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Strategies Preventing Contrast-Induced Nephropathy After Coronary Angiography: A Comprehensive Meta-Analysis and Systematic Review of 125 Randomized Controlled Trials

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Abstract

This systematic review with meta-analysis sought to determine the strength of evidence for the effects of hydration (sodium bicarbonate [SB] and normal saline [NS]), supplementations (*N*-acetylcysteine [NAC] and vitamin C), and some common drugs (adenosine antagonists [AAs], statins, loop diuretics, and angiotensin-converting enzyme inhibitors [ACEIs]) on the incidence of contrast-induced nephropathy (CIN) and requirement for hemodialysis after coronary angiography. After screening, a total of 125 trials that reported outcomes were identified. Pooled analysis indicated beneficial effects of SB versus NS (odds ratio [OR] = 0.73; 95% confidence interval [CI]: 0.56-0.94; $P = .01$), NAC (OR = 0.79; 95% CI: 0.70-0.88; $P = .001$), vitamin C (OR = 0.64; 95% CI: 0.45-0.89; $P = .01$), statins (OR = 0.45; 95% CI: 0.35-0.57; $P = .001$), AA (OR = 0.28; 95% CI: 0.14-0.47; $P = .001$), loop diuretics (OR = 0.97; 95% CI: 0.33-2.85; $P = .9$), and ACEI (OR = 1.06; 95% CI: 0.69-1.61; $P = .8$). Overall, hydration with SB, use of supplements, such as NAC and vitamin C, and administration of statins and AA should always be considered for the prevention of CIN after coronary angiography.

Keywords

contrast-induced nephropathy, antioxidants, vitamin C, *N*-acetylcysteine, hydration, sodium bicarbonate, normal saline, statins, adenosine antagonist, loop diuretics, angiotensin-converting enzyme inhibitors

Introduction

Contrast-induced nephropathy (CIN) is a possible complication after coronary angiography associated with the administration of radiocontrast media. The CIN is a prevalent cause of hospital-acquired acute renal failure accounting for about 10% of all cases.[1] The reported incidence of CIN varies widely from 2% to 50% in low- and high-risk populations, respectively.[2] Risk factors for this common complication include volume and type of contrast agents, history of chronic renal impairment, diabetic nephropathy, heart failure, advanced age, anemia, and reduced effective circulating volume.[2] Increased

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incidence of CIN is usually associated with the need for renal replacement therapy, prolonged length of hospital stay, increased costs, and reduced short- and long-term survival.[3] The complex pathogenesis of CIN involves a combination of insults affecting renal tubular endothelial cells, such as oxidative stress, intrarenal vasoconstriction, reperfusion injury, medullary ischemia, and toxicity of renal cells.[4,5]

The optimal strategy to prevent CIN remains uncertain. However, sufficient hydration, careful use of appropriate renoprotective drugs and avoidance of nephrotoxic drugs, and minimization of the volume of contrast agent are common strategies in the management of this complication in patients requiring coronary diagnostic imaging.[5,6] This comprehensive systematic review with meta-analysis sought to determine the strength of evidence for the effects of hydration (sodium bicarbonate [SB] and sodium chloride), supplementations (*N*-acetylcysteine [NAC] and vitamin C), and further common drugs (adenosine antagonists [AAs], statins, loop diuretics, and angiotensin-converting enzyme inhibitors [ACEIs]) on the incidence of CIN and requirement for hemodialysis after coronary angiography.

Methods and Materials

Literature Search

A comprehensive literature search was performed in major medical databases (MEDLINE/PubMed, EMBASE, Elsevier, Web of Science, and Google Scholar) from their inception through October 20, 2014, to identify randomized controlled trials (RCTs) reporting on the effects of 1 of our 7 therapeutic strategies (strategy 1: normal saline [NS] vs SB; strategy 2: NAC vs placebo; strategy 3: vitamin C vs placebo; strategy 4: statin vs placebo; strategy 5: AA vs placebo; strategy 6: loop diuretic vs placebo; and strategy 7: ACEI or angiotensin receptor blocker vs placebo) on the incidence of CIN and requirement for hemodialysis. Predefined search terms included ''contrast-induced nephropathy,'' ''CIN,'' ''coronary angiography'' and ''*N*-acetyl cysteine,'' ''acetylcysteine,'' ''vitamin C,'' ''ascorbic acid,'' ''sodium bicarbonate,'' ''sodium chloride,'' ''adenosine antagonists,'' ''theophylline,'' ''aminophylline,'' ''atorvastatin,'' ''statin,'' ''furosemide,'' ''loop diuretic,'' ''angiotensin-converting enzyme inhibitors,'' ''ACEI.'' No limitations were imposed on language, study period, or sample size. All retrieved references of the included RCTs and recently published meta-analyses or review articles were also reviewed to determine additional studies not indexed in common databases. Studies were included in the analysis when they met the following criteria: (1) RCT, (2) comparison of SB with NS, NAC with placebo, ascorbic acid with placebo, statins with placebo, AA with placebo, loop diuretics with placebo, ACEI with placebo, and (3) reporting data on the clinical outcomes according to our review checklist. Manuscripts that did not undergo a peer-review process and abstracts from congress presentations were not included.

Data Extraction and Outcome Measures

Six investigators (S.A.-H.-S., S.-J.M., Z.G., E.R., Z.S.-C., and A.A.K.-B.) extracted the data independently, and discrepancies were resolved via a consensus standardized abstraction checklist used for recording data for each study. Any disagreements were resolved through discussion with other senior authors (A.W., M.Z., A.-F.P., and A.S.). Author's name, mean age, gender, sample size, type of radiocontrast agent (low, iso, or high osmolality), details of regimens in studies and control groups, mean baseline serum creatinine, the incidence of CIN, and requirement for hemodialysis were extracted from each group. For exploration of heterogeneity among trials, subgroup analyses were performed for the following items: (1) type of radiocontrast agent (low, iso, high, combined, no exact data); (2) type of coronary angiography (elective, emergency, both, no exact data); and (3) subgroups of certain drug categories (statin: atorvastatin, rosuvastatin, others; AA: theophylline, aminophylline, others; ACEI: captopril, others).

Definitions

The CIN was defined as $\geq$25% and/or $\geq$0.5 mg/dL increase in creatinine from its baseline. According to previous investigations, renal failure was defined as new onset of hemodialysis after receiving radiocontrast agent.

Statistical Analysis, Publication Bias

Data were analyzed by STATA version 11.0 using METAN and METABIAS modules. The effect measured was odds ratio (OR) with 95% confidence interval (CI) for categorical variables. An OR <1 favored study groups and an OR >1 favored control groups. The RCTs with no events in the 2 arms were discarded from pooled analysis. A P value <.1 for Q test or $I^2 >$ 50% indicated significant heterogeneity among the studies. The presence of publication bias was evaluated using the Begg tests. Heterogeneity among trials was accounted for by applying a random-effects model when indicated.

Meta-Regression

Considering interventional nature of these studies and exploration of relationship between variables and outcomes, for moderator analysis, analysis of variance was used for qualitative variables and regression for quantitative ones. For weighting the studies in these tests, the same weight calculated by METAN command in STATA was used. To demonstrate the effect of these variables, error bar in SPSS (version 19) was applied.

Quality Assessment

Quality assessment of RCTs was performed using the Jadad score.[7] The Jadad score assesses 3 items including randomization (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 $P < .05$.

Results

Literature Search Strategy and Included Trials

Overall, for 7 treatment strategies included in the present meta-analysis, our literature search retrieved 7730 studies from the screened databases, of which 7605 were excluded after initial review. The final analysis was conducted using a total of 125 RCTs. Details on therapeutic strategies, excluded trials, and studies finally enrolled in the present meta-analysis are shown in Supplemental Table 1.

Study Characteristics, Effect Measures, and Clinical Outcomes

Normal saline versus SB. A total of 6984 patients were included from 33 RCTs. Patient populations from RCTs ranged from 34 to 502 (Table 1). Of the 6984 patients, 3485 were allocated to the SB group and 3499 to the NS group. The overall incidence of CIN was 10.7% ranging from 3.4% to 20.9%. The incidence of CIN was 9.3% in the SB group and 12.11% in the NS group (Table 2). Pooled treatment effect analysis revealed that SB therapy could significantly decrease the incidence of CIN compared with NS with an OR of 0.73 (95% CI: 0.56-0.94; $P = .01$) using the random-effects model (Figure 1 and Supplemental Figure 1A for fixed model). There was some heterogeneity among the studies analyzed ($\chi^2 = 68.44$, $I^2 = 53.2\%$). There was no publication bias and risk of small study effects among the included RCTs (Begg test, $P = .878$; Supplemental Figure 1B). A subgroup analysis for this heterogeneity is reported in Table 3. The subgroup analysis showed that SB, compared with NS, was associated with stronger preventive effects on the incidence of CIN after coronary angiography using low-osmolarity radiocontrast agents rather than iso- or high-osmolarity (OR = 0.59; 95% CI: 0.47-0.74; $P = .001$) media and in emergency coronary angiography rather than elective angiography (OR = 0.62; 95% CI: 0.46-0.84; $P = .002$). Twenty-one RCTs reported data on the incidence of the need for hemodialysis. The overall incidence of hemodialysis was 0.77%: 0.82% in the SB group and 0.73% in the NS group (Table 2). In fact, 11 of the 21 comparisons did not present any hemodialysis in 2 comparative arms; therefore, the remaining 10 RCTs were used to perform the meta-analysis. Pooled analysis indicated that the incidence of hemodialysis was similarly distributed between the SB and NS groups with an OR of 1.11 (95% CI: 0.58-2.09; $P = .7$) using the fixed-effects model (Supplemental Figure 1B and C for fixed model and random model, respectively).

N-acetylcysteine versus placebo. A total of 11 446 patients were included from 49 RCTs. Patient populations from RCTs ranged from 30 to 2308 (Table 1). Of the 11 446 patients, 5724 were allocated to the NAC group and 5722 to the placebo group. The overall incidence of CIN was 13.1%, ranging from 0% to 29.8% and accounting for 11.7% in the NAC group and 14.4% in the placebo group (Table 2). Pooled treatment effect analysis revealed that NAC could significantly decrease the incidence of CIN compared with placebo with an OR of 0.79 (95% CI: 0.70-0.88; $P = .001$) using the fixed-effects model (Figure 2 and Supplemental Figure 1D for random-effects model). There was no significant heterogeneity among the studies ($\chi^2 = 71.68$, $I^2 = 34.4\%$). There was no publication bias and risk of small study effects among the included RCTs (Begg test, $P = .445$) (Supplemental Figure 2B). Details of a subgroup analysis are presented in Table 3. From 49 included studies on NAC versus placebo, 24 RCTs reported data on the incidence of the need for hemodialysis. The overall incidence of hemodialysis was 2.07%: 1.9% in the NAC group and 2.18% in the placebo group (Table 2). Thirteen of the 21 comparisons did not present any hemodialysis in 2 comparative arms; therefore, the remaining 11 RCTs were used to perform the meta-analysis. Pooled analysis indicated that NAC therapy could not significantly decrease the incidence of hemodialysis with an OR of 1.18 (95% CI: 0.60-2.3; $P = .6$) using the fixed-effects model (Supplemental Figure 1E and F for fixed model and random model, respectively). There was no heterogeneity among the studies ($\chi^2 = 4.97$, $I^2 = 0\%$).

Vitamin C versus placebo. A total of 1243 patients were included from 7 RCTs. Patient populations from RCTs ranged from 81 to 291 (Table 1). Of the 1243 patients, 568 were allocated to the vitamin C group and 675 to the placebo group. The overall incidence of CIN was 14.6%, ranging from 5.59% to 29.5% and accounting for 10.7% in the vitamin C group and 17.9% in the placebo group (Table 2). Pooled treatment effect analysis revealed that vitamin C supplementation was associated with the ability to significantly decrease the incidence of CIN with an OR of 0.64 (95% CI: 0.45-0.89; $P = .01$) using the fixed-effects model (Figure 3 and Supplemental Figure 1G for random model). There was no significant heterogeneity among the studies ($\chi^2 = 5.61$, $I^2 = 0\%$). There was no publication bias and risk of small study effects among the included RCTs (Begg test, $P = .293$; Supplemental Figure 2C). Details of a subgroup analysis are reported in Table 3. From the 7 included studies on vitamin C versus placebo, 5 RCTs reported data on the incidence of the need for hemodialysis. Four of the 5 comparisons did not present any hemodialysis in 2 comparative arms. Therefore, no meta-analysis on the incidence of hemodialysis was conducted in this therapeutic strategy because of the insufficient number of studies (only 1 study).

Statins versus placebo. A total of 5693 patients were included from 12 RCTs. Patient populations from RCTs ranged from 130 to 2998 (Table 1). Of the 5693 patients, 2834 were allocated to the statin group and 2859 to the placebo group. The overall incidence of CIN was 5.51%, ranging from 0.6% to 13.8% accounting for 3.52% in the statin group and 7.48% in the placebo group (Table 2). Pooled treatment effect analysis revealed that patients who underwent treatment with statins had a significantly lower incidence of postangiography CIN with an

Table 1. Demographic Data of Included Studies.

Author	n		Mean Age (years)		Male (%)		Regimen	Mean Baseline Serum Creatinine
	SG	CG	SG	CG	SG	CG		
Hydration: SB versus saline								
Boucek et al[8]	61	59	63	67	75.4	74.5	SB solution was produced by adding 154 mL of 8.4% $NaHCO_3$ to 846 mL of 5% glucose. 1 hour immediately before (at the rate of 3 mL/kg BW/h limited to the maximal amount of 330 mL and for 6 hours following the intervention	119 μmol/L
Brar et al[9]	175	178	71	71	62	65	Infusion was begun 1 hour prior to the start of contrast administration at 3 mL/kg for 1 hour, decreased to 1.5 mL/kg/h during the procedure and for 4 hours following completion of the procedure	1.5 mg/dL
Alessandri et al[10]	138	158	64	65	66.6	67.7	160 mEq of $NaHCO_3$ in 350 mL of 5% glucose solution 2 mL/kg/h since 2 hours before the administration of contrast medium. The infusion prolonged for the following 6 hours after the procedure with an infusion rate of 1 mL/kg/h	1.5 mg/dL
REINFORCE trial et al[11]	71	74	70.1	72.7	74.6	81	154 mEq of 1000 mEq/L of SB in 5% dextrose solution, prepared at the hospital pharmacy by adding 154 mL of 1000 mEq of SB to 846 mL of 5% dextrose solution and adjusting the dextrose concentration to 4.23%. Fluids were administrated IV at the rate of 2 mL/kg BW/h for 2 hours before, at the rate of 1 mL/kg BW/h during, and 6 hours after administration of contrast medium	1.6 mg/dL
Yang et al[12]	159	161	58.7	59.6	52.8	53.4	SB IV infused with 1.5% SB solution at the rate of 1.5 mL/kg/h for 6 hours before the application of the contrast agent. After the contrast exposure was applied, the 1.5% SB infusion was continued for 6 hours	70 μmol/L
Vasheghani-Farhani et al[13]	36	36	61.4	62.7	77.7	80.5	75 mL of 8.4% SB to 1 L of 0.45% SC. IV bolus was given at the rate of 3 mL/kg for 1 hour immediately before contrast injection, followed by an infusion of 1 mg/kg/h for 6 hours after the procedure	1.7 mg/dL
Vasheghani-Farhani et al[14]	135	130	62.9	63.8	91.4	81.5	75 mL of 8.4% SB to 1 L of 0.45% SC. IV bolus was given at the rate of 3 mL/kg for 1 hour immediately before contrast injection, followed by an infusion of 1 mg/kg/h for 6 hours after the procedure	1.6 mg/dL
CINSTEMI trial[15]	181	181	62	63	76.8	80.1	167 mmol/L SB IV as 500 mL in the first hour followed by infusion of 100 mL/h in the next 5 hours	0.8 mg/dL
Ueda et al[16]	30	29	77	75	77	79	0.5 mg/kg SB as soon as possible after hospital admitted, and 1 mL/kg/h during and for 6 hours after the procedure	1.4 mg/dL
Tamura et al[17]	72	72	72.3	73.3	91.7	83.3	20 mEq SB 5 minutes before contrast exposure	1.3 mg/dL
Shavit et al[18]	51	36	72	71	84	70	154 mEq/L SB in 5% dextrose in water mixed by adding 154 mL of the 1000 mEq/L SB to 846 mL of 5% dextrose in water. The initial IV bolus was 3 mL/kg for 1 hour before the procedure, and 1 mL/kg/L for 6 hours after the procedure	1.8 mg/dL
RENO trial[19]	56	55	65	64	68	71	Initial IV bolus 5 mL/kg/h SB with 154 mEq/L $NaHCO_3$ in 5% glucose and H_2O, after contrast same solution continued at 1.5 mL/kg/h for 12 hours the day after contrast	1.0 mg/dL
Ratcliffe et al[20]	19	15	67	64	58	60	154 mEq/L SB in 5% dextrose in water mixed by adding 154 mL of the 1000 mEq/L SB to 846 mL of 5% dextrose in water. The initial IV bolus was 3 mL/kg for 1 hour before the procedure, and 1 mL/kg/L for 6 hours after the procedure	106 μmol/L

(continued)

Table 1. (continued)

Author	n		Mean Age (years)		Male (%)		Regimen	Mean Baseline Serum Creatinine
	SG	CG	SG	CG	SG	CG		
Pakfetrat et al[21]	96	96	57.8	58.5	58.3	64.5	SB solution was prepared in the hospital pharmacy by adding 154 mL 1000 mEq/L SB to 846 mL 5% dextrose in water, and was infused at 3 mL/kg/h starting 1 hour before contrast administration, followed by a 1 mL/kg/h infusion for 6 hours after the procedure	1.1 mg/dL
Ozcan et al[22]	88	88	68	70	72.7	75	SB solution was prepared in the hospital pharmacy by adding 154 mL 1000 mEq/L SB to 846 mL 5% dextrose in water, and was infused at 1 mL/kg/h starting 6 hours before contrast administration, followed by a 1 mL/kg/h infusion for 6 hours after the procedure	1.3 mg/dL
Motohiro et al[23]	78	77	71	74	76	64	SB solution was prepared in the hospital pharmacy by adding 154 mL 1000 mEq/L SB to 846 mL 5% dextrose in water, and was infused at 1 mL/kg/h continued from 3 hours before to 6 hours after the procedure	1.5 mg/dL
Merten et al[24]	60	59	66.7	69.2	73	76	SB solution was prepared in the hospital pharmacy by adding 154 mL 1000 mEq/L SB to 846 mL 5% dextrose in water. The initial IV bolus was 3 mL/kg/h for 1 hour immediately before radiocontrast injection. Following this, same fluid at a rate of 1 mL/kg/h during the contrast exposure and 6 hours after the procedure	1.7 mg/dL
Masuda et al[25]	30	29	75	76	63	59	154 mL SB. The IV bolus was given at the rate of 3 mL/kg for 1 hour before contrast injection, followed by an infusion of 1 mg/kg/h during and 6 hours after the procedure	1.3 mg/dL
Maioli et al[26]	250	252	74	74	57.2	60.7	154 mL SB. The IV bolus was given at the rate of 3 mL/kg for 1 hour before contrast injection, followed by an infusion of 1 mg/kg/h for 6 hours after the procedure	1.2 mg/dL
PREVENT trial[27]	193	189	68.5	67.5	70.5	71.4	154 mL SB. The IV bolus was given at the rate of 3 mL/kg for 1 hour before contrast injection, followed by an infusion of 1 mg/kg/h during and 6 hours after the procedure	1.5 mg/dL
Koc et al[28]	94	101	62	62	58	48	154 mL 1000 mEq/L SB to 846 mL 5% dextrose in water, and was infused at 1 mL/kg/h starting 6 hours before contrast administration, followed by a 1 mL/kg/h infusion for 6 hours after the procedure	1.0 mg/dL
Klima et al[29]	87	89	78	75	66	62	The initial IV bolus SB was 3 mL/kg/h of 166 mEq/L for 1 hour immediately before injection. Following this, the same fluid at a rate of 1 mL/kg/h during the contrast exposure and for 6 hours after the procedure. SB 166 mEq as a bolus administrated over 20 minutes immediately before contrast. Additionally, oral SB (500 mg $NaHCO_3$ per capsule: 1 capsule/10 kg) at the start of infusion and after contrast within 6 hours	137 μmol/L
Heguilén et al[30]	43	38	67.7	69.3	62.7	78.9	154 mEq/L of SB in 5% dextrose in H_2O, mixed by adding 77 mL of 1000 mEq/L SB to 423 mL of 5% dextrose in H_2O, and was infused at 3 mL/kg/h from at least 2 hours before the procedure, and 1 mL/kg/h during and for the next 6-12 hours	1.5 mg/dL
Hafiz et al[31]	159	161	74	73	56.6	57.1	159 mEq/L SB to 5% dextrose in water, and was infused at 3 mL/kg/h starting 1 hour before contrast administration, followed by a 1 mL/kg/h infusion for 6 hours after the procedure	1.6 mg/dL
Gomes et al[32]	150	151	64.1	64.5	69.3	74.8	154 mEq/L SB to 5% dextrose in water, and was infused at 3 mL/kg/h starting 1 hour before contrast administration, followed by a 1 mL/kg/h infusion for 6 hours after the procedure	1.5 mg/dL

(continued)

Table 1. (continued)

Author	n		Mean Age (years)		Male (%)		Regimen	Mean Baseline Serum Creatinine
	SG	CG	SG	CG	SG	CG		
Castini et al[33]	52	51	70	72.7	85	84	IV bolus administration of SB at a rate of 1 mL/kg BW/h for 12 hours before and 12 hours after contrast injection	1.5 mg/dL
Briguori et al[34]	108	111	70	71	88	81	SB solution was prepared in the hospital pharmacy by adding 154 mL 1000 mEq/L SB to 846 mL 5% dextrose in water. The initial IV bolus was 3 mL/kg/h for 1 hour immediately before radiocontrast injection. Following this, same fluid at a rate of 1 mL/kg/h during the contrast exposure and 6 hours after the procedure	2 mg/dL
Mahmoodi et al[35]	175	175	64.9	64.4	43.4	59.4	SB solution was prepared by adding 154 mL of 1000 mEq/L SB to 846 mL of 5% dextrose with water. All the patients received a fixed dose of fluid 6 hours before the procedure and 6 hours after it	1.1 mg/dL
Inda-Filho et al[36]	125	125	56	58.4	59.1	60.5	$NaHCO_3$, prepared by mixing 150 mEq (15 ampoules) of SB with 1 L of 5% dextrose, was given in bolus at 3.5 mL/kg/h before contrast medium was administered, then at 1.18 mL/kg/h. Saline (0.9%, isotonic) was given IV at 1 mL/kg/h	1.2 mg/dL
Manari et al[37]	145	151	72	75	63.9	65	SB solution was obtained by adding 77 mL of 8.4% SB to 433 mL of 5% glucose in H_2O, to reach a final concentration of 154 mEq/L. SB solution received 1 mL/kg BW/h for 12 hours. IV NS (0.9%) at a rate of 1 mL/kg BW/h for 12 hours	1.15 mg/dL
Manari et al[37]	154	142	65.2	65.2	75	77	SB solution was obtained by adding 77 mL of 8.4% SB to 433 mL of 5% glucose in H_2O, to reach a final concentration of 154 mEq/L. NS at a rate of 3 mL/kg BW/h for 1 hour followed by 1 mL/kg BW/h for 11 hours. SB, 3 mL/kg BW/h for 1 hour, followed by 1 mL/kg BW/h for 11 hours	1 mg/dL
Beyazal et al[38]	20	20	62.7	60.8	27.3	39.4	NS: 3 mL/kg isotonic sodium chloride for 1 hour prior to the injection of iohexol. After the iohexol injection, patients were administered a 1 mL/kg/h dose isotonic sodium chloride for 6 hours. SB: 850 mL of 5% dextrose solution with 150 mEq SB at a dose of 3 mL/kg for 1 hour before injection of iohexol. After the iohexol injection, 1 mL/kg/h of SB solution was administered for 6 hours	1.3 mg/dL
Yeganehkhah et al[39]	50	50	60.9	58.5	62	44	SB solution, which was prepared by adding 150 mL NS 8.4% to 850 mL isotonic NS. The first group received 3 mL/kg/h of SB, an hour prior to angiography and 1 mL/kg/h, within 6 hours after angiography. NS: Isotonic NS (1 mL/kg/h; maximum 100 mL/h) was prescribed for 12 hours, before and after angiography	1.1 mg/dL
Solomon et al[40]	195	196	71	72	70	58	5 mL/kg of either SB or sodium chloride over 60 minutes before angiography and 1.5 mL/kg/h during and for 4 hours after angiography	1.9 mg/dL
Supplementations: NAC versus placebo								
ACT trial[41]	1172	1136	68	68.1	62	60.7	A dose of 1200 mg of NAC was administrated orally every 12 hours, for 2 doses before and 2 doses after the procedure	1.2 mg/dL
Albabtain et al[42]	62	66	62	59.8	71	81.8	NAC orally 600 mg twice daily for 2 days starting the evening before the procedure	1.29 mg/dL
Alessandri et al[10]	138	158	64.2	65	66.6	67.7	NAC was administrated twice a day in 2 doses of 600 mg from the day before until the day after the procedure	1.2 mg/dL
Amini et al[43]	45	45	63.2	65	44.4	75.5	NAC was orally administrated at the dose of 600 mg twice a day, starting 24 hours before the procedure(2 doses before and 2 doses after the procedure)	1.7 mg/dL

(continued)

Table 1. (continued)

Author	n		Mean Age (years)		Male (%)		Regimen	Mean Baseline Serum Creatinine
	SG	CG	SG	CG	SG	CG		
Baker et al[44]	41	39	67.4	70.9	90.2	84.6	NAC was administrated IV a dose of 150 mg/kg in 500 mL saline over 30 minutes immediately before contrast exposure, and followed by 50 mg/kg in 500 mlL saline over the subsequent 4 hours	1.8 mg/dL
Baskurt et al[45]	73	72	67.9	67.1	63	56.9	NAC (600 mg orally twice daily the preceding day and the day of angiography	1.3 mg/dL
Berwanger et al[46]	717	678	64.6	64.3	60.8	59.3	A dose of 1200 mg of NAC was administrated orally every 12 hours, for 2 doses before and 2 doses after the procedure	1.1 mg/dL
Briguori et al[47]	92	91	64	64	84	89	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 2 doses	1.5 mg/dL
Azmus et al[48]	196	201	ND	ND	ND	ND	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 2 doses	1.3 mg/dL
Calabrò et al[49]	152	170	54.6	54.1	79.9	71.9	NAC 600 mg was administrated 12 hours before, 1 hour before, and 12 hours after the procedure	0.9 mg/dL
Carbonell et al[50]	107	109	63.1	60.7	80.4	72.5	NAC (600 mg diluted in 50 mL of saline) IV for 30 minutes twice daily for a total of 4 doses	0.9 mg/dL
Carbonell et al[51]	39	42	70	69	80	81	NAC (600 mg diluted in 50 mL of saline) IV for 30 minutes twice daily for a total of 4 doses	2 mg/dL
Castini et al[33]	53	51	70.5	72.7	94	84	NAC orally at the of 600 mg twice daily on the day before and on the day administration of the contrast agent	1.5 mg/dL
Coyle et al[52]	68	69	66.7	63.3	61.8	68.1	NAC 600 mg every 12 hours orally for 2 doses before and 2 doses after the procedure	1.1 mg/dL
Diaz-Sandoval et al[53]	25	29	74	72	68	89.6	NAC (600 mg diluted in 30 mL of ginger ale) orally, twice daily at 4 doses	1.6 mg/dL
Durham et al[54]	38	41	71.4	69.8	63.1	68.2	NAC 1200 mg orally, administrated 1 hour prior to and 3 hours following the procedure	2.2 mg/dL
Ferrario et al[55]	99	101	75	75	68	62	NAC was supplied as tablet 600 mg twice a day for 2 days	1.6 mg/dL
Fung et al[56]	46	45	68.2	68	73.9	66.6	NAC 400 mg orally, thrice daily the day before, and the day the contrast procedure	2.2 mg/dL
Goldenberg et al[57]	41	39	71	69	85.3	79.4	NAC 600 mg thrice daily was administrated orally for a total 48 hours, starting 24 hours before the administration of the contrast agent	1.9 mg/dL
Gomes et al[58]	77	79	63.8	66.5	61	57	NAC was orally administrated at the dose of 600 mg twice a day, starting 1 day before the procedure (2 doses before and 2 doses after the procedure)	117 μmol/L
Gulel et al[59]	25	25	61.4	61.5	80	72	NAC 600 mg orally, twice daily the day before, and the day the contrast procedure	1.7 mg/dL
Günebakmaz et al[60]	40	40	64.7	66.4	72.5	62.5	600 mg NAC every 12 hours for 4 days; 4 doses before the procedure day, 2 doses on the day of the procedure, and 2 doses after day of the procedure	1.4 mg/dL
Heng et al[61]	28	32	ND	ND	ND	ND	NAC 1200 mg twice daily	ND
Hölscher et al[62]	139	139	ND	ND	ND	ND	Two oral doses 600 mg NAC	1.6 mg/dL
Jaffery et al[63]	192	206	65.1	65.6	59.4	67	NAC 1200 mg bolus followed by 200 mg/h for 24 hours	1.08 mg/dL
Kay et al[64]	102	98	69	69	60	63	NAC 600 mg tablet twice daily	1.2 mg/dL
Kim et al[65]	80	86	62	62	63	58	NAC 600 mg twice a day, on the day before procedure	1 mg/dL
Kinbara et al[66]	15	15	70	70	60	60	704 mg orally twice daily, the day before and the day of the procedure	0.9 mg/dL
Koc et al[67]	80	80	62	65	76	79	NAC 600 mg IV bolus twice daily before and on the day of the procedure	1.3 mg/dL
MacNeil et al[68]	21	22	72.1	72.9	76.1	95.4	Two doses of NAC 600 mg was administrated prior to the procedure, the first at time of randomization, the second 4 hours later	1.8 mg/dL
Miner et al[69]	95	85	71	69	68	66	2000 mg NAC/dose twice a day for 3 doses	127 μmol/L

(continued)

Table 1. (continued)

Author	n		Mean Age (years)		Male (%)		Regimen	Mean Baseline Serum Creatinine
	SG	CG	SG	CG	SG	CG		
Ochoa et al[70]	36	44	73	70	44	41	Two doses of NAC (1000 mg diluted in 20 mL of diet cola) orally 1 hour prior to exposure, 4 hours later	2 mg/dL
Oldemeyer et al[71]	49	47	77	75	55.1	55.3	1500 mg NAC, starting the evening before the procedure, and given every 12 hours for 4 doses	1.6 mg/dL
Ratcliffe et al[20]	21	15	65	64	52	60	NAC 1200 mg IV bolus was administrated 1 hour before, and 1200 mg orally twice daily for 48 hours after the procedure	109 μmol/L
Ratcliffe et al [20]	23	19	65	67	70	58	NAC 1200 mg IV bolus was administrated 1 hour before, and 1200 mg orally twice daily for 48 hours after the procedure	103 μmol/L
Seyon et al[72]	20	20	76.4	74.7	60	70	600 mg NAC orally for a total 4 doses	130 μmol/L
Shyu et al[73]	60	61	70	70	70	65.5	400 mg NAC twice daily	2.8 mg/dL
Wang et al[74]	23	23	65.8	69.2	56.5	60	NAC (5 g) to a total volume of 1000 mL during and for 10 hours after the procedure	1.2 mg/dL
Thiele et al[75]	126	123	68	68	70	65.6	High-dose NAC (2× 1200 mg/d) for 48 hours	79.5 μmol/L
Brueck et al[76]	192	193	75	74	65.3	62.1	600 mg NAC IV twice (at 24 and 1 hour before angiography)	1.5 mg/dL
Webb et al[77]	220	227	70.8	70	59.5	62	IV NAC 500 mg immediately before the procedure	141 μmol/L
Kefer et al[78]	53	51	62	62	77	76	1200 mg NAC in 0.9% saline IV over 60 minutes, 12 hours before and 0 hour after the procedure	1.11 mg/dL
Arabmomeni et al[79]	28	30	64.5	65	39.3	43.3	600 mg NAC IV twice a day (from 24 hours before to 48 hours after administration of contrast material)	1.11 mg/dL
Kumar et al[80]	90	90	ND	ND	ND	ND	600 mg NAC twice daily	ND
Yeganehkhah et al[39]	50	50	58.1	58.5	50	44	Oral NAC (600 mg twice a day) 1 day before angiography and on the day of angiography, in addition to isotonic NS (1 mL/kg/h; maximum 100 mL/h) for 12 hours before and after angiography.	1.12 mg/dL
Inda-Filho et al[36]	126	125	59.2	60.5	61.9	58.4	Medications IV 60 minutes immediately before, during, and 6 hours immediately after contrast medium was administered. NAC in 500 mL of 5% dextrose was given in bolus at 150 mg/kg/h before contrast medium was administered, then at 50 mg/kg/h	1 mg/dL
Chong et al[81]	156	153	67	68.4	77.6	77.8	Patients in the NAC group received 1.2 g oral NAC (2 tablets of 600 mg NAC dissolved in approximately 250 mL of water) twice a day for 3 consecutive days, starting from the day before angiography (to a total of 6 doses)	140.2 μmol/L
Thayssen et al[15]	176	181	63	63	72.2	80.1	NAC 1200 mg orally before the PCI followed by 1200 mg daily during the next 48 hours	0.87 mg/dL
Thayssen et al[15]	177	181	63	62	78.5	76.8	NAC 1200 mg orally before the PCI followed by 1200 mg daily during the next 48 hours	0.88 mg/dL
Supplementations: vitamin C versus placebo								
Albabtain et al[42]	57	66	58.7	59.8	66.7	81.8	Vitamin C supplied as tablet 3 g for 2 hours before the procedure, 2 hours after the procedure, and 2 g for 24 hours after the procedure	1.2 mg/dL
Boscheri et al[82]	74	69	ND	ND	ND	ND	1 g ascorbic acid orally 20 minutes before exposure to CM; 500 mL NS 2 hours before and 500 mL during angiography and subsequent 6 hours	1.4 mg/dL
Brueck et al[76]	98	193	75	74	63.7	62.1	1500 mg in 250 mL NS infusion IV (over 30 minutes) at 24 hours and 1 hour before exposure to CM. NS (1 mg/kg/h) for 12 hours before to 12 hours after CM exposure	1.5 mg/dL
Briguori et al[34]	107	111	69	71	78.5	81	3000 mg vitamin C was given IV 2 hours before followed by 2000 mg the night and the morning after the procedure	1.9 mg/dL
Dvoršaket al[83]	40	41	70.7	70.7	77.5	68.3	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	136.35 μmol/L

(continued)

Table 1. (continued)

Author	n		Mean Age (years)		Male (%)		Regimen	Mean Baseline Serum Creatinine
	SG	CG	SG	CG	SG	CG		
Zhou and Chen[84]	74	82	71.8	71.4	68	57.3	IV 3 g morning of the procedure, oral 0.5 g on the night of the procedure and next morning (all doses 12 hours apart). IV NS hydration 1 mg/kg/h for 4 hours before and at least 12 hours after angiography	1.2 mg/dL
Spargias et al[85]	118	113	67	64	90.6	93.8	Vitamin C orally 3 g at least 2 hours before the procedure, 2 g night before and morning after the procedure	1.3 mg/dL
Line 4: drugs: statins versus placebo								
Toso et al[86]	151	152	75	76	68	60	80 mg/d atorvastatin for 48 hours before and 48 hours after CM administration plus oral NAC 1200 mg twice daily from the day before to a day after the procedure	1.19 mg/dL
Acikel et al[87]	80	80	58.7	60.8	63.8	63.8	40 mg/d atorvastatin started 3 days before CAG and continued for 48 hours after the procedure	0.8 mg/dL
Han et al[88]	1498	1500	61.45	61.44	64.3	66.1	10 mg/d rosuvastatin for 5 days (2 days before and 3 days after the procedure)	95 μmol/L
PROMISS trial[89]	118	118	65	66.1	72.5	71.5	160 mg total, 40 mg orally every 12 hours starting evening before and ending morning after the procedure	1.2 mg/dL
PRATO-ACS trial[90]	252	252	66.2	66.1	65.9	65.5	40 mg rosuvastatin on admission, followed by 20 mg/d plus 1200 mg NAC twice daily from the day before through the day after angiography	0.9 mg/dL
Li et al[91]	78	83	66.3	65.4	74.4	77.1	High-dose atorvastatin 80 mg prior to the procedure and 40 mg everyday thereafter	82.4 μmol/L
Ozhan et al[92]	60	70	54	55	61.6	57.1	High-dose atorvastatin 80 mg plus 600 mg NAC twice daily in first day followed by 80 mg atorvastatin for 2 days after the procedure	0.8 mg/dL
ARMYDA-CIN[93]	120	121	65	66	76	79	80 mg atorvastatin 12 hours before intervention with another 40 mg 2-hour before the procedure, after the procedure everyone put on 40 mg/d	1.04 mg/dL
Quintavalle et al[94]	202	208	70	70	51	58	80 mg atorvastatin within 24 hours before CM exposure plus NAC 1200 mg twice daily, orally the day before and day of CM administration	1.3 mg/dL
Bidram et al[95]	100	100	59.9	60.4	90	92	80 mg oral atorvastatin (2 40-mg tablets) 12 hours before contrast injection	1.16 mg/dL
Abaci et al[96]	110	110	67.5	67.7	64	73.4	40 mg of rosuvastatin <24 hours before coronary angiography and then received 20 mg/d for 2 days	1.35 mg/dL
Shehata et al[97]	65	65	55	57	53	56	receive atorvastatin (80 mg daily for 48 hours)	177 μmol/L
Drugs: AA versus placebo								
Bilasy et al[98]	30	30	56.8	57.2	70	50	200 mg of theophylline IV 30 minutes before CM administration	1.4 mg/dL
Kinbara et al[66]	15	15	71	70	66.6	60	Aminophylline 250 mg IV 30 minutes before CM administration	0.9 mg/dL
Rohani[99]	30	30	ND	ND	ND	ND	Aminophylline 250 mg IV 30 minutes before CM administration	1.8 mg/dL
Abizaid et al[100]	20	20	75	75	65	70	Aminophylline 4-mg/kg bolus then 0.4 mg/kg/h IV 2 hours before CM administration	2.1 mg/dL
Baskurt et al[45]	72	73	67.1	67.9	59.7	63	Theophylline 200 mg orally twice daily before and on the day	1.43 mg/dL
Huber et al[101]	50	50	68.8	68.9	88	78	Theophylline 200 mg IV 30 minutes before CM administration	1.2 mg/dL
Kapoor et al[102]	35	35	54.5	51.9	94.2	88.5	Theophylline 200 mg orally twice daily 24 hours before and 48 hours after CM administration	1.1 mg/dL
Matejka et al[103]	31	25	75	75	58	64	Theophylline 205.7 mg IV 1 hour before CM administration	2 mg/dL
Malhis et al[104]	128	152	51.8	48.5	60.9	58.6	Theophylline 200 mg orally twice daily 24 hours before and 48 hours after; or 200 mg IV 30 minutes before and 200 mg orally twice daily 48 hours after	1.3 mg/dL
Arabmomeni et al[79]	28	32	64.5	59.7	39.3	46.9	200 mg theophylline tablet from 24 hours before to 48 hours after administration of CM	1 mg/dL

(continued)

Table 1. (continued)

Author	n		Mean Age (years)		Male (%)		Regimen	Mean Baseline Serum Creatinine
	SG	CG	SG	CG	SG	CG		
Line 6: drugs: furosemide (loop diuretic) versus placebo								
Gu et al[105]	422	437	58	59	69.4	74.8	20 mg furosemide IV before angiography	90.1 μmol/L
Majumdar et al[106]	46	46	64	63	89	65	100 mg furosemide IV	2.8 mg/dL
Marenzi et al[107]	87	83	73	74	78	78	Furosemide was then administered as a single IV bolus of 0.5 mg/kg (up to a maximum of 50 mg)	1.8 mg/dL
Shemirani and Pourrmoghaddas[108]	60	60	66	65	48.3	53.3	ND	1.09 mg/dL
Solomon et al[109]	25	28	63	67	48	82.1	80 mg furosemide IV before angiography	1.9 mg/dL
Drugs: ACEI versus placebo								
Oguzhan et al[110]	45	45	66.3	62.07	60	66.7	Three doses of amlodipine and valsartan 5/160 mg: 1 dose was given 24 hours before the procedure, the second was given on the morning before and the last dose was given 24 hours after contrast media exposure	1.1 mg/dL
Gupta et al[111]	35	36	55.8	56	91.4	88.9	Captopril in a dose of 25 mg thrice a day for 3 days, starting 1 h prior to angiography	1.3 mg/dL
Toprak et al[112]	48	32	58.6	57.7	52.1	56.3	25 mg captopril orally 8 hours and an hour before CM	0.97 mg/dL
Hashemi et al[113]	42	46	55.1	53.6	71.4	71.7	Captopril was administered as 12.5 mg every 8 hours from 2 hours prior the procedure until 48 hours thereafter	1.01 mg/dL
Shemirani and Pourrmoghaddas[108]	60	60	64	63	43.3	48.3	ND	1.1 mg/dL
Li et al[114]	52	62	60.8	61.8	57.7	56.5	benazepril tablets 10 mg/d at least for 3 days before the procedure	0.9 mg/dL
Rosenstock et al[115]	113	63	71.8	68.5	54	63.5	ND	1.6 mg/dL
Wolak et al[116]	33	61	67.6	62.9	56.3	72.1	ND	0.97 mg/dL
Bainey et al[117]	102	106	72.4	73.2	73.5	73.6	ND	1.6 mg/dL

Abbreviations: AA, adenosine antagonists; ACEI, angiotensin converting enzyme inhibitors; BW, body weight; CAG, coronary artery angiography; CG, control group; C, control; CM, contrast medium; IV, intravenously; NAC, N-acetylcysteine; ND, no data; NS, normal saline; N, number; PCI, percutaneous coronary intervention; SB, sodium bicarbonate; SG, study group.

OR of 0.45 (95% CI: 0.35-0.57; $P = .001$) using the fixed-effects model (Figure 4 and Supplemental Figure 1H for random model). There was no significant heterogeneity among the studies ($\chi^2 = 12.68$, $I^2 = 13.3\%$). There was no publication bias and risk of small study effects among the included RCTs (Begg test, $P = .998$; Supplemental Figure 2D). A subgroup analysis reported on preventive effects of statins regarding CIN in both elective (OR = 0.45; 95% CI: 0.30-0.67; $P = .001$) and emergency (OR = 0.34; 95% CI: 0.21-0.55; $P = .001$) coronary angiographies. From 12 included studies, 6 RCTs reported data on the incidence of hemodialysis. In fact, 3 of the 6 comparisons did not present any hemodialysis in 2 comparative arms; therefore, the remaining 3 RCTs were used to perform the meta-analysis. Pooled analysis indicated that the incidence of hemodialysis was not statistically significant between the statin and placebo groups with an OR of 0.23 (95% CI: 0.03-1.3; $P = .1$) using the fixed-effects model (Supplemental Figure 1I and J for fixed model and random model, respectively). There was no heterogeneity among the studies ($\chi^2 = 0.07$, $I^2 = 0\%$).

Adenosine antagonist versus placebo. A total of 901 patients were included from 10 RCTs. Patient populations from RCTs ranged from 30 to 280 (Table 1). Of the 901 patients, 439 were allocated to the AA group and 462 to the placebo group. The overall incidence of CIN was 9.98%, ranging from 4.82% to 32.5% with 4.78% in the AA group and 14.93% in the placebo group (Table 2). Pooled treatment effect analysis revealed that AA could significantly reduce the incidence of CIN with an OR of 0.28 (95% CI: 0.14-0.47; $P = .001$) using the fixed-effects model (Figure 5 and Supplemental Figure 1K for random model). There was no significant heterogeneity among the studies ($\chi^2 = 15.53$, $I^2 = 42.1\%$). There was no publication bias and risk of small study effects among the included RCTs (Begg test, $P = .325$; Supplemental Figure 2E). Details of a subgroup analysis are presented in Table 3. From 10 included studies, 5 RCTs reported data on the incidence of the need for hemodialysis. Three of the 5 comparisons did not present any hemodialysis in 2 comparative arms; therefore, the remaining 2 RCTs were used to perform the meta-analysis. Pooled analysis reported that the incidence of hemodialysis was similar in the AA therapy and placebo groups with an OR of 3.37 (95% CI: 0.34-33.15; $P = .2$) using the fixed-effects model (Supplemental Figure 1L and M). There was no heterogeneity among the studies ($\chi^2 = 0.00$, $I^2 = 0\%$).

Loop diuretics versus placebo. A total of 1294 patients were included from 5 RCTs. Patient populations from RCTs ranged from 53 to 859 (Table 1). Of the 1294 patients, 640 were

Table 2. Clinical Outcomes of Included Studies.

Author	Incidence of CIN		Incidence of Hemodialysis		Jadad Score
	SG	CG	SG	CG	
Hydration: sodium bicarbonate versus normal saline					
Boucek et al[8]	7	5	0	0	4
Brar et al[9]	26	30	1	2	4
Alessandri et al[10]	10	15	ND	ND	3
REINFORCE trial[11]	3	2	3	2	5
Yang et al[12]	8	5	ND	ND	3
Vasheghani-Farhani[13]	1	2	ND	ND	5
Vasheghani-Farhani[14]	4	4	ND	ND	5
CINSTEMI trial[15]	33	43	0	0	3
Ueda et al[16]	2	8	0	0	4
Tamura et al[17]	9	1	0	1	3
Shavit et al[18]	5	3	0	0	2
RENO trial[19]	1	12	1	3	2
Ratcliffe et al[20]	2	1	ND	ND	3
Pakfetrat et al[21]	4	12	0	0	5
Ozcan et al[22]	4	12	1	1	2
Motohiro et al[23]	2	10	0	0	3
Merten et al[24]	1	8	0	0	3
Masuda et al[25]	2	10	1	3	3
Maioli et al[26]	25	29	1	1	5
PREVENT trial[27]	10	17	4	1	5
Koc et al[28]	17	7	ND	ND	2
Klima et al[29]	15	2	2	0	4
Heguilen et al[30]	3	6	ND	N.D	3
Hafiz et al[31]	14	19	ND	ND	3
Gomes et al[32]	9	9	0	0	2
Castini et al[33]	13	11	0	0	2
Briguori et al[34]	2	11	1	1	3
Mahmoodi et al[35]	12	34	ND	ND	2
Inda-Filho et al[36]	7	14	0	0	4
Manari et al[37]	24	29	ND	ND	4
Manariet al[37]	27	27	ND	ND	4
Beyazal et al[38]	6	5	ND	ND	2
Yeganehkhah et al[39]	6	7	ND	ND	2
Solomon et al[40]	26	18	8	6	5
Supplementations: NAC versus placebo					
ACT trial[41]	147	142	3	3	5
Albabtain et al[42]	12	13	ND	ND	3
Alessandri et al[10]	10	15	ND	ND	3
Amini et al[43]	5	6	ND	ND	3
Baker et al[44]	2	8	ND	ND	3
Baskurt et al[45]	7	5	0	0	3
Berwanger et al[46]	97	98	2	2	5
Briguori et al[47]	6	10	0	1	3
Azmus et al[48]	14	17	1	1	3
Calabrò et al[49]	4	19	ND	ND	3
Carbonell et al[50]	11	11	0	0	5
Carbonell et al[51]	2	10	0	1	4
Castini et al[33]	14	11	0	0	3
Coyle et al[52]	6	1	ND	ND	3
Diaz-Sandoval et al[53]	2	13	ND	ND	4
Durham et al[54]	10	9	ND	ND	4
Ferrario et al[55]	8	6	ND	ND	4
Fung et al[56]	8	6	0	0	3
Goldenberg et al[57]	4	3	ND	ND	5
Gomes et al[58]	8	8	2	0	3

(continued)

Table 2. (continued)

Author	Incidence of CIN		Incidence of Hemodialysis		Jadad Score
	SG	CG	SG	CG	
Gulel et al[59]	3	2	0	0	3
Günebakmaz et al[60]	9	11	ND	ND	3
Heng et al[61]	2	3	ND	ND	3
Hölscher et al[62]	6	10	ND	ND	3
Jaffery et al[63]	33	25	3	2	4
Kay et al[64]	4	12	0	0	4
Kim et al[65]	3	7	ND	ND	3
Kinbara et al[66]	0	4	ND	ND	2
Koc et al[67]	2	13	ND	ND	3
MacNeil et al[68]	1	7	ND	ND	3
Miner et al[69]	9	19	1	0	3
Ochoa et al[70]	3	11	0	0	4
Oldemeyer et al[71]	4	3	0	0	4
Ratcliffe et al[20]	1	1	ND	ND	2
Ratcliffe et al[20]	1	2	ND	ND	2
Seyon et al[72]	1	2	0	0	3
Shyu et al[73]	2	15	0	1	2
Wang et al[74]	0	0	ND	ND	4
Thiele et al[75]	18	25	4	1	4
Brueck et al[76]	53	62	ND	ND	5
Webb et al[77]	25	24	0	0	5
Kefer et al[78]	2	3	ND	ND	4
Arabmomeni et al[79]	2	6	ND	ND	5
Kumar et al[80]	18	31	ND	ND	2
Yeganehkhah et al[39]	6	7	ND	ND	3
Inda-Filho et al[36]	9	14	0	0	5
Chong et al[81]	16	19	0	1	3
Thayssen[15]	32	43	0	0	5
Thayssen[15]	33	33	0	0	5
Supplementations: vitamin C versus placebo					
Albabtain et al[42]	4	13	ND	ND	2
Boscheri et al[82]	5	3	0	0	3
Brueck et al[76]	24	62	0	0	5
Briguori et al[34]	11	11	4	1	3
Dvoršak et al[83]	2	3	0	0	4
Zhou and Chen[84]	4	6	ND	ND	3
Spargias et al[85]	11	23	0	0	5
Line 4: drugs: statins versus placebo					
Toso et al[86]	15	16	0	0	3
Acikel et al[87]	0	1	ND	ND	3
Han et al[88]	34	58	0	2	3
PROMISS trial[89]	3	4	0	1	5
PRATO-ACS trial[90]	17	38	0	2	3
Li et al[91]	2	13	ND	ND	5
Ozhan et al[92]	2	7	ND	ND	2
ARMYDA-CIN[93]	6	16	ND	ND	5
Quintavalle et al[94]	9	37	ND	ND	3
Bidram et al[95]	1	2	ND	ND	3
Abaci et al[96]	6	9	0	0	3
Shehata et al[97]	5	13	0	0	4
Drugs: adenosine antagonists versus placebo					
Bilasy et al[98]	0	6	ND	ND	4
Kinbara et al[66]	0	4	0	0	2
Rohani[99]	4	6	ND	ND	2
Abizaid et al[100]	7	6	1	0	4
Baskurt et al[45]	0	7	0	0	3

(continued)

Table 2. (continued)

Author	Incidence of CIN		Incidence of Hemodialysis		Jadad Score
	SG	CG	SG	CG	
Huber et al[101]	2	10	N.D	ND	2
Kapoor et al[102]	1	11	0	0	2
Matejka et al[103]	3	0	ND	ND	4
Malhis et al[104]	2	12	1	0	2
Arabmomeni et al[79]	2	7	ND	ND	5
Line 6: drugs: furosemide (loop diuretic) versus placebo					
Gu et al[105]	34	62	1	1	3
Majumdar et al[106]	23	13	5	4	5
Marenzi et al[107]	4	15	1	3	4
Shemirani and Pourrmoghaddas[108]	1	2	ND	ND	3
Solomon et al[109]	10	3	1	0	3
Line 7: drugs: ACEI versus placebo					
Oguzhan et al[110]	8	3	0	0	3
Gupta et al[111]	2	10	0	0	2
Toprak et al[112]	5	1	ND	ND	1
Hashemi et al[113]	5	5	ND	ND	3
Shemirani and Pourrmoghaddas[108]	2	3	ND	ND	3
Li et al[114]	2	6	ND	ND	3
Rosenstock et al[115]	7	4	0	0	3
Wolak et al[116]	1	5	ND	ND	2
Bainey et al[117]	19	11	4	0	4

Abbreviations: ACEI, angiotensin converting enzyme inhibitors; CG, control group; CIN, contrast-induced nephropathy; NAC, *N*-acetylcysteine; ND, no data; SG, study group.

allocated to the loop diuretic group and 654 to the placebo group. The overall incidence of CIN was 12.9%, ranging from 2.5% to 39.1% accounting for 11.25% in the loop diuretic group and 14.52% in the placebo group (Table 2). Pooled treatment effect analysis revealed that loop diuretics did not have the ability to reduce the incidence of CIN with an OR of 0.97 (95% CI: 0.33-2.85; $P = .9$) using the random-effects model (Figure 6 and Supplemental Figure 1N for fixed model). Also, there was a significant heterogeneity among the studies analyzed ($\chi^2 = 21.99$, $I^2 = 81.8\%$). There was no publication bias and risk of small study effects among the included RCTs (Begg test, $P = .327$; Supplemental Figure 2F). From the 5 included studies, 4 RCTs reported data on the incidence of the need for hemodialysis. Pooled analysis reported that the incidence of hemodialysis was statistically similar in loop diuretic and placebo groups with an OR of 1.0 (95% CI: 0.37-2.67; $P = .9$) using the fixed-effects model (Supplemental Figure 1O and P for fixed model and for random model, respectively). There was no heterogeneity among the studies ($\chi^2 = 1.7$, $I^2 = 0\%$).

Angiotensin-converting enzyme inhibitor versus placebo. A total of 1041 patients were included from 9 RCTs. Patient populations from RCTs ranged from 71 to 208 (Table 1). Of the 1041 patients, 530 were allocated to the ACEI group and 511 to the placebo group. The overall incidence of CIN was 9.51%, ranging from 4.1% to 16.9%, whereas CIN was observed in 9.62% in the ACEI group and in 9.39% in the placebo group (Table 2). Pooled treatment effect analysis revealed that ACEI could not reduce the incidence of CIN with an OR of 1.06 (95% CI: 0.69-1.61; $P = .8$) using the fixed-effects model (Figure 7 and Supplemental Figure 1Q for random model). There was no significant heterogeneity among the studies ($\chi^2 = 13.9$, $I^2 = 42.7\%$). There was no publication bias and risk of small study effects among the included RCTs (Begg test, $P = .677$; Supplemental Figure 2G). From 9 included studies about ACEI versus placebo, 4 RCTs reported data on the incidence of the need for hemodialysis. In fact, 3 of the 4 comparisons did not present any hemodialysis in 2 comparative arms; therefore, no meta-analysis on the incidence of hemodialysis was conducted due to insufficient number of studies (only 1 study).

Correlation Between CIN and Hemodialysis

In order to explore whether there is a correlation between CIN and hemodialysis, the Pearson test was used. There was a significant correlation between the 2 clinical variables (correlation coefficient: 0.370, $P = .003$).

Meta-Regression

A meta-regression analysis was conducted to determine whether there was any association between rate of CIN and several variables such as type of contrast agent, history of CKD, history of diabetes mellitus, baseline serum creatinine, and mean age of patients. Overall, there was no significant association detected when considering contrast agent ($P = .78$), history of kidney disease ($P = .15$), history of diabetes

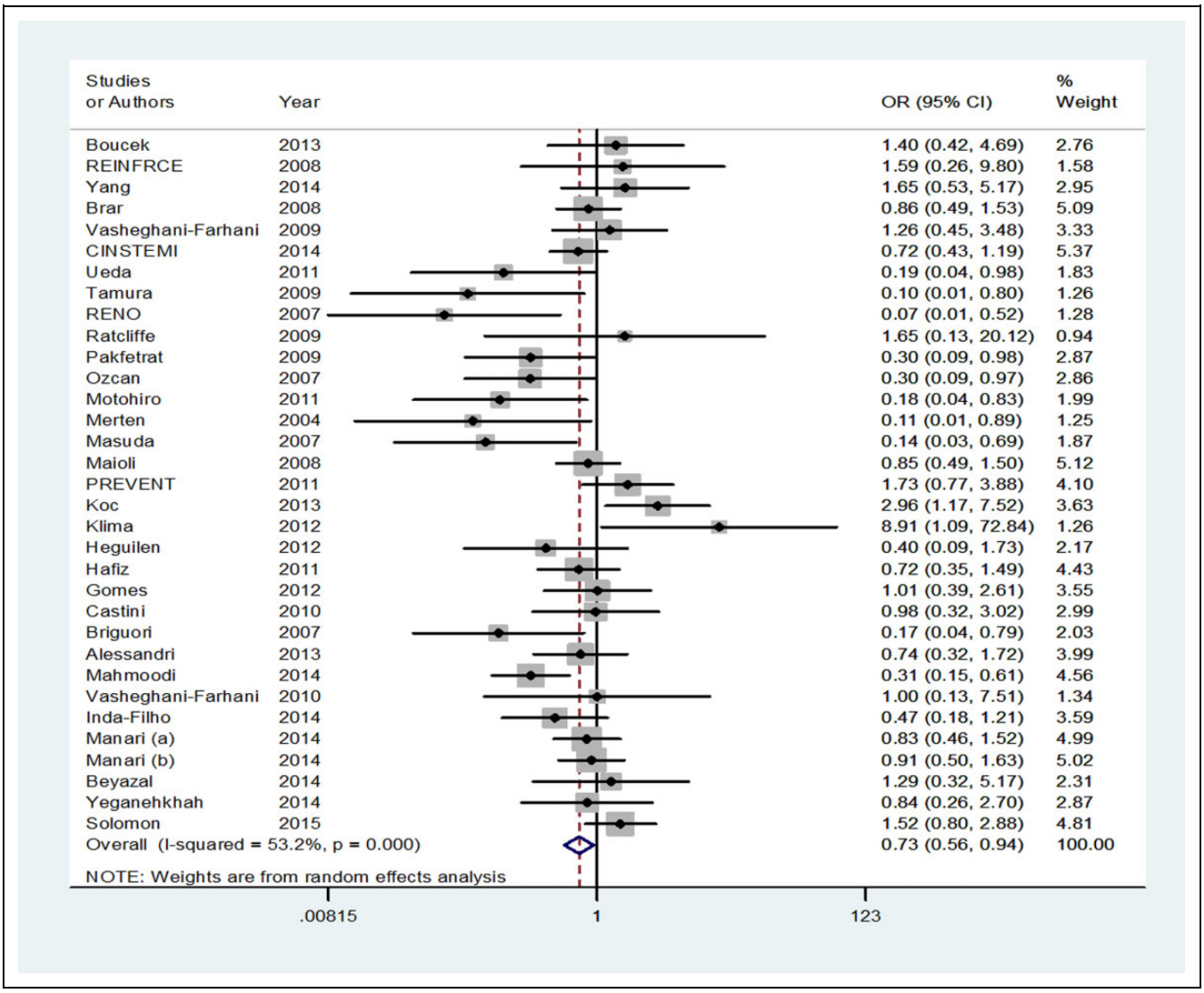

Figure 1. Forest plot of odds ratio (OR) for effects of normal saline versus sodium bicarbonate on contrast-induced nephropathy.

mellitus ($P = .47$), baseline serum creatinine ($P = .51$), mean age of patients ($P = .31$), and quality of included studies ($P = .53$) among all studies.

Discussion

The increasing incidence of ischemic heart disease has accentuated the importance of timely diagnosis and appropriate treatment.[1] Coronary angiography is a commonly used diagnostic procedure that is commonly performed worldwide.[1] Acute kidney injury following the use of radiocontrast agents is an important complication of coronary angiography.[1,2] The incidence of CIN can lead to renal failure, need for hemodialysis, increased morbidity, longer hospital stay, greater cost of treatment, and higher mortality.[1,2] Although sufficient hydration and consumption of drugs with renoprotective effects can decrease the incidence of CIN, there are still various controversies regarding the prevention and treatment of CIN. In this comprehensive study, we conducted a parallel meta-analysis and systematic review to evaluate various prophylactic effects on the incidence of CIN after coronary angiography.

Regarding the role of oxygen-free radicals as an important part of the pathogenesis of CIN, SB with its alkali nature might have a prophylactic effect on CIN. Considering hydration, we tried to compare the effects of hydration with NS and SB. The results of our study revealed that SB had noticeably more ability to decrease the incidence of CIN compared with NS. Subgroup analysis indicated that prophylactic effects of SB against CIN were higher when radiocontrast angiography was performed using low-osmolarity radiocontrast agents. According to the results of the present study, hydration with SB is also more beneficial than NS in patients requiring emergency coronary angiography. This is also consistent with the study by Jang et al who reported that hydration with SB is clearly better than NS, particularly for patients undergoing emergency angiography.[118] Our previous study showed that despite more

Table 3. Subgroup Analysis for Clinical Outcomes.

Subgroup	Studies (N)	Odd ratio (95% CI)	*P*-value
SGA for CIN and hydration according to OR			
Radio-contrast			
Low osmolality	20	0.59 (0.47-0.74)	0.001
Iso-osmolality	9	0.83 (0.68-1.10)	0.2
High osmolality	1	0.47 (0.13-1.20)	0.1
Combined	–	–	–
ND	3	1.16 (0.81-1.65)	0.4
Type of coronary angiography			
Elective	21	0.85 (0.69-1.06)	0.1
Emergency	6	0.65 (0.46-0.84)	0.002
Both	1	0.86 (0.48-1.52)	0.6
ND	5	0.58 (0.38-0.88)	0.01
SGA for CIN and NAC according to OR			
Radio-contrast			
Low osmolality	32	0.61 (0.52-0.73)	0.001
Iso-osmolality	10	0.93 (0.72-1.21)	0.6
High osmolality	1	0.61 (0.25-1.46)	0.2
Combined	5	0.98 (0.81-1.17)	0.8
ND	–	–	–
Type of coronary angiography			
Elective	34	0.79 (0.69-0.90)	0.001
Emergency	7	0.87 (0.67-1.13)	0.3
Both	1	0.27 (0.07-1.06)	0.06
ND	6	0.65 (0.44-0.96)	0.03
SGA for CIN and vitamin C according to OR			
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
ND	–	–	–
Type of coronary angiography			
Elective	5	0.68 (0.47-0.99)	0.04
Emergency	–	–	–
Both	1	0.30 (0.09-1.0)	0.06
ND	1	0.72 (0.19-2.67)	0.6
SGA for CIN and statins according to OR			
Radio-contrast			
Low osmolality	6	0.34 (0.20-0.56)	0.001
Iso-osmolality	6	0.48 (0.37-0.64)	0.001
High osmolality	–	–	–
Combined	–	–	–
ND	–	–	–
Type of coronary angiography			
Elective	7	0.45 (0.30-0.67)	0.001
Emergency	3	0.34 (0.21-0.55)	0.001
Both	1	0.57 (0.37-0.88)	0.01
ND	1	0.31 (0.06-1.55)	0.1
Type of statin			
Atorvastatin	8	0.36 (0.24-0.52)	0.001
Rosuvastatin	3	0.52 (0.37-0.72)	0.001
Simvastatin	1	0.74 (0.16-3.97)	0.7
SGA for CIN and Adenosine antagonists according to OR			
Radio-contrast			
Low osmolality	8	0.27 (0.15-0.47)	0.001
Iso-osmolality	1	6.23 (0.30-127.1)	0.2
High osmolality	1	0.06 (0.008-0.53)	0.01
Combined	–	–	–
ND	–	–	–
Type of coronary angiography			
Elective	7	0.27 (0.11-0.47)	0.001
Emergency	–	–	–
Both	1	6.23 (0.30-127.1)	0.2
ND	2	0.34 (0.11-0.88)	0.02
Type of adenosine antagonist			
Theophylline	7	0.19 (0.10-0.37)	0.001
Aminophylline	3	0.62 (0.26-1.47)	0.2
SGA for CIN and loop diuretic according to OR			
Radio-contrast			
Low osmolality	2	0.93 (0.50-1.7)	0.8
Iso-osmolality	–	–	–
High osmolality	–	–	–
Combined	1	5.55 (1.31-23.4)	0.02
ND	2	0.52 (0.34-0.81)	0.004
Type of coronary angiography			
Elective	2	2.06 (0.93-4.56)	0.07
Emergency	–	–	–
Both	2	0.46 (0.30-0.70)	0.001
ND	1	5.55 (1.31-23.4)	0.02
SGA for CIN and ACEI according to OR			
Radio-contrast			
Low osmolality	4	1.74 (0.97-3.11)	0.06
Iso-osmolality	1	0.97 (0.27-3.47)	0.9
High osmolality	–	–	–
Combined	–	–	–
ND	4	0.46 (0.21-1.01)	0.05
Type of coronary angiography			
Elective	6	1.55 (0.92-2.61)	0.09
Emergency	–	–	–
Both	–	–	–
ND	3	0.43 (0.19-0.97)	0.04
Type of ACEI			
Captopril	4	0.68 (0.32-1.41)	0.3
Others	5	1.32 (0.78-2.23)	0.2

Abbreviations: ACEIs, angiotensin converting enzyme inhibitors; CI, confidence interval; CIN, contrast-induced nephropathy; NAC, *N*-acetylcysteine; ND, no data; OR, odds ratio; SGA, subgroup analysis.

prophylactic effects, SB was not associated with major adverse cardiovascular events compared with NS; therefore, we recommend hydration using SB, where only a monitoring of potassium level and acid–base balance is required.[119] The current analysis with larger studies and patient cohorts enrolled the preference of using SB compared with NS is even more enhanced, although both hydration strategies appear to have the same effect on preventing the need for hemodialysis.

Since the toxicity of renal cells and oxygen-free radicals are known as important pathogens in the incidence of CIN, using antioxidant supplements can possibly have protective effects on renal cells.[120,121] Cellular damage is mediated by an alteration in the antioxidant status, which increases the concentration of reactive oxygen species in oxidative stress. Oxidative stress mediates a wide spectrum of renal impairments from acute renal failure, obstructive nephropathy, to chronic renal failure and hemodialysis.[120,121] In terms of various supplementations, we examined the effects of the commonly used antioxidants,

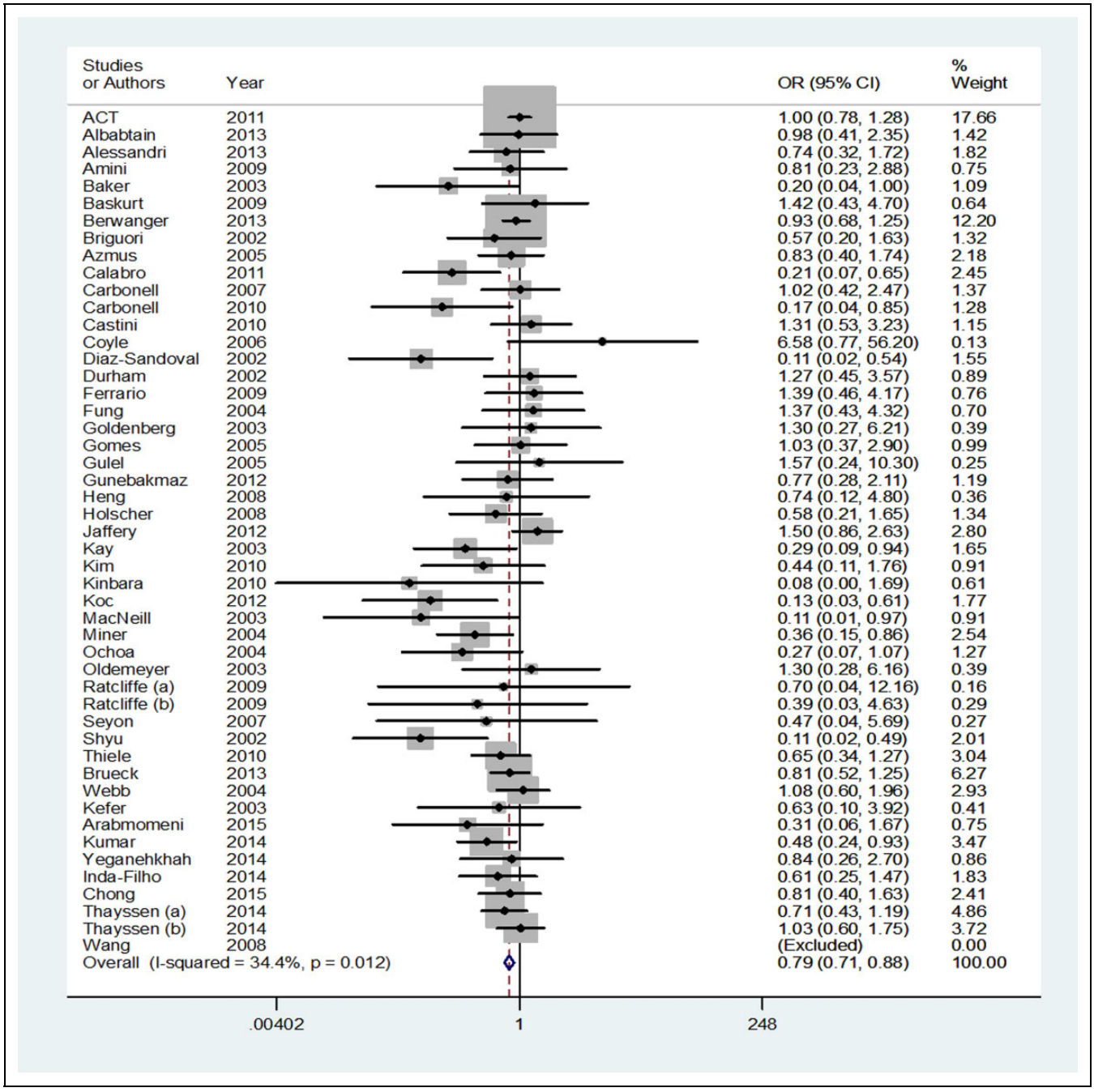

Figure 2. Forest plot of odds ratio (OR) for effects of N-acetylcysteine (NAC) on contrast-induced nephropathy.

NAC, and ascorbic acid. The results indicated that administration of NAC in candidates for angiography could significantly reduce the incidence of CIN, though without any significant effect on the need for hemodialysis. The present study showed that administration of vitamin C could clearly reduce the incidence of CIN, whereas its renoprotective effects were even better when applied to patients undergoing angiography using low-osmolarity radiocontrast agents. Albabtain et al[42] also found that administration of vitamin C, NAC, and a combination of both could prevent CIN, although their effects were nothing more than hydration. They also believed that using antioxidants in patients undergoing coronary angiography was complication free. Therefore, in addition to prophylactic effects of NAC and vitamin C against CIN, their safety can justify their usage as a standard treatment.[42]

Statins are widely administered for primary and secondary prevention of coronary artery disease. They are able to reduce oxygen-free radicals and inflammation, upregulate inhibitors of transforming growth factor-β signaling, and decrease renal fibrosis.[122,123] The results of the present study revealed that statins could also significantly reduce the incidence of CIN while having a slight trend toward decreasing the incidence

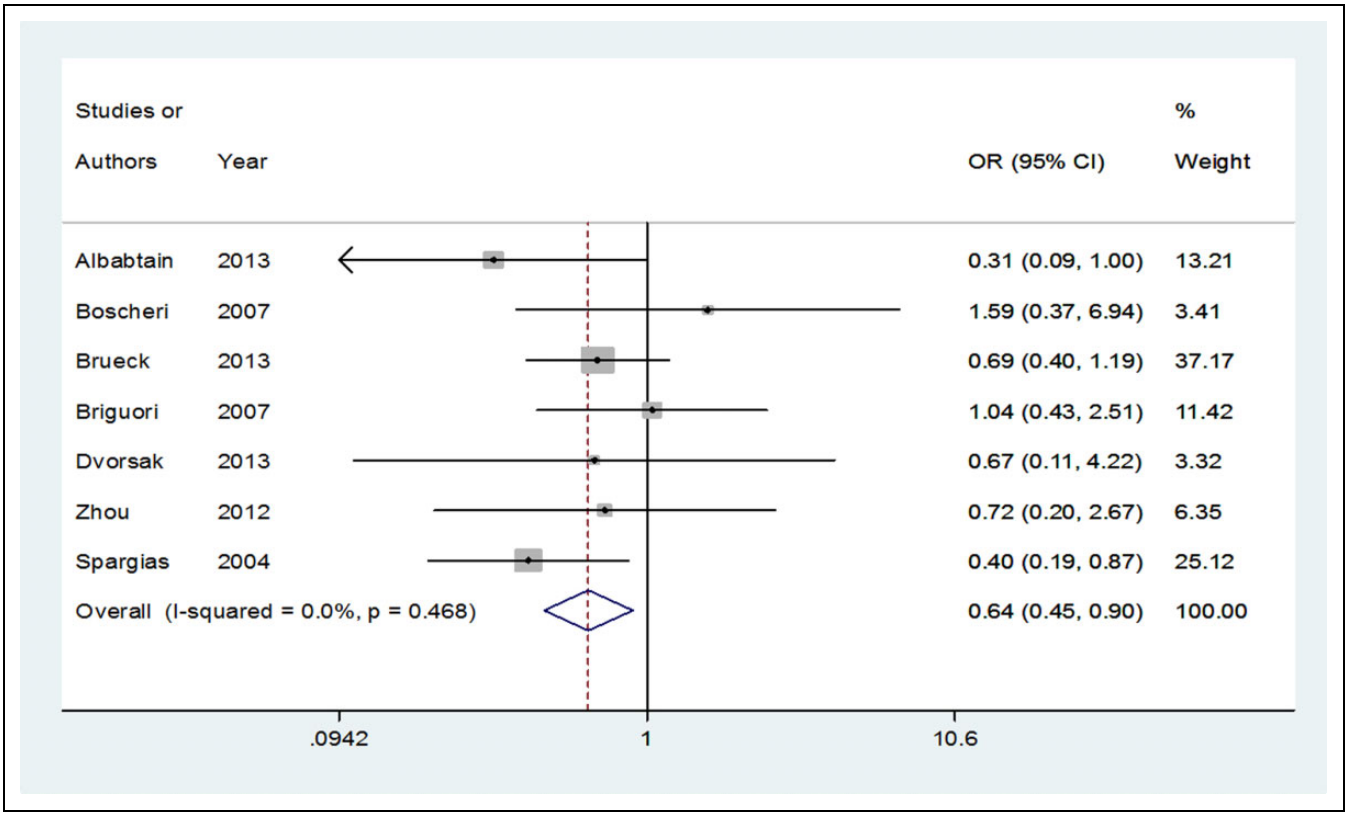

Figure 3. Forest plot of odds ratio (OR) for effects of vitamin C on contrast-induced nephropathy.

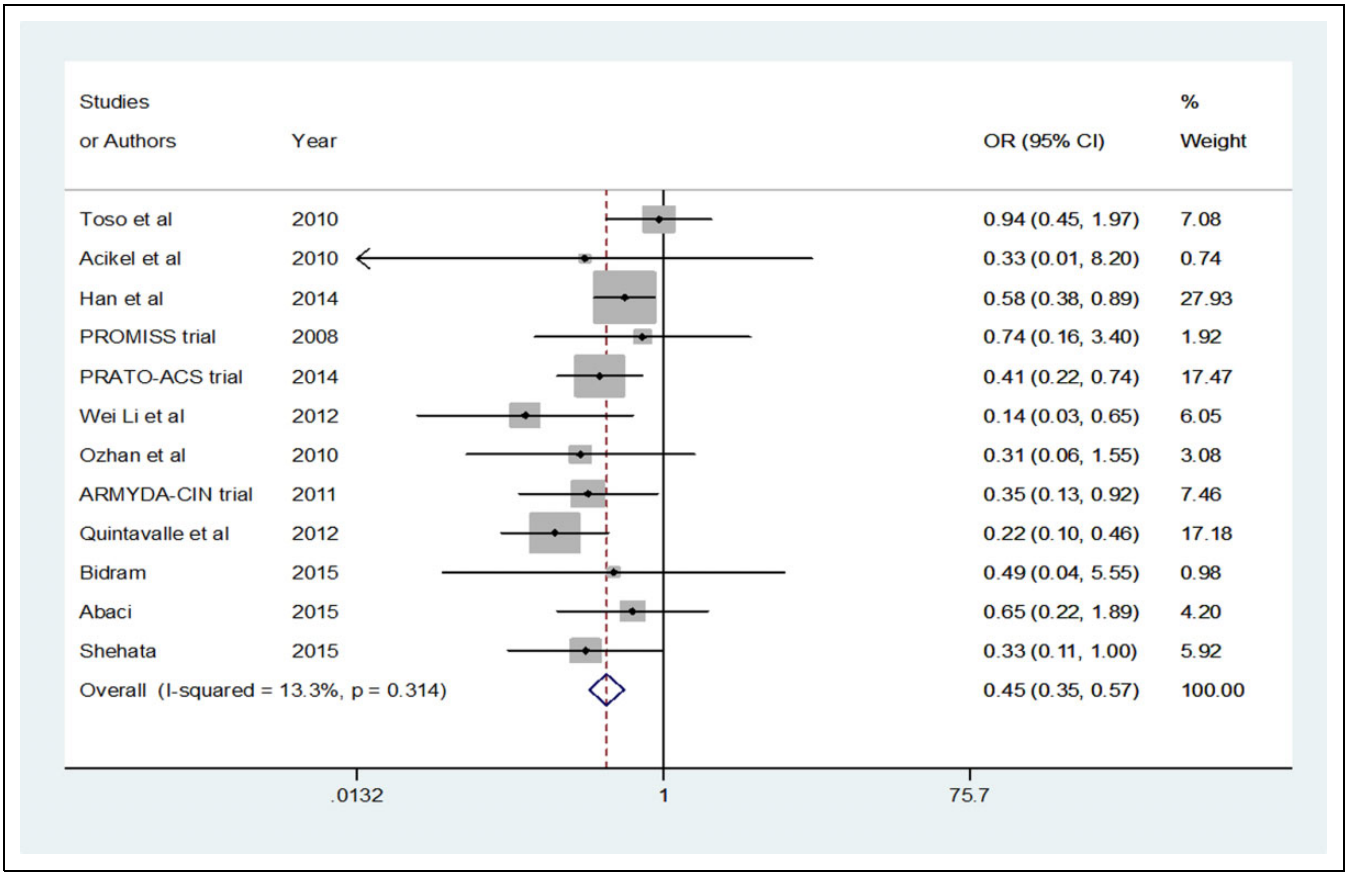

Figure 4. Forest plot of odds ratio (OR) for effects of statins on contrast-induced nephropathy.

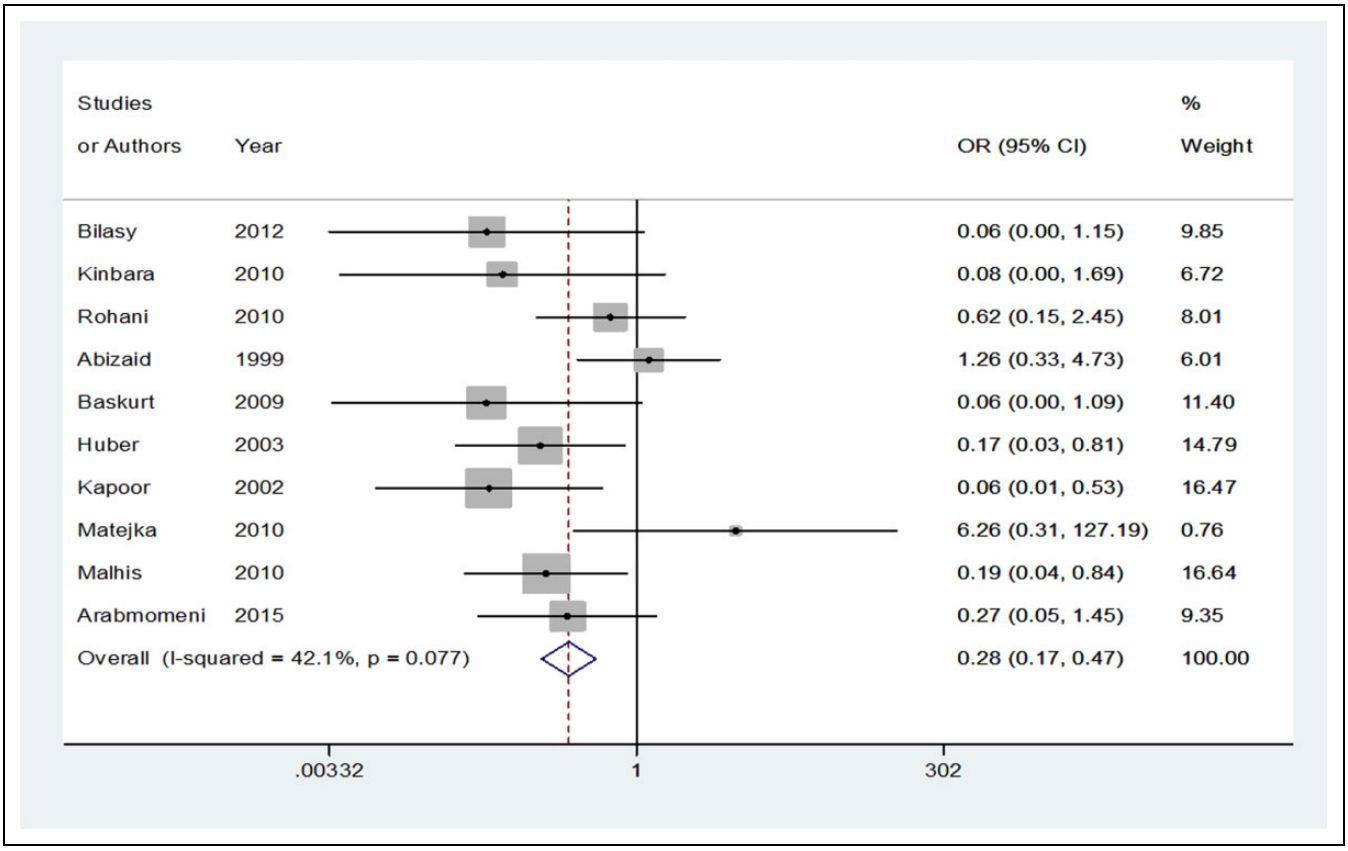

Figure 5. Forest plot of odds ratio (OR) for effects of adenosine antagonists on contrast-induced nephropathy.

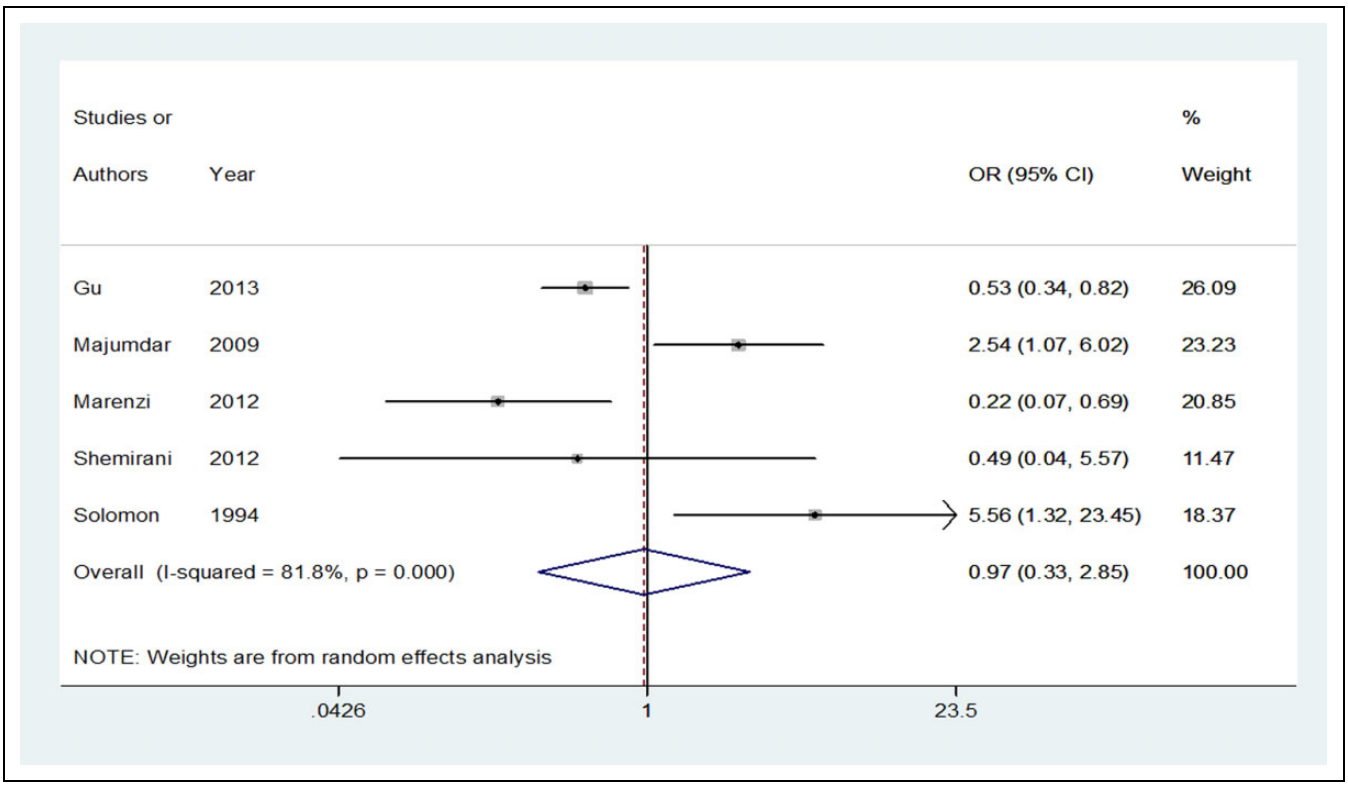

Figure 6. Forest plot of odds ratio (OR) for effects of loop diuretic on contrast-induced nephropathy.

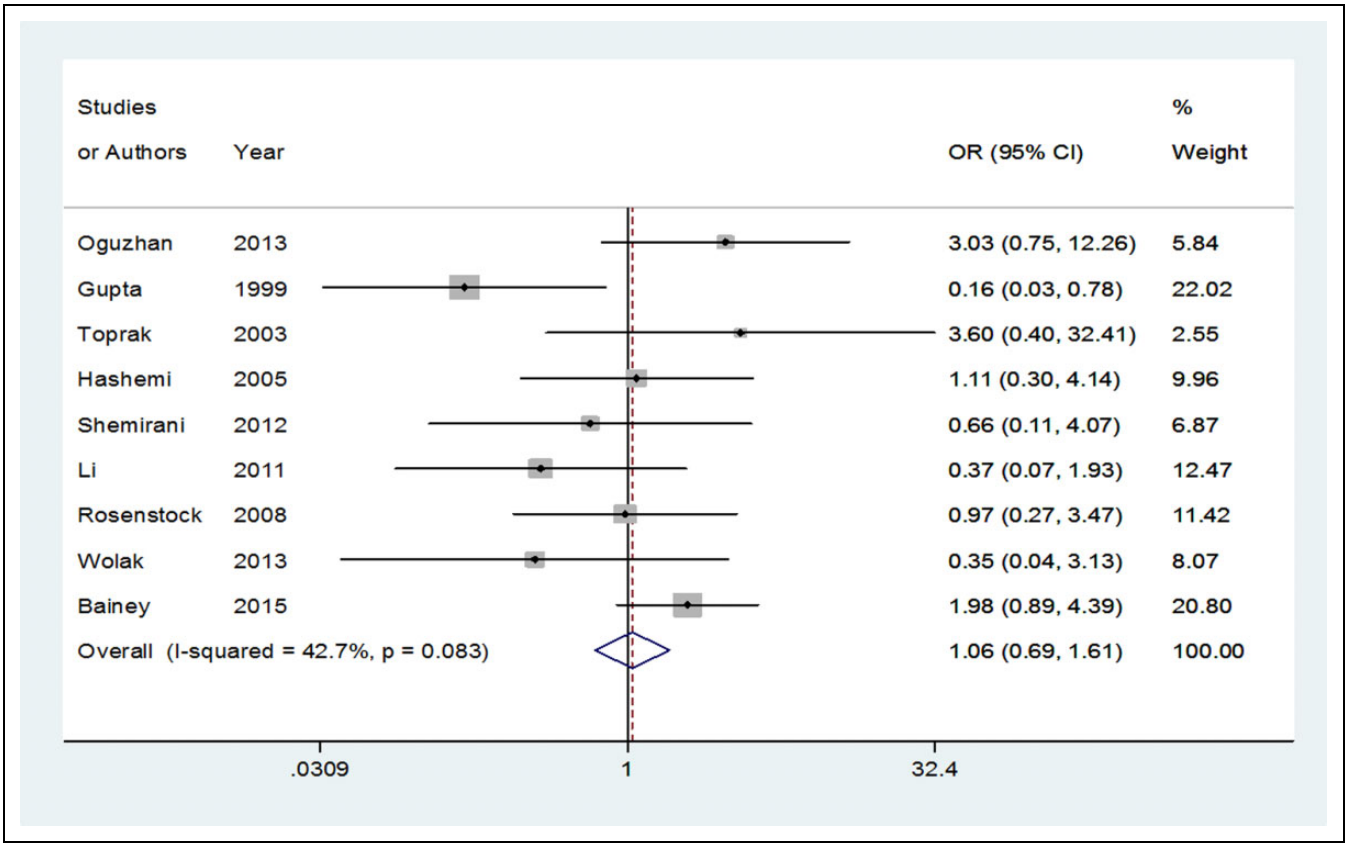

Figure 7. Forest plot of odds ratio (OR) for effects of angiotensin-converting enzyme inhibitors (ACEI) on contrast-induced nephropathy.

of the need for hemodialysis. According to our subgroup analysis, statins showed noticeable prophylactic effects on reducing the incidence of CIN in angiography using low- and iso-osmolarity radiocontrast agents and, on the other hand, in both elective and emergency angiography. Lee et al confirmed that using statins at a daily dosage of > 40 mg could significantly reduce CIN.[124] Also, they reported no statistically meaningful difference in muscle pain and disorders, abnormality of liver function, gastrointestinal disease, edema, and rash between the statin and placebo groups.[124] Singh et al reported that statins could decrease CIN and should be used in all cases of coronary angiography and interventional procedures using radiocontrast agents.[125] In addition to the above-mentioned administration for primary and secondary prevention of coronary artery disease, previous literature reported on further beneficial effects of statins in patients undergoing PCI, beyond cholesterol lowering. Such cholesterol-independent or ''pleiotropic'' effects may improve endothelial function, leading to the stability of atherosclerotic plaques and less oxidative stress. Moreover, inflammatory and thrombogenic response can be inhibited by this mechanism facilitating better prognosis.[122] Nevertheless, further studies are required for the determination of the pretreatment dosing, regimen, and duration of statin application.[125]

Animal models indicated that adenosine may mediate renal vasoconstriction after administration of radiocontrast agents.[126] Adenosine receptor antagonists, such as theophylline and aminophylline, are effective in preserving glomerular filtration rate following injections of radiocontrast agents.[126-128] The present study found that using AAs in patients undergoing coronary angiography could greatly reduce CIN, while having no effect on the need for hemodialysis. Interestingly, our subgroup analysis revealed that the renoprotective effects of AAs were only related to theophylline, whereas aminophylline was not associated with such effects. Also, AAs were found to be more effective in reducing CIN when used in angiography with low-osmolarity radiocontrast agents and in elective angiography.

Similar to our results, Dai et al showed in their meta-analysis of RCTs (published in 2012) that theophylline could considerably reduce the incidence of CIN and had modest improvement in renal function.[129] However, they noted that administration of theophylline in patients with baseline serum creatinine >1.5 mg/dL was not associated with beneficial effects in terms of protection against CIN.[129]

The ACEI are generally used in patients with cardiovascular diseases including hypertension, CAD, heart failure, and cardiomyopathy, as well as renal diseases, such as diabetic nephropathy and chronic kidney disease.[130] Loop diuretics, such as furosemide, can theoretically lower the risk of fluid overload, protect renal tissue, and reduce the incidence of CIN through volume expansion. However, practically, there is a notable controversy in terms of clinical effects of furosemide

on the incidence of CIN.[131] The findings of our study showed that treatment with furosemide did not lead to a decreased incidence of CIN and renal failure requiring hemodialysis. Also, a relatively common finding in patients treated with a loop or thiazide diuretics, which may lead to gouty arthritis over a period of time, is hyperuricemia. Dependent on the dose administered, diuretics reduce urate excretion by both directly and indirectly increasing urate reabsorption and decreasing urate secretion.[132] However, treatment of asymptomatic hyperuricemia is not necessary. If diuretic-induced gout occurs, it is usually treated with a urate-lowering drug such as allopurinol.[133] A subgroup analysis of our study indicated that ACEI in patients undergoing elective angiography, even if performed using low-osmolarity radiocontrast agents, had even a trend to increase the incidence of CIN.

In the present study, we tried to examine different therapeutic strategies to prevent CIN in patients undergoing coronary angiography. In general, according to these results, several renoprotective therapeutic strategies can be applied to reduce the incidence of CIN, such as hydration that is considered the first line of preventing CIN with more renoprotective effects when using SB as compared with NS. On the other hand, being complication free and safe with a great ability in reducing the incidence of CIN, administration of vitamin C and NAC antioxidant supplementations is highly recommended for patients undergoing angiography. In terms of further drugs examined in this study, statins and theophylline may also be able to decrease the incidence of CIN, whereas furosemide and ACEI did not show such effect. Subgroup analyses suggested that therapeutic effects of sufficient hydration with SB, effects of NAC and vitamin C supplementations, as well as statin and theophylline therapy may only have beneficial effects when angiography is carried out using low-osmolarity radiocontrast agents. Also, for cases of emergency angiography, the best possible preventive strategy seems to be hydration with SB and using low-osmolarity radiocontrast agents. Due to the fact that CIN is a multifactorial adverse event, more optimal outcomes might be achieved by considering multiple prevention strategies. In many centers for the diagnosis and treatment of cardiovascular diseases, hydration is still solely performed to prevent CIN. Considering combined prophylactic strategies that might improve outcome as shown in our analysis, such as hydration using SB (while monitoring acid–base balance and potassium level) accompanied by the administration of NAC or vitamin C supplements as well as statins and theophylline before and after injection of radiocontrast agents, may prove promising. However, such combinations should be evaluated in trials before application in clinical practice.

Limitations

The Jadad score used in our analysis might be less adequate for validity appraisal, whereas Cochrane risk of bias might be more suitable for RCTs.[134] Although in most studies included in the present analysis renal failure was defined as new-onset hemodialysis during hospitalization after angiography, such definition may ignore a significant proportion of patients with considerable renal failure, however not yet advanced enough for the need of hemodialysis. Thus, further research should pay more attention to the evaluation of the incidence of renal failure in patients with or without the need of hemodialysis. Also, the duration of follow-up should be extended in the future studies.

Authors' Note

All authors contributed to: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and (3) final approval of the version to be published.

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Supplemental Material

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References

1. Pavlidis AN, Jones DA, Sirker A, Mathur A, Smith EJ. Prevention of contrast-induced acute kidney injury after percutaneous coronary intervention for chronic total coronary occlusions. *Am J Cardiol*. 2015;115(6):844-851. doi:10.1016/j.amjcard.2014.12.047.
2. Narula A, Mehran R, Weisz G, et al. Contrast-induced acute kidney injury after primary percutaneous coronary intervention: results from the HORIZONS-AMI substudy. *Eur Heart J*. 2014;35(23):1533-1540. doi:10.1093/eurheartj/ehu063.
3. Hoshi T, Sato A, Kakefuda Y, et al. Preventive effect of statin pretreatment on contrast-induced acute kidney injury in patients undergoing coronary angioplasty: propensity score analysis from a multicenter registry. *Int J Cardiol*. 2014;171(2):243-249. doi:10.1016/j.ijcard.2013.12.017.
4. Azzalini L, Spagnoli V, Ly HQ. Contrast-induced nephropathy: From pathophysiology to preventive strategies. *Can J Cardiol*. 2016;32(2):247-255.
5. Andreucci M, Faga T, Pisani A, Sabbatini M, Russo D, Michael A. Prevention of contrast-induced nephropathy through a knowledge of its pathogenesis and risk factors. *Sci World J*. 2014;2014:823169. doi:10.1155/2014/823169.
6. Solomon R, Deray G. How to prevent contrast-induced nephropathy and manage risk patients: practical recommendations. *Kidney Int*. 2006;69(100):S51-S53.
7. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17(1):1-12.
8. Boucek P, Havrdova T, Oliyarnyk O, et al. Prevention of contrast-induced nephropathy in diabetic patients with impaired renal function: a randomized, double blind trial of sodium

bicarbonate versus sodium chloride-based hydration. *Diabetes Res Clin Pract* 2013;101:303-8
9. Brar SS, Shen AY, Jorgensen MB, et al. Sodium bicarbonate vs sodium chloride for the prevention of contrast medium-induced nephropathy in patients undergoing coronary angiography: a randomized trial. *JAMA*. 2008;300(9):1038-1046.
10. Alessandri N, Lanzi L, Garante CM, et al. Prevention of acute renal failure post-contrast imaging in cardiology: a randomized study. *Eur Rev Med Pharmacol Sci*. 2013;17(suppl 1):13-21.
11. Adolph E, Holdt-Lehmann B, Chatterjee T, et al. Renal Insufficiency Following Radiocontrast Exposure Trial (REINFORCE): a randomized comparison of sodium bicarbonate versus sodium chloride hydration for the prevention of contrast-induced nephropathy. *Coron Artery Dis*. 2008;19(6):413-419.
12. Yang K, Liu W, Ren W, Lv S. Different interventions in preventing contrast-induced nephropathy after percutaneous coronary intervention. *Int Urol Nephrol*. 2014;46(9):1801-1807.
13. Vasheghani-Farahani A, Sadigh G, Kassaian SE, et al. Sodium bicarbonate in preventing contrast nephropathy in patients at risk for volume overload: a randomized controlled trial. *J Nephrol*. 2010;23(2):216-223.
14. Vasheghani-Farahani A, Sadigh G, Kassaian SE, et al. Sodium bicarbonate plus isotonic saline versus saline for prevention of contrast-induced nephropathy in patients undergoing coronary angiography: a randomized controlled trial. *Am J Kidney Dis*. 2009;54(4):610-618.
15. Thayssen P, Lassen JF, Jensen SE, et al. Prevention of contrast-induced nephropathy with N-acetylcysteine or sodium bicarbonate in patients with ST-segment-myocardial infarction: a prospective, randomized, open-labeled trial. *Circ Cardiovasc Interv*. 2014;7(2):216-224.
16. Ueda H, Yamada T, Masuda M, et al. Prevention of contrast-induced nephropathy by bolus injection of sodium bicarbonate in patients with chronic kidney disease undergoing emergent coronary procedures. *Am J Cardiol*. 2011;107(8):1163-1167.
17. Tamura A, Goto Y, Miyamoto K, et al. Efficacy of single-bolus administration of sodium bicarbonate to prevent contrast-induced nephropathy in patients with mild renal insufficiency undergoing an elective coronary procedure. *Am J Cardiol*. 2009;104(7):921-925.
18. Shavit L, Korenfeld R, Lifschitz M, Butnaru A, Slotki I. Sodium bicarbonate versus sodium chloride and oral N-acetylcysteine for the prevention of contrast-induced nephropathy in advanced chronic kidney disease. *J Interv Cardiol*. 2009;22(6):556-563.
19. Recio-Mayoral A, Chaparro M, Prado B, et al. The reno-protective effect of hydration with sodium bicarbonate plus N-acetylcysteine in patients undergoing emergency percutaneous coronary intervention: the RENO Study. *J Am Coll Cardiol*. 2007;49(12):1283-1288.
20. Ratcliffe JA, Thiagarajah P, Chen J, et al. Prevention of contrast-induced nephropathy: a randomized controlled trial of sodium bicarbonate and N-acetylcysteine. *Int J Angiol*. 2009;18(4):193-197.
21. Pakfetrat M, Nikoo MH, Malekmakan L, et al. A comparison of sodium bicarbonate infusion versus normal saline infusion and its combination with oral acetazolamide for prevention of contrast-induced nephropathy: a randomized, double-blind trial. *Int Urol Nephrol*. 2009;41(3):629-634.
22. Ozcan EE, Guneri S, Akdeniz B, et al. Sodium bicarbonate, N-acetylcysteine, and saline for prevention of radiocontrast-induced nephropathy. A comparison of 3 regimens for protecting contrast-induced nephropathy in patients undergoing coronary procedures. A single-center prospective controlled trial. *Am Heart J*. 2007;154(3):539-544.
23. Motohiro M, Kamihata H, Tsujimoto S, et al. A new protocol using sodium bicarbonate for the prevention of contrast-induced nephropathy in patients undergoing coronary angiography. *Am J Cardiol*. 2011;107(11):1604-1608.
24. Merten GJ, Burgess WP, Gray LV, et al. Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. *JAMA*. 2004;291(19):2328-2334.
25. Masuda M, Yamada T, Mine T, et al. Comparison of usefulness of sodium bicarbonate versus sodium chloride to prevent contrast-induced nephropathy in patients undergoing an emergent coronary procedure. *Am J Cardiol*. 2007;100(5):781-786.
26. Maioli M, Toso A, Leoncini M, et al. Sodium bicarbonate versus saline for the prevention of contrast-induced nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. *J Am Coll Cardiol*. 2008;52(8):599-604.
27. Lee SW, Kim WJ, Kim YH, et al. Preventive strategies of renal insufficiency in patients with diabetes undergoing intervention or arteriography (the PREVENT trial). *Am J Cardiol*. 2011;107(10):1447-1452.
28. Koc F, Ozdemir K, Altunkas F, et al. Sodium bicarbonate versus isotonic saline for the prevention of contrast-induced nephropathy in patients with diabetes mellitus undergoing coronary angiography and/or intervention: a multicenter prospective randomized study. *J Investig Med*. 2013;61(5):872-877.
29. Klima T, Christ A, Marana I, et al. Sodium chloride vs. sodium bicarbonate for the prevention of contrast medium-induced nephropathy: a randomized controlled trial. *Eur Heart J*. 2012;33(16):2071-2079.
30. Heguilén RM, Liste AA, Payaslian M, Ortemberg MG, Albarracín LM, Bernasconi AR. N-acethyl-cysteine reduces the occurrence of contrast-induced acute kidney injury in patients with renal dysfunction: a single-center randomized controlled trial. *Clin Exp Nephrol*. 2013;17(3):396-404.
31. Hafiz AM, Jan MF, Mori N, et al. Prevention of contrast-induced acute kidney injury in patients with stable chronic renal disease undergoing elective percutaneous coronary and peripheral interventions: randomized comparison of two preventive strategies. *Catheter Cardiovasc Interv*. 2012;79(6):929-937.
32. Gomes VO, Lasevitch R, Lima VC, et al. Hydration with sodium bicarbonate does not prevent contrast nephropathy: a multicenter clinical trial. *Arq Bras Cardiol*. 2012;99(6):1129-1134.
33. Castini D, Lucreziotti S, Bosotti L, et al. Prevention of contrast-induced nephropathy: a single center randomized study. *Clin Cardiol*. 2010;33(3):E63-E68.
34. Briguori C, Airoldi F, D'Andrea D, et al. Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAL): a randomized comparison of 3 preventive strategies. *Circulation*. 2007;115(10):1211-1217.

35. Mahmoodi K, Sohrabi B, Ilkhchooyi F, Malaki M, Khaniani ME, Hemmati M. The efficacy of hydration with normal saline versus hydration with sodium bicarbonate in the prevention of contrast-induced nephropathy. *Heart Views*. 2014;15(2):33-36.
36. Inda-Filho AJ, Caixeta A, Manggini M, Schor N. Do intravenous N-acetylcysteine and sodium bicarbonate prevent high osmolal contrast-induced acute kidney injury? A randomized controlled trial. *PLoS One*. 2014;9(9):e107602. doi:10.1371/journal.pone.0107602.
37. Manari A, Magnavacchi P, Puggioni E, et al. Acute kidney injury after primary angioplasty: effect of different hydration treatments. *J Cardiovasc Med (Hagerstown)*. 2014;15(1):60-67.
38. Beyazal H, Caliskan Z, Utaç C. Comparison of effects of isotonic sodium chloride with diltiazem in prevention of contrast-induced nephropathy. *Ren Fail*. 2014;36(3):351-355.
39. Yeganehkhah MR, Iranirad L, Dorri F, et al. Comparison between three supportive treatments for prevention of contrast-induced nephropathy in high-risk patients undergoing coronary angiography. *Saudi J Kidney Dis Transpl*. 2014;25(6):1217-1223.
40. Solomon R, Gordon P, Manoukian SV, et al. Randomized trial of bicarbonate or saline study for the prevention of contrast-induced nephropathy in patients with CKD. *Clin J Am Soc Nephrol*. 2015;10(9):1519-1524.
41. ACT Investigators. Acetylcysteine for prevention of renal outcomes in patients undergoing coronary and peripheral vascular angiography: main results from the randomized Acetylcysteine for Contrast-induced nephropathy Trial (ACT). *Circulation*. 2011;124(11):1250-1259.
42. Albabtain MA, Almasood A, Alshurafah H, Alamri H, Tamim H. Efficacy of ascorbic acid, N-acetylcysteine, or combination of both on top of saline hydration versus saline hydration alone on prevention of contrast-induced nephropathy: a prospective randomized study. *J Interv Cardiol*. 2013;26(1):90-96.
43. Amini M, Salarifar M, Amirbaigloo A, Masoudkabir F, Esfahani F. N-acetylcysteine does not prevent contrast-induced nephropathy after cardiac catheterization in patients with diabetes mellitus and chronic kidney disease: a randomized clinical trial. *Trials*. 2009;10:45.
44. Baker CS, Wragg A, Kumar S, De Palma R, Baker LR, Knight CJ. A rapid protocol for the prevention of contrast-induced renal dysfunction: the RAPPID study. *J Am Coll Cardiol*. 2003;41(12):2114-2118.
45. Baskurt M, Okcun B, Abaci O, et al. N-acetylcysteine versus N-acetylcysteine + theophylline for the prevention of contrast nephropathy. *Eur J Clin Invest*. 2009;39(9):793-799.
46. Berwanger O, Cavalcanti AB, Sousa AM, et al. Acetylcysteine for the prevention of renal outcomes in patients with diabetes mellitus undergoing coronary and peripheral vascular angiography: a substudy of the acetylcysteine for contrast-induced nephropathy trial. *Circ Cardiovasc Interv*. 2013;6(2):139-145.
47. Briguori C, Manganelli F, Scarpato P, et al. Acetylcysteine and contrast agent-associated nephrotoxicity. *J Am Coll Cardiol*. 2002;40(2):298-303.
48. Azmus AD, Gottschall C, Manica A, et al. Effectiveness of acetylcysteine in prevention of contrast nephropathy. *J Invasive Cardiol*. 2005;17(2):80-84.
49. Calabrò P, Bianchi R, Crisci M, et al. Use and efficacy of saline hydration and N-acetyl cysteine to prevent contrast-induced nephropathy in low-risk populations undergoing coronary artery angiography. *Intern Emerg Med*. 2011;6(6):503-507.
50. Carbonell N, Blasco M, Sanjuán R, et al. Intravenous N-acetylcysteine for preventing contrast-induced nephropathy: a randomised trial. *Int J Cardiol*. 2007;115(1):57-62.
51. Carbonell N, Sanjuán R, Blasco M, Jordá A, Miguel A. N-acetylcysteine: short-term clinical benefits after coronary angiography in high-risk renal patients. *Rev Esp Cardiol*. 2010;63(1):12-19.
52. Coyle LC, Rodriguez A, Jeschke RE, Simon-Lee A, Abbott KC, Taylor AJ. Acetylcysteine In Diabetes (AID): a randomized study of acetylcysteine for the prevention of contrast nephropathy in diabetics. *Am Heart J*. 2006;151(5):1032.e9-e12.
53. Diaz-Sandoval LJ, Kosowsky BD, Losordo DW. Acetylcysteine to prevent angiography-related renal tissue injury (the APART trial). *Am J Cardiol*. 2002;89(3):356-358.
54. Durham JD, Caputo C, Dokko J, et al. A randomized controlled trial of N-acetylcysteine to prevent contrast nephropathy in cardiac angiography. *Kidney Int*. 2002;62(6):2202-2207.
55. Ferrario F, Barone MT, Landoni G, et al. Acetylcysteine and non-ionic isosmolar contrast-induced nephropathy—a randomized controlled study. *Nephrol Dial Transplant*. 2009;24(10):3103-3107.
56. Fung JW, Szeto CC, Chan WW, et al. Effect of N-acetylcysteine for prevention of contrast nephropathy in patients with moderate to severe renal insufficiency: a randomized trial. *Am J Kidney Dis*. 2004;43(5):801-808.
57. Goldenberg I, Shechter M, Matetzky S, et al. Oral acetylcysteine as an adjunct to saline hydration for the prevention of contrast-induced nephropathy following coronary angiography. A randomized controlled trial and review of the current literature. *Eur Heart J*. 2004;25(3):212-218.
58. Gomes VO, Poli de Figueredo CE, Caramori P, et al. N-acetylcysteine does not prevent contrast induced nephropathy after cardiac catheterisation with an ionic low osmolality contrast medium: a multicenter clinical trial. *Heart*. 2005;91(6):774-778.
59. Gulel O, Keles T, Eraslan H, Aydogdu S, Diker E, Ulusoy V. Prophylactic acetylcysteine usage for prevention of contrast nephropathy after coronary angiography. *J Cardiovasc Pharmacol*. 2005;46(4):464-467.
60. Günebakmaz O, Kaya MG, Koc F, et al. Does nebivolol prevent contrast-induced nephropathy in humans? *Clin Cardiol*. 2012;35(4):250-254.
61. Heng AE, Cellarier E, Aublet-Cuvelier B, et al. Is treatment with N-acetylcysteine to prevent contrast-induced nephropathy when using bicarbonate hydration out of date? *Clin Nephrol*. 2008;70(6):475-484.
62. Hölscher B, Heitmeyer C, Fobker M, Breithardt G, Schaefer RM, Reinecke H. Predictors for contrast media-induced nephropathy and long-term survival: prospectively assessed data from the randomized controlled Dialysis-Versus-Diuresis (DVD) trial. *Can J Cardiol*. 2008;24(11):845-850.
63. Jaffery Z, Verma A, White CJ, et al. A randomized trial of intravenous N-acetylcysteine to prevent contrast induced

nephropathy in acute coronary syndromes. *Catheter Cardiovasc Interv*. 2012;79(6):921-926.
64. Kay J, Chow WH, Chan TM, et al. Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention: a randomized controlled trial. *JAMA*. 2003;289(5):553-558.
65. Kim BJ, Sung KC, Kim BS, et al. Effect of N-acetylcysteine on cystatin C-based renal function after elective coronary angiography (ENABLE Study): a prospective, randomized trial. *Int J Cardiol*. 2010;138(3):239-245.
66. Kinbara T, Hayano T, Ohtani N, Furutani Y, Moritani K, Matsuzaki M. Efficacy of N-acetylcysteine and aminophylline in preventing contrast-inducednephropathy. *J Cardiol*. 2010;55(2):174-179.
67. Koc F, Ozdemir K, Kaya MG, et al. Intravenous N-acetylcysteine plus high-dose hydration versus high-dose hydration and standard hydration for the prevention of contrast-induced nephropathy: CASIS— a multicenter prospective controlled trial. *Int J Cardiol*. 2012;155(3):418-423.
68. MacNeill BD, Harding SA, Bazari H, et al. Prophylaxis of contrast-induced nephropathy in patients undergoing coronary angiography. *Catheter Cardiovasc Interv*. 2003;60(4):458-461.
69. Miner SE, Dzavik V, Nguyen-Ho P, et al. N-acetylcysteine reduces contrast-associated nephropathy but not clinical events during long-term follow-up. *Am Heart J*. 2004;148(4):690-695.
70. Ochoa A, Pellizzon G, Addala S, et al. Abbreviated dosing of N-acetylcysteine prevents contrast-induced nephropathy after elective and urgent coronary angiography and intervention. *J Interv Cardiol*. 2004;17(3):159-165.
71. Oldemeyer JB, Biddle WP, Wurdeman RL, Mooss AN, Cichowski E, Hilleman DE. Acetylcysteine in the prevention of contrast-induced nephropathy after coronary angiography. *Am Heart J*. 2003;146(6):E23.
72. Seyon RA, Jensen LA, Ferguson IA, Williams RG. Efficacy of N-acetylcysteine and hydration versus placebo and hydration in decreasing contrast-induced renal dysfunction in patients undergoing coronary angiography with or without concomitant percutaneous coronary intervention. *Heart Lung*. 2007;36(3):195-204.
73. Shyu KG, Cheng JJ, Kuan P. Acetylcysteine protects against acute renal damage in patients with abnormal renal function undergoing a coronary procedure. *J Am Coll Cardiol*. 2002; 40(8):1383-1388.
74. Wang JH, Subeq YM, Tsai WC, Lee RP, Hsu BG. Intravenous N-acetylcysteine with saline hydration improves renal function and ameliorates plasma total homocysteine in patients undergoing cardiac angiography. *Ren Fail*. 2008;30(5):527-533.
75. Thiele H, Hildebrand L, Schirdewahn C, et al. Impact of high-dose N-acetylcysteine versus placebo on contrast-induced nephropathy and myocardial reperfusion injury in unselected patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. The LIPSIA-N-ACC (Prospective, Single-Blind, Placebo-Controlled, Randomized Leipzig Immediate PercutaneouS Coronary Intervention Acute Myocardial Infarction N-ACC) Trial. *J Am Coll Cardiol* 2010;55:2201-2209.
76. Brueck M, Cengiz H, Hoeltgen R, et al. Usefulness of N-acetylcysteine or ascorbic acid versus placebo to prevent contrast-induced acute kidney injury in patients undergoing elective cardiac catheterization: a single-center, prospective, randomized, double-blind, placebo-controlled trial. *J Invasive Cardiol* 2013;25:276-83.
77. Webb JG, Pate GE, Humphries KH, et al. A randomized controlled trial of intravenous N-acetylcysteine for the prevention of contrast-induced nephropathy after cardiac catheterization: lack of effect. *Am Heart J*. 2004;148(3):422-429.
78. Kefer JM, Hanet CE, Boitte S, Wilmotte L, De Kock M. Acetylcysteine, coronary procedure and prevention of contrast-induced worsening of renal function: which benefit for which patient? *Acta Cardiol*. 2003;58(6):555-560.
79. Arabmomeni M, Najafian J, Abdar Esfahani M, Samadi M, Mirbagher L. Comparison between theophylline, N-acetylcysteine, and theophylline plus N-acetylcysteine for the prevention of contrast-induced nephropathy. *ARYA Atheroscler*. 2015;11(1):43-49.
80. Kumar A, Bhawani G, Kumari N, Murthy KS, Lalwani V, Raju ChN. Comparative study of renal protective effects of allopurinol and N-acetyl-cysteine on contrast induced nephropathy in patients undergoing cardiac catheterization. *J Clin Diagn Res*. 2014;8(12): HC03-HC07.
81. Chong E, Poh KK, Lu Q, et al. Comparison of combination therapy of high-dose oral N-acetylcysteine and intravenous sodium bicarbonate hydration with individual therapies in the reduction of Contrast-induced Nephropathy during Cardiac Catheterisation and Percutaneous Coronary Intervention (CONTRAST): a multi-centre, randomised, controlled trial. *Int J Cardiol*. 2015; 201:237-242.
82. Boscheri A, Weinbrenner C, Botzek B, Reynen K, Kuhlisch E, Strasser RH. Failure of ascorbic acid to prevent contrast-media induced nephropathy in patients with renal dysfunction. *Clin Nephrol*. 2007;68(5):279-286.
83. Dvoršak B, Kanič V, Ekart R, Bevc S, Hojs R. Ascorbic acid for the prevention of contrast-induced nephropathy after coronary angiography in patients with chronic renal impairment: a randomized controlled trial. *Ther Apher Dial*. 2013;17(4):384-390.
84. Zhou L, Chen H. Prevention of contrast-induced nephropathy with ascorbic acid. *Intern Med* 2012;51:531-535.
85. Spargias K, Alexopoulos E, Kyrzopoulos S, et al. Ascorbic acid prevents contrast-mediated nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. *Circulation* 2004;110:2837-2842.
86. Toso A, Maioli M, Leoncini M, et al. Usefulness of atorvastatin (80 mg) in prevention of contrast-induced nephropathy in patients with chronic renal disease. *Am J Cardiol* 2010;105:288-292.
87. Acikel S, Muderrisoglu H, Yildirir A, et al. Prevention of contrast-induced impairment of renal function by short-term or long-term statin therapy in patients undergoing elective coronary angiography. *Blood Coagul Fibrinolysis*. 2010; 21(8):750-757.
88. Han Y, Zhu G, Han L, et al. Short-term rosuvastatin therapy for prevention of contrast-induced acute kidney injury in patients with diabetes and chronic kidney disease. *J Am Coll Cardiol*. 2014;63(1):62-70.
89. Jo SH, Koo BK, Park JS, et al. Prevention of radiocontrast medium-induced nephropathy using short-term high-dose

simvastatin in patients with renal insufficiency undergoing coronary angiography (PROMISS) trial—a randomized controlled study. *Am Heart J*. 2008;155(3):499.e1-e8.
90. Leoncini M, Toso A, Maioli M, Tropeano F, Villani S, Bellandi F. Early high-dose rosuvastatin for contrast-induced nephropathy prevention in acute coronary syndrome: Results from the PRATO-ACS Study (Protective Effect of Rosuvastatin and Antiplatelet Therapy On contrast-induced acute kidney injury and myocardial damage in patients with Acute Coronary Syndrome). *J Am Coll Cardiol*. 2014;63(1):71-79.
91. Li W, Fu X, Wang Y, et al. Beneficial effects of high-dose atorvastatin pretreatment on renal function in patients with acute ST-segment elevation myocardial infarction undergoing emergency percutaneous coronary intervention. *Cardiology*. 2012; 122(3):195-202.
92. Ozhan H, Erden I, Ordu S, et al. Efficacy of short-term high-dose atorvastatin for prevention of contrast-induced nephropathy in patients undergoing coronary angiography. *Angiology*. 2010; 61(7):711-714.
93. Patti G, Ricottini E, Nusca A, et al. Short-term, high-dose atorvastatin pretreatment to prevent contrast-induced nephropathy in patients with acute coronary syndromes undergoing percutaneous coronary intervention (from the ARMYDA-CIN [atorvastatin for reduction of myocardial damage during angioplasty – contrast-induced nephropathy] trial. *Am J Cardiol*. 2011;108(1):1-7.
94. Quintavalle C, Fiore D, De Micco F, et al. Impact of a high loading dose of atorvastatin on contrast-induced acute kidney injury. *Circulation*. 2012;126(25):3008-3016.
95. Bidram P, Roghani F, Sanei H, et al. Atorvastatin and prevention of contrast induced nephropathy following coronary angiography. *J Res Med Sci*. 2015;20(1):1-6.
96. Abaci O, Arat Ozkan A, Kocas C, et al. Impact of rosuvastatin on contrast-induced acute kidney injury in patients at high risk for nephropathy undergoing elective angiography. *Am J Cardiol*. 2015;115(7):867-871.
97. Shehata M, Hamza M. Impact of high loading dose of atorvastatin in diabetic patients with renal dysfunction undergoing elective percutaneous coronary intervention: a randomized controlled trial. *Cardiovasc Ther*. 2015;33(2):35-41.
98. Bilasy ME, Oraby MA, Ismail HM, Maklady FA. Effectiveness of theophylline in preventing contrast-induced nephropathy after coronary angiographic procedures. *J Interv Cardiol*. 2012;25(4): 404-410.
99. Rohani A. Effectiveness of aminophylline prophylaxis of renal impairment after coronary angiography in patients with chronic renal insufficiency. *Indian J Nephrol*. 2010;20(2):80-83.
100. Abizaid AS, Clark CE, Mintz GS, et al. Effects of dopamine and aminophylline on contrast-induced acute renal failure after coronary angioplasty in patients with preexisting renal insufficiency. *Am J Cardiol*. 1999;83(2):260-263, A5.
101. Huber W, Schipek C, Ilgmann K, et al. Effectiveness of theophylline prophylaxis of renal impairment after coronary angiography in patients with chronic renal insufficiency. *Am J Cardiol*. 2003;91(10):1157-1162.
102. Kapoor A, Kumar S, Gulati S, Gambhir S, Sethi RS, Sinha N. The role of theophylline in contrast-induced nephropathy: a case–control study. *Nephrol Dial Transplant*. 2002;17(11): 1936-1941.
103. Matejka J, Varvarovsky I, Vojtisek P, et al. Prevention of contrast-induced acute kidney injury by theophylline in elderly patients with chronic kidney disease. *Heart Vessels*. 2010;25(6): 536-542.
104. Malhis M, Al-Bitar S, Al-Deen Zaiat K. The role of theophylline in prevention of radiocontrast media-induced nephropathy. *Saudi J Kidney Dis Transpl*. 2010;21(2):276-283.
105. Gu GQ, Lu R, Cui W, et al. Low-dose furosemide administered with adequate hydration reduces contrast-induced nephropathy in patients undergoing coronary angiography. *Cardiology*. 2013; 125(2):69-73.
106. Majumdar SR, Kjellstrand CM, Tymchak WJ, Hervas-Malo M, Taylor DA, Teo KK. Forced euvolemic diuresis with mannitol and furosemide for prevention of contrast-induced nephropathy in patients with CKD undergoing coronary angiography: a randomized controlled trial. *Am J Kidney Dis*. 2009;54(4):602-609.
107. Marenzi G, Ferrari C, Marana I, et al. Prevention of contrast nephropathy by furosemide with matched hydration: the MYTHOS (Induced Diuresis With Matched Hydration Compared to Standard Hydration for Contrast Induced Nephropathy Prevention) trial. *JACC Cardiovasc Interv*. 2012;5(1):90-97.
108. Shemirani H, Pourrmoghaddas M. A randomized trial of saline hydration to prevent contrast-induced nephropathy in patients on regular captopril or furosemide therapy undergoing percutaneous coronary intervention. *Saudi J Kidney Dis Transpl*. 2012;23(2):280-285.
109. Solomon R, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. *N Engl J Med*. 1994;331(21):1416-1420.
110. Oguzhan N, Cilan H, Sipahioglu M, et al. The lack of benefit of a combination of an angiotensin receptor blocker and calcium channel blocker on contrast-induced nephropathy in patients with chronic kidney disease. *Ren Fail*. 2013;35(4):434-439.
111. Gupta RK, Kapoor A, Tewari S, Sinha N, Sharma RK. Captopril for prevention of contrast-induced nephropathy in diabetic patients: a randomised study. *Indian Heart J*. 1999;51(5): 521-526.
112. Toprak O, Cirit M, Bayata S, Yeşil M, Aslan SL. [The effect of pre-procedural captopril on contrast-induced nephropathy in patients who underwent coronary angiography]. *Anadolu Kardiyol Derg*. 2003;3(2):98-103.
113. Hashemi M, Kharazi A, Shahidi S. Captopril for prevention of contrast induced nephropathy in patients undergoing coronary angioplasty: a double blind placebo controlled clinical trial. *J Res Med Sci*. 2005;10(6):305-308.
114. Li XM, Cong HL, Li TT, He LJ, Zhou YJ. Impact of benazepril on contrast-induced acute kidney injury for patients with mild to moderate renal insufficiency undergoing percutaneous coronary intervention. *Chin Med J (Engl)*. 2011;124(14):2101-2106.
115. Rosenstock JL, Bruno R, Kim JK, et al. The effect of withdrawal of ACE inhibitors or angiotensin receptor blockers prior to coronary angiography on the incidence of contrast-induced nephropathy. *Int Urol Nephrol* 2008;40:749-755.

116. Wolak T, Aliev E, Rogachev B, et al. Renal safety and angiotensin II blockade medications in patients undergoing nonemergent coronary angiography: a randomized controlled study. *Isr Med Assoc J* 2013;15:682-687.
117. Bainey KR, Rahim S, Etherington K, et al. Effects of withdrawing vs continuing renin-angiotensin blockers on incidence of acute kidney injury in patients with renal insufficiency undergoing cardiac catheterization: results from the Angiotensin Converting Enzyme Inhibitor/Angiotensin Receptor Blocker and Contrast Induced Nephropathy in Patients Receiving Cardiac Catheterization (CAPTAIN) trial. *Am Heart J*. 2015;170(1):110-116.
118. Jang JS, Jin HY, Seo JS, et al. Sodium bicarbonate therapy for the prevention of contrast-induced acute kidney injury – a systematic review and meta-analysis. *Circ J*. 2012;76(9): 2255-2265.
119. Ali-Hassan-Sayegh S, Mirhosseini SJ, Rahimizadeh E, et al. Current status of sodium bicarbonate in coronary angiography: an updated comprehensive meta-analysis and systematic review. *Cardiol Res Pract*. 2015;2015:690308.
120. Ali-Hassan-Sayegh S, Mirhosseini SJ, Ghodratipour Z, et al. Protective effects of anti-oxidant supplementations on contrast induced nephropathy after coronary angiography: an updated and comprehensive meta-analysis and systematic review. *Kardiol Pol*. 2016 Jan 18. doi:10.5603/KP.a2016.0007.
121. Papapetrou A, Moris D, Patelis N, et al. Oxidative stress and total antioxidant status during internal carotid artery clamping with or without shunting: an experimental pilot study. *Med Sci Monit Basic Res*. 2015;21:200-205.
122. Liao JK, Laufs U. Pleiotropic effects of statins. *Annu Rev Pharmacol Toxicol* 2005;45:89-118.
123. Chade AR, Zhu XY, Grande JP, Krier JD, Lerman A, Lerman LO. Simvastatin abates development of renal fibrosis in experimental renovascular disease. *J Hypertens*. 2008;26(8): 1651-1660.
124. Lee JM, Park J, Jeon KH, et al. Efficacy of short-term high-dose statin pretreatment in prevention of contrast-induced acute kidney injury: updated study-level meta-analysis of 13 randomized controlled trials. *PLOS ONE*. 2014;9(11):e111397.
125. Singh N, Lee JZ, Huang JJ, et al. Benefit of statin pretreatment in prevention of contrast-induced nephropathy in different adult patient population: systematic review and meta-analysis. *Open Heart*. 2014;1(1):e000127.
126. Erley CM, Heyne N, Burgert K, Langanke J, Risler T, Osswald H. Prevention of radiocontrast-induced nephropathy by adenosine antagonists in rats with chronic nitric oxide deficiency. *J Am Soc Nephrol*. 1997;8(7):1125-1132.
127. Arend LJ, Bakris GL, Burnett JC Jr, Megerian C, Spielman WS. Role for intrarenal adenosine in the renal hemodynamic response to contrast media. *J Lab Clin Med*. 1987;110(4):406-411.
128. Arakawa K, Suzuki H, Naitoh M, et al. Role of adenosine in the renal responses to contrast medium. *Kidney Int*. 1996;49(5): 1199-1206.
129. Dai B, Liu Y, Fu L, Li Y, Zhang J, Mei C. Effect of theophylline on prevention of contrast-induced acute kidney injury: a meta-analysis of randomized controlled trials. *Am J Kidney Dis*. 2012; 60(3):360-370.
130. Wu Z, Zhang H, Jin W, et al. The effect of renin-angiotensin-aldosterone system blockade medications on contrast-induced nephropathy in patients undergoing coronary angiography: a meta-analysis. *PLOS ONE*. 2015;10(6):e0129747.
131. Duan N, Zhao J, Li Z, et al. Furosemide with saline hydration for prevention of contrast-induced nephropathy in patients undergoing coronary angiography: a meta-analysis of randomized controlled trials. *Med Sci Monit*. 2015;21:292-297.
132. Reyes AJ. The increase in serum uric acid concentration caused by diuretics might be beneficial in heart failure. *Eur J Heart Fail*. 2005;7(4):461-467.
133. Robinson PC, Stamp LK. The management of gout: much has changed. *Aust Fam Physician*. 2016;45(5):299-302.
134. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomized trials. *BMJ*. 2011;343:d5928.