 mg orally twice daily the preceding day and the day of angiography)	NAC	56.9	63	67.1	67.9	72	73	Baskurt [19]
1.1 mg/dL	Low, iso, and high osmolality	A dose of 1200 mg of NAC was administered orally every 12 h, for two doses before and two doses after the procedure	NAC	59.3	60.8	64.3	64.6	678	717	Berwanger [20]
1.5 mg/dL	Non-ionic, low osmolality contrast medium	NAC was given orally at a dose of 600 mg twice daily, on the day before and on the day of administration of the contrast agent, for a total of two doses	NAC	89	84	64	64	91	92	Briguori [21]
1.3 mg/dL	Low and high osmolality	NAC was given orally at a dose of 600 mg twice daily, on the day before and on the day of administration of the contrast agent, for a total of two doses	NAC	ND	ND	ND	ND	201	196	Azmus [22]
0.9 mg/dL	Non-ionic, low osmolality contrast medium	NAC 600 mg was administered 12 h before, 1 h before and 12 h after the procedure	NAC	71.9	79.9	54.1	54.6	170	152	Calabro [23]
0.9 mg/dL	Non-ionic, low osmolality contrast medium	NAC (600 mg diluted in 50 mL of saline) intravenously for 30 min twice daily for a total of four doses	NAC	72.5	80.4	60.7	63.1	109	107	Carbonell [24]
2 mg/dL	Non-ionic, low osmolality contrast medium	NAC (600 mg diluted in 50 mL of saline) intravenously for 30 min twice daily for a total of four doses	NAC	81	80	69	70	42	39	Carbonell [25]
1.5 mg/dL	Non-ionic, low osmolality contrast medium	NAC orally at the of 600 mg twice daily on the day before and on the day administration of the contrast agent	NAC	84	94	72.7	70.5	51	53	Castini [26]

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Table 1. cont. Demographic data of included studies

Mean baseline sCr	Contrast media	AO regimen	AO type	Male (%)		Mean age [years]		N		Author
				C	AO	C	AO	C	AO	
1.1 mg/dL	Low and iso osmolality	NAC 600 mg every 12 h by mouth for two doses before and two doses after procedure	NAC	68.1	61.8	63.3	66.7	69	68	Coyle [27]
1.6 mg/dL	Non-ionic, low osmolality contrast medium	NAC (600 mg diluted in 30 mL of ginger ale) orally, twice daily at four doses	NAC	89.6	68	72	74	29	25	Diaz-Sandoval [28]
2.2 mg/dL	Non-ionic, low osmolality contrast medium	NAC 1200 mg orally, administered 1 h prior to and 3 h following procedure	NAC	68.2	63.1	69.8	71.4	41	38	Durham [29]
133 μmol/L	Non-ionic, low osmolality contrast medium	NAC 1 g twice daily 24 h before and after angiography	NAC	92	87.5	66	68	25	24	Efrati [30]
1.6 mg/dL	Non-ionic, iso osmolality contrast medium	NAC was supplied as tablet 600 mg twice a day for two days	NAC	62	68	75	75	101	99	Ferrario [31]
2.2 mg/dL	Non-ionic, low osmolality contrast medium	NAC 400 mg orally, thrice daily the day before, and the day the contrast procedure	NAC	66.6	73.9	68	68.2	45	46	Fung [32]
1.9 mg/dL	Non-ionic, low osmolality contrast medium	NAC 600 mg thrice daily was administered orally for a total 48 h, starting 24 h before the administration of the contrast agent	NAC	79.4	85.3	69	71	39	41	Goldenberg [33]
117 μmol/L	Ionic, low osmolality contrast medium	NAC was orally administered at the dose of 600 mg twice a day, starting a one day before the procedure (two doses before and two doses after the procedure)	NAC	57	61	66.5	63.8	79	77	Gomes [34]
1.7 mg/dL	Low osmolality contrast medium	NAC 600 mg orally, twice daily the day before, and the day the contrast procedure	NAC	72	80	61.5	61.4	25	25	Gulel [35]
1.4 mg/dL	Non-ionic, low osmolality contrast medium	600 mg NAC every 12 h for four days, four doses before the procedure day, two doses on the day of the procedure, and two doses after day of the procedure	NAC	62.5	72.5	66.4	64.7	40	40	Gunebakmaz [36]
ND	Non-ionic, low osmolality contrast medium	NAC 1200 mg twice daily the day before, and the day the contrast procedure	NAC	ND	ND	ND	ND	32	28	Heng [37]
1.6 mg/dL	Non-ionic, iso osmolality contrast medium	Two oral doses 600 mg NAC before and after angiography (total dose: 1200 mg)	NAC	ND	ND	ND	ND	139	139	Holscher [38]
1.08 mg/dL	Non-ionic iso-tonic contrast medium	NAC 1200 mg bolus followed by 200 mg/h for 24 h	NAC	67	59.4	65.6	65.1	206	192	Jaffery [39]
1.2 mg/dL	Non-ionic, low osmolality contrast medium	NAC 600 mg tablet on the day before and after coronary angiography; three doses were given before and one dose after angiography	NAC	63	60	69	69	98	102	Kay [40]

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Table 1. cont.. Demographic data of included studies

Mean baseline sCr	Contrast media	AO regimen	AO type	Male (%)		Mean age [years]		N		Author
				C	AO	C	AO	C	AO	
1 mg/dL	Iodixanol, Iobitridol, and Iopamidol	NAC 600 mg twice a day, on the day before of procedure and the day of coronary angiography	NAC	58	63	62	62	86	80	Kim [41]
0.9 mg/dL	Iopamidol	704 mg orally twice daily, the day before and the day of procedure	NAC	60	60	70	70	15	15	Kinbara [42]
1.3 mg/dL	Non-ionic, low osmolality contrast medium	NAC 600 mg IV bolus twice daily before and on the day of procedure	NAC	79	76	65	62	80	80	Koc [43]
1.8 mg/dL	Non-ionic, low osmolality contrast medium	Two doses of NAC 600 mg was administered prior to procedure, the first at time of randomisation, the second 4 h later	NAC	95.4	76.1	72.9	72.1	22	21	MacNeill [44]
127 μmol/L	Omnipaque	2000 mg NAC/dose twice a day for three doses before angiography and two doses after angiography	NAC	66	68	69	71	85	95	Miner [45]
2 mg/dL	Ioxaglate, Iohexol, and Iodixonal	Two doses of NAC (1000 mg diluted in 20 mL of diet cola) orally 1 h prior to exposure, 4 h later	NAC	41	44	70	73	44	36	Ochoa [46]
1.6 mg/dL	Non-ionic, low osmolality contrast medium	1500 mg NAC, starting the evening before procedure, and given every 12 h for four doses	NAC	55.3	55.1	75	77	47	49	Oldemeyer [47]
109 μmol/L	Non-ionic, iso osmolality contrast medium	NAC 1200 mg IV bolus was administered 1 h before, and 1200 mg orally twice daily for 48 h after procedure	NAC	60	52	64	65	15	21	Ratcliffe (a) [48]
103 μmol/L	Non-ionic, iso osmolality contrast medium	NAC 1200 mg IV bolus was administered 1 h before, and 1200 mg orally twice daily for 48 h after procedure	NAC	58	70	67	65	19	23	Ratcliffe (b) [48]
130 μmol/L	Iohexol, and Iodixonal	600 mg of NAC orally per dose, for a total of four doses (the first dose at day of the procedure and three doses after coronary angiography)	NAC	70	60	74.7	76.4	20	20	Seyon [49]
2.8 mg/dL	Iopamidol	NAC was given orally at a dose of 400 mg twice a day, on the day before and on the day of coronary angiography, for a total of two days	NAC	65.5	70	70	70	61	60	Shyu [50]
1.2 mg/dL	Non-ionic, low osmolality contrast medium	NAC (5 g) to a total volume of 1000 mL during and for 10 h after procedure	NAC	60	56.5	69.2	65.8	23	23	Wang [51]
79.5 μmol/L	Non-ionic, low osmolality contrast medium	High-dose NAC (2 × 1,200 mg/day for 48 h	NAC	65.6	70	68	68	123	126	Thiele [52]
1.2 mg/dL	Ionic, low osmolality contrast medium	Vitamin C supplied as tablet 3 g 2 h before the procedure, 2 h after procedure, and 2 g 24 h after the procedure	Vita-min C	81.8	66.7	59.8	58.7	66	57	Albabtain [15]
1.4 mg/dL	ND	1 g ascorbic acid orally 20 min before exposure to contrast; 500 mL NS 2 h before and 500 mL during angiography and subsequent 6 h	Vita-min C	ND	ND	ND	ND	69	74	Boscheri [53]

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Table 1. cont.. Demographic data of included studies.

Mean baseline sCr	Contrast media	AO regimen	AO type	Male (%)		Mean age [years]		N		Author
				C	AO	C	AO	C	AO	
1.5 mg/dL	Non-ionic, low osmolality contrast medium	1500 mg in 250 mL NS infusion IV (over 30 min) at 24 h and 1 h before exposure to contrast. NS (1 mg/kg/h) for 12 h before to 12 h after contrast exposure	Vitamin C	62.1	63.7	74	75	193	98	Brueck [54]
1.9 mg/dL	Non-ionic, iso-osmolality contrast medium	3000 mg vitamin C was given IV 2 h before followed by 2000 mg the night and the morning after the procedure	Vitamin C	81	78.5	71	69	111	107	Briguori [55]
136.35 μmol/L	Non-ionic, low osmolality contrast medium	Ascorbic acid in 500 mg capsules, 3 g orally before the procedure, and 2 g after the procedure in the evening and the next morning	Vitamin C	68.3	77.5	70.7	70.7	41	40	Dvorsak [56]
1.2 mg/dL	Iopromide, Iohexol, and Iodixonal	IV 3 g morning of procedure, oral 0.5 g on the night of procedure and next morning (all doses 12 h apart); IV NS hydration 1 mg/kg/h for 4 h before and at least 12 h after angiography	Vitamin C	57.3	68	71.4	71.8	82	74	Zhou [57]
1.3 mg/dL	Non-ionic, low and iso osmolality contrast medium	Vitamin C orally 3 g at least 2 h before procedure, 2 g night before and morning after procedure. Hydration with NS 50–125 mL/h IV from time of randomisation to at least 6 h after procedure	Vitamin C	93.8	90.6	64	67	113	118	Spargias [58]
1.5 mg/dL	Non-ionic, low osmolality contrast medium	350 mg/day alpha-tocopherol and 300 mg/day gamma-tocopherol, was initiated five days prior to the procedure, and continued for a further two days after procedure	Vitamin E	70.3	73.5	66	68	101	204	Tasanarong [59]
1.6 mg/dL	Non-ionic, low osmolality contrast medium	Oral alpha-tocopherol (525 U) at 48 h, 24 h and in the morning before the procedure	Vitamin E	69.2	78.4	65	68	52	51	Tasanarong [60]
0.8 mg/dL	Non-ionic, low osmolality contrast medium	Three doses of thioctacid 600 mg, 30 min before and at the 24th h and 48th h of procedure	ALA	59	61.5	66.5	64.3	39	39	Cicek [61]
114 μmol/L	Non-ionic, low and iso osmolality contrast medium	ALA at a dose of 600 mg orally every 8 h before coronary angiography (starting the afternoon prior to the procedure) and three times after angiography (beginning the afternoon on the day of the procedure). A total of 3600 mg of ALA was administered in six 600-mg doses	ALA	50	51	72.9	72	102	100	Jo [62]

ALA — alpha-lipoic acid; AO — anti-oxidant group; C — control group; IV — intravenously; N — number; NAC — N-acetyl cysteine; ND — no data; NS — normal saline; sCr — serum creatinine

Table 2. Clinical outcomes of included studies

Jadad	Mortality		Changes of serum levels of creatinine		Haemodialysis		CIN		Author
	C	AO	C	AO	C	AO	C	AO	
5	24	23	ND	ND	3	3	142	147	ACT trial [14]
3	ND	ND	0.02 ± 0.38	0.03 ± 0.25	ND	ND	13	12	Albabtain [15]
3	ND	ND	ND	ND	ND	ND	15	10	Alessandri [16]
3	ND	ND	–0.018 ± 0.4	–0.016 ± 0.3	ND	ND	6	5	Amini [17]
3	ND	ND	0.05 ± 0.31	–0.08 ± 0.34	ND	ND	8	2	Baker [18]
3	0	0	0.08 ± 0.34	0.08 ± 0.44	0	0	5	7	Baskurt [19]
5	13	14	ND	ND	2	2	98	97	Berwanger [20]
3	ND	ND	–0.01 ± 0.58	–0.04 ± 0.57	1	0	10	6	Briguori [21]
3	6	5	1.38 ± 0.39	1.3 ± 0.43	1	1	17	14	Azmus [22]
3	ND	ND	ND	ND	ND	ND	19	4	Calabro [23]
5	5	3	0.03 ± 0.28	0.05 ± 0.28	0	0	11	11	Carbonell [24]
4	7	4	0.28 ± 1.17	–0.11 ± 1.13	1	0	10	2	Carbonell [25]
3	ND	ND	–0.08 ± 0.53	–0.12 ± 0.44	0	0	11	14	Castini [26]
3	ND	ND	0.08 ± 0.11	0.14 ± 0.47	ND	ND	1	6	Coyle [27]
4	ND	ND	0.3 ± 0.006	–0.1 ± 0.06	ND	ND	13	2	Diaz-Sandoval [28]
4	ND	ND	ND	ND	ND	ND	9	10	Durham [29]
3	ND	ND	0.12 ± 0.07	–0.02 ± 0.11	ND	ND	ND	ND	Efrati [30]
4	0	0	ND	ND	ND	ND	6	8	Ferrario [31]
3	ND	ND	0.03 ± 0.92	0.18 ± 0.84	0	0	6	8	Fung [32]
5	ND	ND	–0.04 ± 0.47	–0.02 ± 0.67	ND	ND	3	4	Goldenberg [33]
3	2	5	0.07 ± 0.29	0.09 ± 0.4	0	2	8	8	Gomes [34]
3	ND	ND	–0.1 ± 1	–0.1 ± 1.07	0	0	2	3	Gulel [35]
3	ND	ND	0.07 ± 0.3	0.05 ± 0.31	ND	ND	11	9	Gunebakmaz [36]
3	ND	ND	ND	ND	ND	ND	3	2	Heng [37]
3	22	24	ND	ND	ND	ND	10	6	Holscher [38]
4	3	3	0.06 ± 0.5	0.07 ± 0.5	2	3	25	33	Jaffery [39]
4	ND	ND	ND	ND	0	0	12	4	Kay [40]
3	ND	ND	ND	ND	ND	ND	7	3	Kim [41]
2	ND	ND	0.34 ± 0.29	–0.33 ± 0.39	ND	ND	4	0	Kinbara [42]
3	ND	ND	0 ± 0.2	–0.05 ± 0.1	ND	ND	13	2	Koc [43]
3	ND	ND	0.26 ± 0.96	0.01 ± 0.52	ND	ND	7	1	MacNeill [44]
3	2	0	ND	ND	0	1	19	9	Miner [45]
4	0	0	0.17 ± 0.9	0.08 ± 0.98	0	0	11	3	Ochoa [46]
4	ND	ND	ND	ND	0	0	3	4	Oldemeyer [47]
2	ND	ND	ND	ND	ND	ND	1	1	Ratcliffe (a) [48]
2	ND	ND	ND	ND	ND	ND	2	1	Ratcliffe (b) [48]
3	ND	ND	ND	ND	0	0	2	1	Seyon [49]
2	ND	ND	0.3 ± 1.28	–0.3 ± 1.28	1	0	15	2	Shyu [50]
4	ND	ND	–0.09 ± 0.7	–0.18 ± 1.09	ND	ND	ND	ND	Wang [51]
4	4	3	ND	ND	1	4	25	18	Thiele [52]
2	ND	ND	ND	ND	ND	ND	13	4	Albabtain [15]
3	ND	ND	ND	ND	0	0	3	5	Boscheri [53]
5	ND	ND	0.2 ± 0.35	0.17 ± 0.37	0	0	62	24	Brueck [54]
3	ND	ND	–0.07 ± 0.49	–0.05 ± 0.42	1	4	11	11	Briguori [55]
4	ND	ND	ND	ND	0	0	3	2	Dvorsak [56]
3	0	0	0.02 ± 0.21	0.01 ± 0.14	ND	ND	6	4	Zhou [57]
5	ND	ND	0.14 ± 0.3	0.06 ± 0.35	ND	ND	23	11	Spargias [58]
4	ND	ND	0.14 ± 0.64	0.015 ± 0.56	ND	ND	15	22	Tasanarong [59]
3	ND	ND	0.23 ± 0.71	0.02 ± 0.33	ND	ND	12	3	Tasanarong [60]
2	ND	ND	ND	ND	0	0	3	3	Cicek [61]
2	ND	ND	ND	ND	ND	ND	7	3	Jo [62]

AO — anti-oxidant group; C — control group; CIN — contrast induced nephropathy; ND — no data

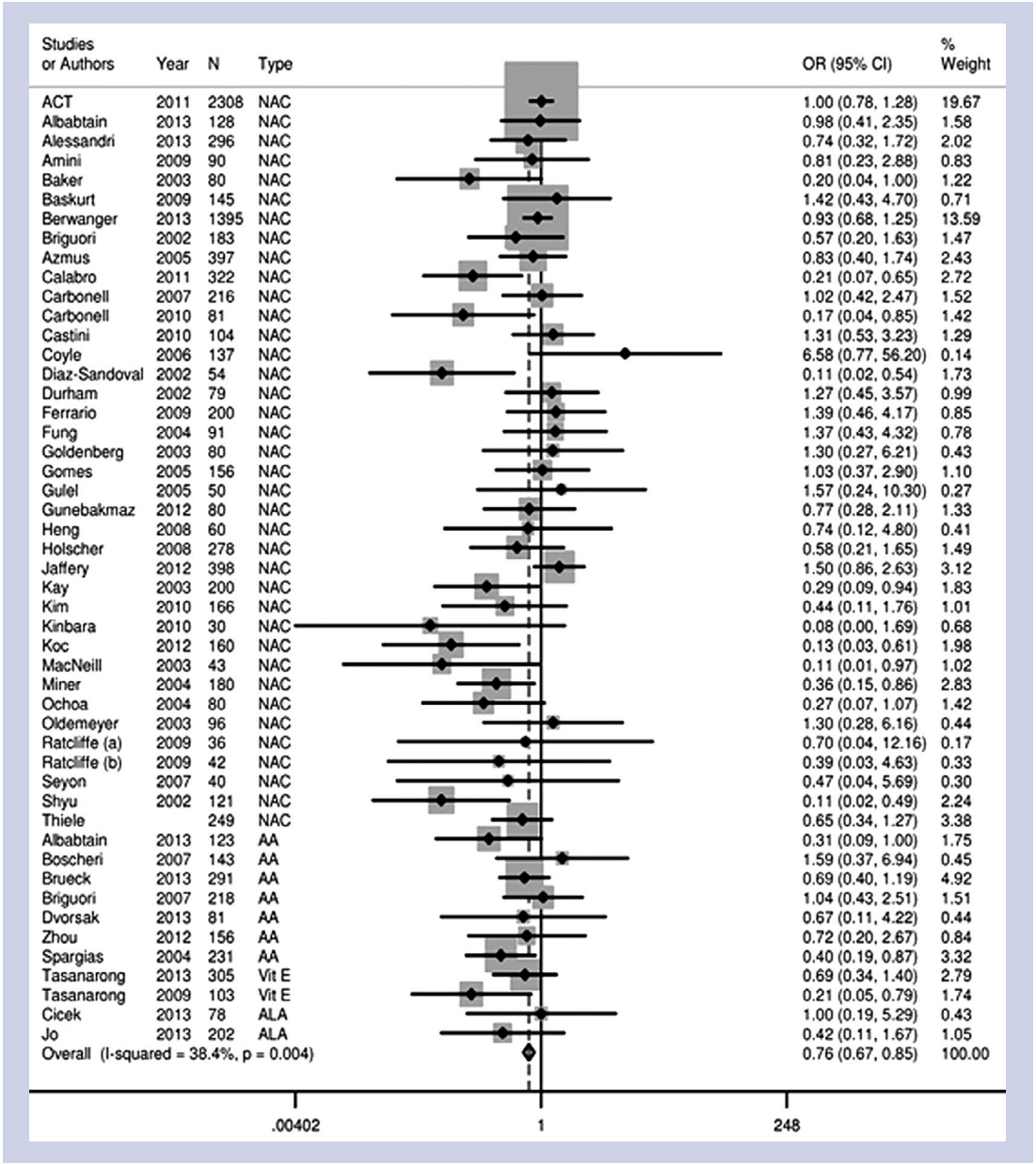

Figure 1. Forest plot of odds ratio (OR) for effects of antioxidants on contrast induced nephropathy; AA — ascorbin acid; ALA — alpha-lipoic acid; CI — confidence interval; NAC — N-acetyl cysteine

A total of 896 cases were included from four RCTs reporting data about vitamin C supplementation only (Tables 1, 2). Pooled treatment effect analysis demonstrated that vitamin C therapy could not reduce mean level of serum creatinine with an SMD of –0.08 (95% CI –0.22 – –0.04; p = 0.1) using a fixed model. A total of 408 patients were included from two RCTs reporting data about vitamin E supplementation only. Pooled treatment effect analysis indicated that vitamin E therapy could not decrease mean level of serum creatinine with an SMD of -0.25 (95% CI –0.46 – –0.05; p = 0.1) using a fixed model.

DISCUSSION

In the present study, the effects of antioxidants such as NAC, vitamin C, vitamin E, and alpha-lipoic acid on the incidence of CIN, requirement for haemodialysis, level of serum creatinine, and mortality were investigated. The results of our study revealed that antioxidants in general were able to significantly reduce the incidence of CIN after angiography. The effect of NAC supplementation was not dependent on a particular route of administration: both intravenous (IV) and oral administration were able to reduce CIN. Possibly the renal system response to NAC is dose-dependent since, according to our

Table 3. Subgroup analysis for clinical outcomes

Subgroup	Studies (N)	OR or SMD (95% CI)	P
Subgroup analysis for CIN and NAC according to OR			
Dose:			
< 2400	6	0.573 (0.398–0.827)	0.003
2400	20	0.747 (0.590–0.945)	0.015
> 2400	12	0.883 (0.744–1.048)	0.155
Route of administration:			
Orally	29	0.809 (0.702–0.933)	0.003
Intravenous	7	0.731 (0.532–1.005)	0.05
Radio-contrast:			
Low osmolality	26	0.563 (0.454–0.699)	0.000
Iso osmolality	6	1.195 (0.81–1.764)	0.368
High osmolality	–	–	–
Combined	6	0.930 (0.777–1.114)	0.43
Type of angiography:			
Elective	28	0.789 (0.682–0.912)	0.001
Non-elective	5	0.907 (0.633–1.299)	0.593
Elective and non-elective	1	0.273 (0.070–1.068)	0.062
No exact data	4	0.784 (0483–1.272)	0.325
Subgroup analysis for CIN and vitamin C according to OR			
Route of administration:			
Orally	4	0.484 (0.28–0.837)	0.009
Intravenous	2	0.769 (0.438–1.224)	0.268
Radio-contrast:			
Low osmolality	4	0.651 (0.415–1.02)	0.062
Iso osmolality	1	1.042 (0.431–2.515)	0.928
High osmolality	–	–	–
Combined	2	0.467 (0.241–0.905)	0.024
Subgroup analysis for mean changes of serum creatinine and NAC according to SMD			
Dose:			
< 2400	4	–0.128 (–0.279 to 0.023)	0.097
2400	13	–0.053 (–0.152 to 0.046)	0.292
> 2400	7	–0.276 (–0.425 to –0.128)	0.000
Route of administration:			
Orally	17	–0.135 (–0.226 to –0.044)	0.004
Intravenous	7	–0.90 (–0.210 to 0.031)	0.145
Radio-contrast:			
Low osmolality	18	–0.157 (–0.251 to –0.064)	0.001
Iso osmolality	3	0.025 (–0.136 to 0.186)	0.762
High osmolality	–	–	–
Combined	3	–0.149 (–0.315 to 0.016)	0.077
Type of angiography:			
Elective	17	–0.166 (–0.255 to –0.077)	0.000
Non-elective	4	–0.011 (–0.155 to 0.133)	0.881
Elective and non-elective	1	–0.096 (–0.563 to 0.345)	0.671
No exact data	2	–0.132 (–0.405 to 0.140)	0.341

CI — confidence interval; CIN — contrast induced nephropathy; N — number; NAC — N-acetyl cysteine, OR — odds ratio; SMD — standard mean differences

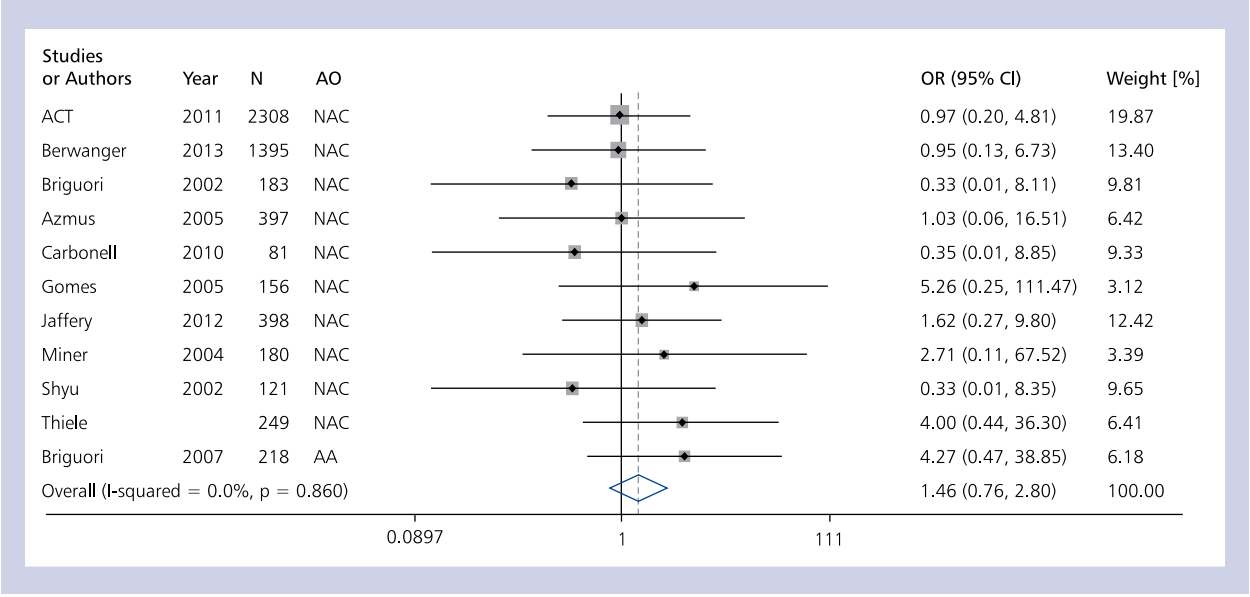

Figure 2. Forest plot of odds ratio (OR) for effects of antioxidants on incidence of requirement dialysis; AA — ascorbin acid; AO — anti-oxidant group; CI — confidence interval; NAC — N-acetyl cysteine

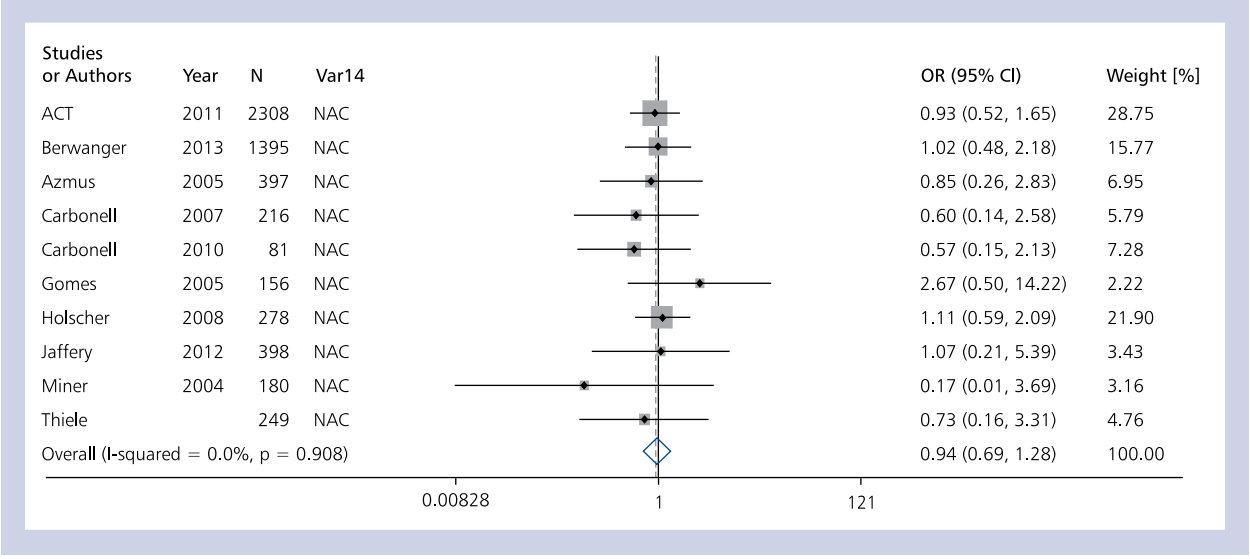

Figure 3. Forest plot of odds ratio (OR) for effects of antioxidants on incidence of mortality; CI — confidence interval; NAC — N-acetyl cysteine

results, doses equal to or less than 2400 mg of NAC reduced CIN significantly while such prophylactic effects were not seen with higher doses. Interestingly, Marenzi et al. [63] also reported that the pattern of response to NAC was dose-dependent in patients undergoing percutaneous coronary interventions. However, in contrast to our study, higher doses of NAC had more significant effects in terms of prevention of CIN. Nevertheless, the mechanisms underlying the improvement of outcomes are not yet completely understood, so the issue regarding the optimal NAC dose should be elaborated in further studies. A subgroup analysis revealed that the least incidence of CIN following NAC administration was when the patients underwent low osmolality radiocontrast angiography with an adequate hydration plus NAC. Therefore, iso-osmolality radiocontrast not only increases the incidence of CIN, but also prevents the appearance of NAC effects. Loomba et al. [64] pointed out that NAC might be able to reduce the incidence of CIN if administered intravenously; however, this was not the case for oral administration. The present study indicated that vitamin C could reduce CIN significantly. A subgroup

analysis showed that the lowest incidence of CIN following vitamin C administration was when the patients underwent low osmolality radiocontrast angiography with adequate hydration plus vitamin C. In another study, Zhou et al. [57] argued that bioavailability and maintenance time of oral and IV administrations were not similar; therefore, oral high-dose vitamin C could have antioxidant effects on renal function. Vitamin E and alpha-lipoic acid each had only two related studies, which had found vitamin E to significantly reduce CIN while alpha-lipoic acid showed just a trend towards decreased CIN. CIN following angiography could predispose the incidence of renal failure and the requirement of dialysis in high-risk patients such as those with a history of chronic renal impairment, diabetic nephropathy, and heart failure [3, 4]. Despite the low incidence of requirement for dialysis, it is of high importance because the patients with this complication generally become prone to morbidity, suffer a decrease in quality of life, and an increase in the requirement for renal transplantation. Our findings indicated that the incidence of requirement for haemodialysis was 0.51% in general, and AO administration could not decrease this complication. Therefore, although AO administration can generally reduce CIN, it does not have a significant reducing effect on the incidence of requirement for haemodialysis. This result may be explained by the fact that in patients requiring dialysis in the period of follow-up, in addition to a history of renal disease before angiography, renal cell toxicity becomes too severe after exposure to radiocontrast agent, leading to a crisis of symptoms and higher incidence of severe CIN. This condition is malignant to such an extent that not only hydration, but also pharmacotherapy and supplements cannot have protective effects. Loomba et al. [64] reported that the decrease in CIN following AO administration may be negligible, despite being significant, because there was a very small difference in OR and no significant difference on clinical endpoints, such as need for dialysis and mortality. A study carried out by Albabtain et al. [15] showed that use of ascorbic acid, NAC, or a combination of both drugs could not be superior than the standard hydration in preventing CIN or renal function deteriorations parameters. Despite the absence of side effects, their findings did not warrant the use of antioxidants as a standard of care to prevent CIN. Another study conducted by Brueck et al. [54] indicated that there was no evidence that standard dosage of NAC or ascorbic acid administered intravenously the day before and on the day of contrast dye exposure provided any benefit over placebo with respect to CIN prevention in patients with renal insufficiency undergoing cardiac catheterisation. They suggested that correct indication for the contrast media administration, peri-procedural hydration, the use of a small amount of low-osmolality contrast agent, and the avoidance of repetitive administration of closely spaced contrast dye remain the most important determinants in the prevention of CIN. Changes in creatinine levels within 24 h to 48 h after exposure to radiocontrast agents could be considered as an equivalent indicator for new onset CIN. Therefore, an increase of 0.5 mg/dL after angiography demonstrates acute nephropathy. NAC but no vitamin C and vitamin E could significantly reduce the mean creatinine level within 48 h after angiography.

CONCLUSIONS

Our analysis showed that NAC can decrease mean changes of creatinine levels in elective coronary angiography compared to non-elective. Our findings confirmed that application of low osmolality radiocontrast agents led to less rise in creatinine levels in comparison with iso and high osmolality agents. If AOs are used following a low osmolality radiocontrast imaging, they have more protective effects. Finally, it is concluded that AOs such as NAC, vitamin C, and vitamin E could reduce the incidence of CIN. NAC but not vitamin C and vitamin E could decrease serum creatinine levels after coronary angiography, while AO administration could not decrease the requirement for haemodialysis and mortality. Also, this study suggested that coronary angiography performed using lower osmolality radiocontrast agents with adequate hydration and administration of antioxidant supplements could significantly prevent acute renal complications.

Conflict of interest: *none declared*

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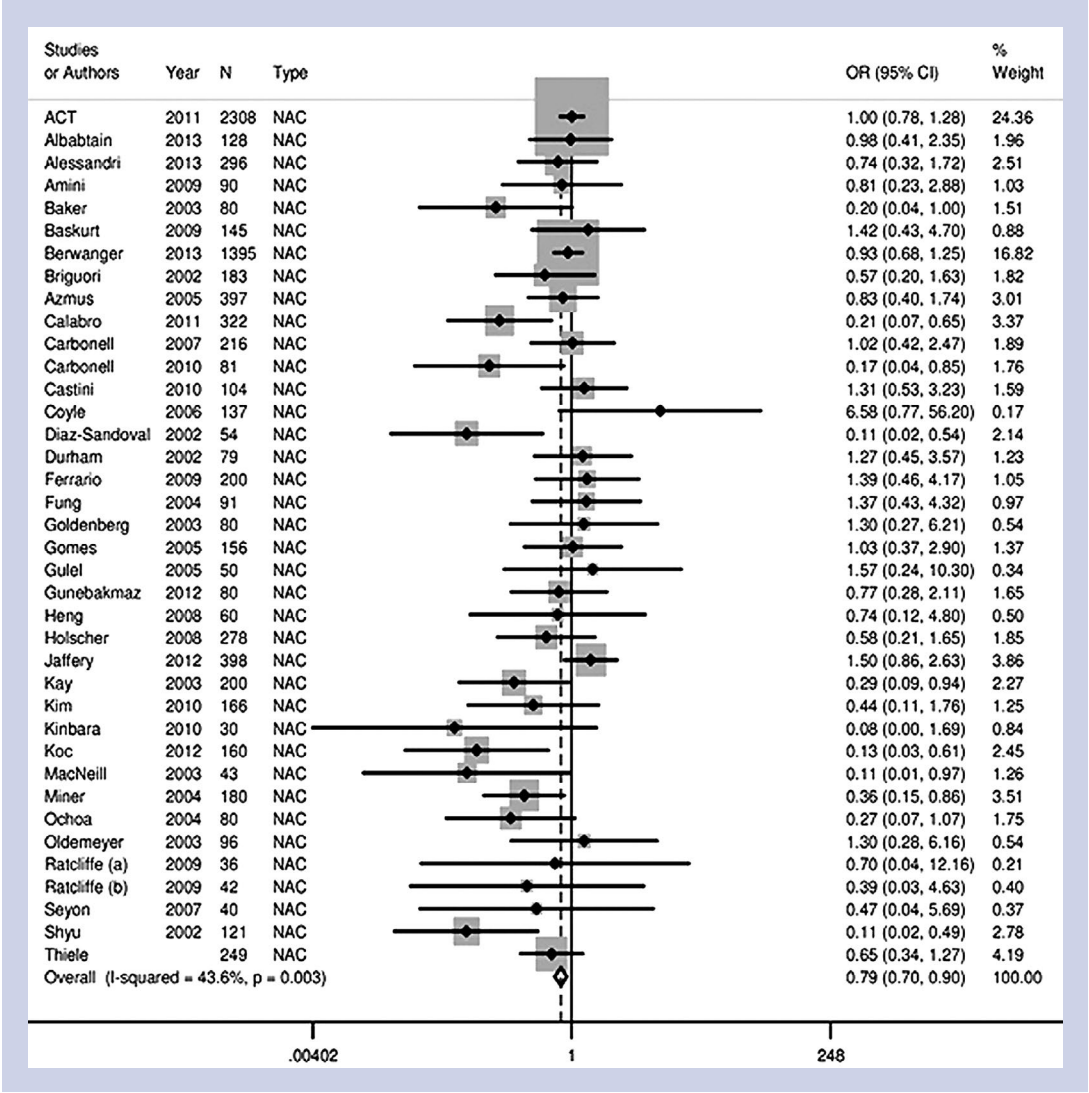
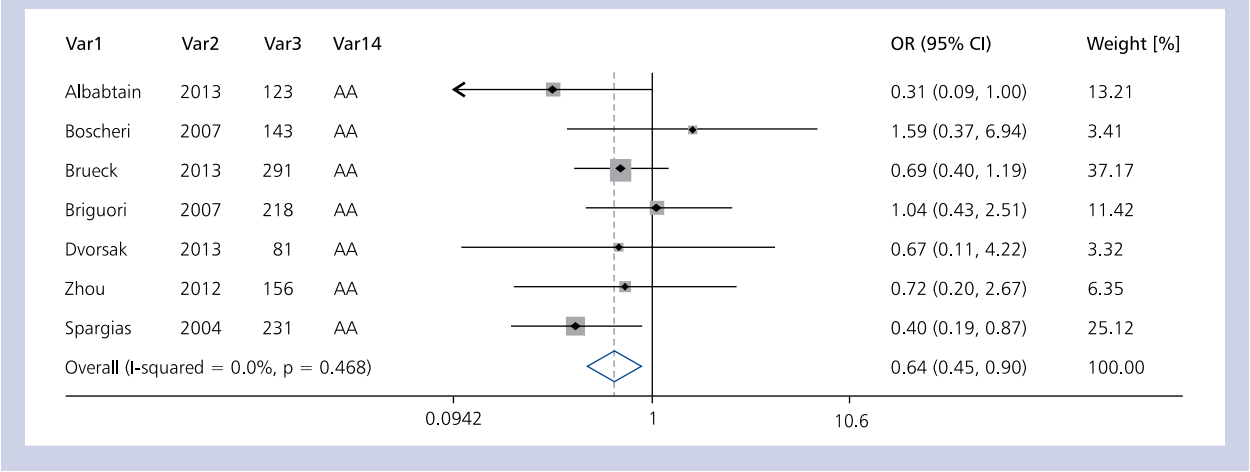
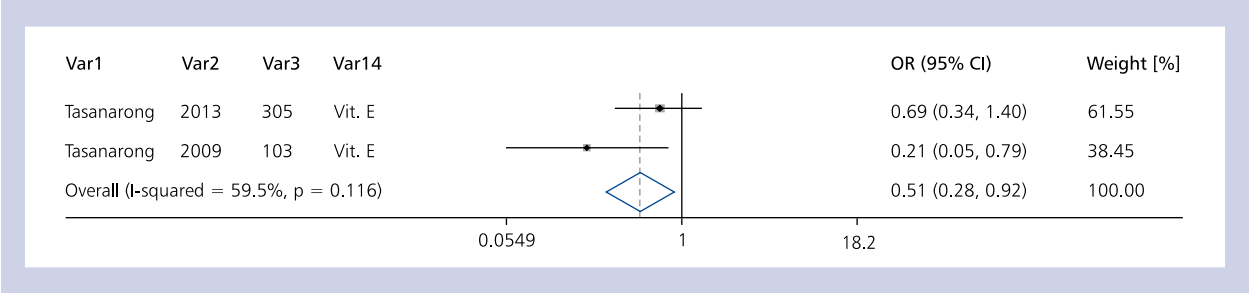


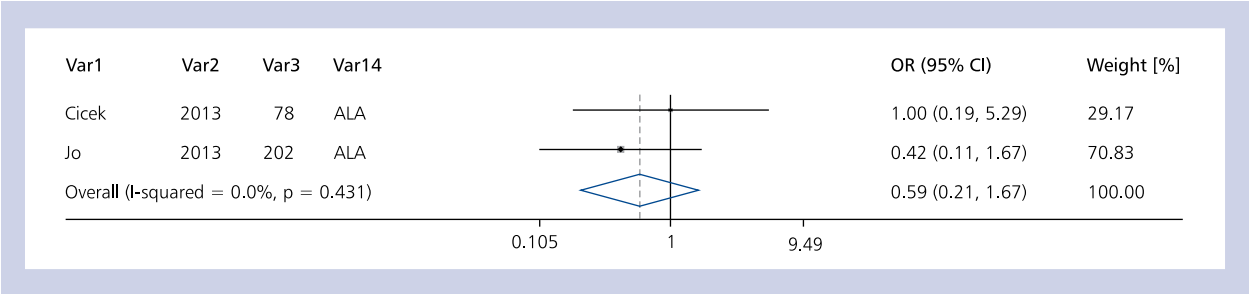
Supplemental Figure 1. Forest plot of odds ratio (OR) for effects of N-acetyl cysteine (NAC) on contrast-induced nephropathy; CI — confidence interval



Supplemental Figure 2. Forest plot of odds ratio (OR) for effects of ascorbin acid (AA) on contrast-induced nephropathy; CI — confidence interval



Supplemental Figure 3. Forest plot of odds ratio (OR) for effects of vitamin E on contrast-induced nephropathy; CI — confidence interval



Supplemental Figure 4. Forest plot of odds ratio (OR) for effects of alpha-lipoic acid (ALA) on contrast-induced nephropathy; CI — confidence interval

Ochronny wpływ stosowania antyoksydantów powodujący zmniejszenie częstości występowania nefropatii pokontrastowej: obszerny przegląd systematyczny z metaanalizą aktualnych badań

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Streszczenie

Wstęp i cel: Niniejszy przegląd systematyczny z metaanalizą ma na celu określenie siły dowodów potwierdzających wpływ antyoksydantów (AO), takich jak N-acetylocysteina (NAC), witamina C, witamina E i kwas alfa-liponowy na zapadalność na nefropatię pokontrastową (CIN), konieczność hemodializoterapii, stężenie kreatyniny w surowicy i śmiertelność po koronarografii.

Materiały i wyniki: W wyniku wyszukiwania w bazach Medline, Embase, Elsevier, Sciences online database i Google Scholar wybrano badania z randomizacją i grupą kontrolną do metaanalizy. Miarą wielkości efektu w przypadku analizy danych kategorycznych był iloraz szans (OR), a w przypadku obliczania różnic między średnimi zmianami stężenia kreatyniny w surowicy w grupie interwencji i w grupie kontrolnej była standaryzowana średnia różnica (SMD) z 95-procentowym przedziałem ufności. Wartość p wynosząca $< 0,1$ w teście Q lub współczynnik I^2 wynoszący $> 50\%$ wskazywały na istotne różnice między badaniami. Po wyszukiwaniu publikacji we wszystkich najważniejszych bazach danych uzyskano 2350 badań. Po selekcji wybrano łącznie 49 badań, w których dostępne były potrzebne dane. Łączna analiza efektu terapeutycznego wykazała, że NAC (OR 0,79; 95% CI: 0,69–0,9; p = 0,000), witamina C (OR 0,63; 95% CI: 0.45–0,89; p = 0,000) i witamina E (OR 0,5; 95% CI: 0,27–0,2; p = 0,026) mogły istotnie zmniejszyć zapadalność na CIN. W przeciwieństwie do NAC (SMD –0,119; 95% CI: –0,191 – –0,046; p = 0,000) witamina C (SMD –0,08; 95% CI: –0,22–0,04; p = 0,1) ani witamina E (–0,25; 95% CI: –0.46 – –0,05; p = 0,1) nie powodowały istotnego zmniejszenia średniego stężenia kreatyniny w surowicy. Jednak stosowanie AO nie wiązało się z redukcją śmiertelności (OR 0,94; 95% CI: 0,69–1,28; p = 0,7).

Wnioski: Podsumowując, antyoksydanty, takie jak NAC, witamina C i witamina E mogą zmniejszyć zapadalność na CIN, ale tylko NAC może spowodować istotne obniżenie stężenia kreatyniny w surowicy. Suplementacja AO nie wpływa na śmiertelność.

Słowa kluczowe: nefropatia pokontrastowa, antyoksydant, witamina C, N-acetylocysteina, witamina E, kwas alfa-liponowy, koronarografia

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