Cardiovascular Revascularization Medicine 20 (2019) 29–37

Contents lists available at ScienceDirect

Cardiovascular Revascularization Medicine

A Bayesian network meta-analysis of preventive strategies for contrast-induced nephropathy after cardiac catheterization

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ARTICLE INFO

Article history:
Received 9 April 2018
Received in revised form 6 June 2018
Accepted 7 June 2018

Keywords:
Contrast induced nephropathy
Contrast induced acute renal insufficiency
Statins
Cardiac catheterization

ABSTRACT

Background: The optimal preventive strategy for contrast induced acute kidney injury (CIAKI) in patients undergoing cardiac catheterization remains uncertain.
Objective: We conducted Bayesian network meta-analysis (NMA) to compare different preventive strategies for CIAKI in these cohorts.
Methods: Forty-nine randomized controlled trials were extracted using MEDLINE, EMBASE and CENTRAL data bases (inception-1st December 2017). We calculated median of the odds ratio (OR) with the corresponding 95% credible interval (CrI). The ranking probability of each treatment was based on SUCRA (surface under the cumulative ranking curve).
Results: In NMA of 28,063 patients [normal saline (NS: 9716 patients), sodium bicarbonate (NaHCO3: 4484 patients), statin (2542 patients), N-acetylcysteine (NAC: 3006 patients), NAC + NaHCO3 (774 patients), NS + NAC (3807 patients), NS + NaHCO3 (135 patients) and placebo (3599 patients)], statins reduced the relative risk of CIAKI compared with NS (OR: 0.50; 95% CrI, 0.25–0.99), and placebo (OR: 0.44; 95% CrI, 0.24–0.83). Subgroup analyses showed that in patients receiving low osmolar contrast, statins reduced the relative risk of CIAKI by 58% versus NS, and 51% versus placebo. There were no significant differences across all the treatments in terms of risk of hemodialysis or all-cause mortality. Statins had the highest probability for reducing the risk of CIAKI (SUCRA, 0.86), risk of hemodialysis (SUCRA, 0.88) and all-cause mortality (SUCRA, 0.81).
Conclusion: Statins were the superior preventive strategy for reducing the risk of CIAKI compared with NS alone and placebo.

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1. Introduction

Over the last few decades, the rise in cardiac catheterization procedures has resulted in an increased incidence of contrast induced acute kidney injury (CIAKI) and subsequently enhanced the risk of renal replacement therapy, prolonged duration of hospital stay, increased cost of care and mortality [1]. This issue has generated enthusiasm among the medical professionals to investigate the optimal therapy for prevention of CIAKI. However, due to significant heterogeneity across the published literature, the best preventive strategy for CIAKI remains uncertain. Intravascular volume expansion is considered standard of care for prevention of CIAKI [2, 3], but the contemporary AMACING trial (Prophylactic Hydration to Protect Renal Function from Intravascular Iodinated Contrast Material in Patients at High Risk of Contrast Induced Nephropathy) has challenged this notion and demonstrated that absence of prophylactic hydration did not increase the risk of CIAKI, hemodialysis or death compared with prophylactic hydration [4]. Similarly, in the more recent PRESERVE trial (Prevention of Serious Adverse Events Following Angiography), there was no benefit of intravenous sodium bicarbonate (NaHCO3) over normal saline (NS) or of oral N-acetylcysteine (NAC) over placebo in terms of mortality, need for dialysis or CIAKI in patients undergoing coronary angiography [5]. Due to this controversy, we performed Bayesian network meta-analysis (NMA) to compare all relevant treatment approaches employed in current clinical practice to prevent CIAKI after cardiac catheterization [6].

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https://doi.org/10.1016/j.carrev.2018.06.005
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2. Methods

This NMA is performed and reported in compliance with the Cochrane Collaboration guidelines [7] and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) Extension statement for systematic reviews incorporating network meta-analyses for health care interventions [8].

2.1. Search strategy

Two authors (HR, MUK) conducted the electronic data base search using MEDLINE, EMBASE and CENTRAL (Cochrane Central Register of Controlled Trials) from inception to 1st December 2017. Following search terms were used to generate search algorithm: "contrast induced nephropathy", "CIN", "acute kidney injury", "AKI", "contrast induced acute kidney injury" "acute renal failure", "ARF", "coronary angiography", "cardiac catheterization", "angioplasty", "percutaneous coronary interventions" and "PCI". We also reviewed online libraries of www.clinicaltrials.gov, www.clinicaltrialsregister.eu, www.clinicaltrialresults.gov, www.acc.org, www.esccardio.org, www.tctmd.com, and bibliographies of the relevant articles. The search was restricted to randomized controlled trials (RCTs), full text articles and human subjects. There was no restriction on language and publication year. All the results were downloaded to Endnote X7 (Thompson ISI ResearchSoft, Philadelphia, Pennsylvania, USA) and duplicates were identified and removed manually and via EndNote.

2.2. Study selection

The pre-defined inclusion criteria were: [1] RCTs which had compared two or more preventive strategies for CIAKI in adults patients (age ≥ 18 years) undergoing diagnostic or interventional cardiac catheterization, [2] studies which reported at least one clinical event for CIAKI, [3] studies with sample size of at least 100 patients (to avoid small study effects), and [4] full text articles. We excluded observational studies and trials assessing strategies that are not widely practiced and have limited clinical applicability (xanthine, ascorbic acid, dopaminergic drugs, natriuretic peptide and peripheral ischemic preconditioning). Similarly, we also excluded trials which have compared protocol based hydration strategies rather than comparing two different treatment arms for prevention of CIN. The POSEIDON (Prevention of Contrast Renal Injury with Different Hydration Strategies) trial compared left ventricular end diastolic pressure (LVEDP) guided hydration strategy versus standard hydration. Based on a priori exclusion criteria, this trial was not selected for final analysis [9]. There were no restrictions on comorbidities or follow up duration. Study screening was done by two authors (HR and MUK) and any conflicts were resolved by consulting third author (SUK).

2.3. Data extraction and quality assessment

Two authors (MUK and HR) independently abstracted data on study, baseline characteristics of the participants, co-morbidities, number of events, and number of patients at risk, sample size, data adjudication time and follow-up duration on a pre-specified data collection form. When available, we extracted data based on intention to treat principle. Any divergence was resolved by referring back to the original article, and/or opinion of third reviewer (SUK). The primary endpoint was CIAKI. The secondary outcomes were risk of hemodialysis and all-cause mortality. A notable number of studies did not report risk of hemodialysis or all-cause mortality leading to a relatively lesser number of comparisons for secondary endpoints' analyses. In accordance with a prior NMA [10], we defined CIAKI as a relative increase of ≥25% or an absolute increase of ≥0.5 mg/dL in serum creatinine within 48–72 h after the procedure. The risk of bias of individual studies was assessed using Cochrane bias risk assessment tool [11] (Supplement (S) Table 1).

2.4. Statistical analysis

The Bayesian NMA was conducted using NetMetaXL 1.6.1 (Canadian Agency for Drugs and Technologies in Health; Ottawa, Canada) and winBUGS 1.4.3 (MRC Biostatistics Unit; Cambridge, United Kingdom). Since we made no assumptions regarding the efficacy of these treatments from data outside the included trials, random effects vague priors' model was used to estimate the posterior distribution of all parameters. For all outcomes, convergence was achieved at 40,000 iterations and auto correlation was checked and confirmed. The convergence was assessed using the Brooks-Gelman-Rubin method and by checking whether the MCMC error is <5% of the standard deviation of the effect estimates and between-study variance [12]. The median of the posterior distribution was reported as odds ratio (OR) with the corresponding 95% credible interval (CrI) ranging from 2.5th to the 97.5th centiles of the distribution. The between-study variance was interpreted as low ($\tau^2 = 0.04$), moderate ($\tau^2 = 0.14$) and high ($\tau^2 = 0.40$) [13].

Markov chain Monte Carlo (MCMC) modeling was used to estimate the relative ranking probability of each treatment group based on SUCRA (surface under the cumulative ranking curve) [14, 15]. A SUCRA is a numerical representation of the probability of safety or efficacy of the treatment i.e. higher values represent better efficacy or safety of the treatment. Prespecified subgroup analyses were conducted to assess the effects of the treatments based on osmolarity of the contrast and setting of cardiac catheterization (emergent or elective procedure). The comparisons are shown in the form of league tables with OR < 1 means the treatment in the top left is more effective at reducing the incidence of CIN compared with rest of the treatments.

3. Results

This initial search yielded a total of 3423 records. Out of which 1902 citations were duplicates, and 865 studies were excluded at title and abstract level. Further 607 articles were removed at full text screening based on predefined inclusion/exclusion criteria. Ultimately, 49 RCTs were included in final analysis (Fig. 1). A total of 28,063 patients [NS (9716 patients), NaHCO3 (4484 patients), Statin (2542 patients), NAC (3006 patients), NAC + NaHCO3 (774 patients), NS + NAC (3807 patients), NS + NaHCO3 (135 patients) and placebo (3599 patients)] were included in this NMA. The mean age of the study population was 67 ± 5 years, 69% were men, 68% had hypertension and 49% had diabetes mellitus. Baseline serum creatinine was 1.3 ± 0.3 mg/dL. The endpoint adjudication time varied from 24 h to 240 h (Table 1).

The NMA showed that statins were associated with 50% relative risk reduction of CIAKI compared with NS alone (OR: 0.50; 95% CrI, 0.25–0.99), and 56% risk reduction compared with placebo (OR: 0.44; 95% CrI, 0.24–0.83). There were no statistical differences among rest of the treatment strategies. The MCMC modeling suggested that statins had the highest probability of having the lowest rate of CIAKI (SUCRA, 0.86), followed by NAC (SUCRA, 0.75), NaHCO3 + NAC (SUCRA, 0.64), NaHCO3 (SUCRA, 0.54), NS + NAC (SUCRA, 0.45), NS + NaHCO3 (SUCRA, 0.29) and NS (SUCRA, 0.25) (Fig. 2).

The NMA did not demonstrate statistical differences between statins, NS, NAC, NS + NAC, NaHCO3, NaHCO3 + NAC or placebo with regards to risk of hemodialysis (Fig. 3). In the probability analysis, the MCMC modeling suggested that statins had the highest probability of having lowest risk of hemodialysis (SUCRA, 0.88), followed by NS (SUCRA, 0.60) and NAC (SUCRA, 0.59) (Fig. 3). The NMA also failed to demonstrate significant differences in terms of all-cause mortality among statins, NaHCO3, NAC, NS, NS + NAC, NaHCO3 + NAC and placebo. The MCMC modeling suggested that statins had the highest probability of reducing all-cause mortality (SUCRA, 0.81), followed by

Table 1
Baseline characteristics of the trials; CrCl (Creatinine Clearance) DM (Diabetes Mellitus); eGFR (Estimated Glomerular Filtration Rate); HTN (Hypertension); IO (Iso Osmolar contrast); LO (Low Osmolar contrast); NS (Normal Saline); NaHCO3 (Sodium Bicarbonate); NAC (N-Acetyl Cysteine).

Studies	Groups	n	Mean age (year)	Men (%)	Baseline creatinine (mg/dL)	HTN (%)	DM (%)	*Baseline eGFR or CrCl	Contrast % (n)	Contrast volume (mL)	Adjudication time (hours)
Boucek [27]	NS	59	67	74.5	1.8	–	100	44.6	LO = 100	110	48
	NaHCO3	61	63	75.4	2	–	100	43.6	(120)		
Brar [24]	NS	178	71	64.8	1.49	–	45.5	48.3	LO = 100	131.6	24–96
	NaHCO3	175	71	62.3	1.49	–	43.4	47.7	(353)		
Vasheghani-Farahani A [28]	NS	130	63.8	81.5	1.66	55.8	25	45.4	LO = 100	117.5	48
	NaHCO3 + NS	135	62.9	84.4	1.63	42.6	26	46.4	(72)		
Thayssen [29]	NS	181	63.0	80.1	0.87	32.8	9.9	94.3	IO = 100	140	24–72
	NAC	176	63.0	72.2	0.84	34.5	8.5	91.4	(538)		
	NaHCO3	181	62.0	76.8	0.87	35.6	9.4	90.8			
Tamura [30]	NS	72	73.3	83.3	1.38	83.3	56.9	38.2	LO = 100	85.0	72
	NaHCO3	72	72.3	91.7	1.55	84.7	59.7	40.0	(144)		
Pakfetrat [31]	NS	96	58.5	64.5	1.1	–	32.3	72.6	IO = 100	62.5	48
	NaHCO3	96	57.8	58.3	1.1	–	27.1	73.2	(192)		
Ozcan EE [32]	NS	88	70	75	1.40	80.7	47.7	49.8	LO = 100	110.0	48
	NS + NAC	88	67	76.1	1.40	68.2	45.5	45.3	(264)		
	NaHCO3	88	68	72.7	1.36	75.4	42	52.9			
Motohiro [33]	NS	77	74	64	1.55	83	63	42.8	–	135.0	48
	NaHCO3	78	71	76	1.54	86	56	45.7			
Merten [34]	NS	59	69.2	76	1.71	–	46	45.0	LO = 100	134.0	48
	NaHCO3	60	66.7	73	1.89	–	50	41.0	(119)		
Maioli [35]	NS + NAC	252	74	61	1.21	57	23	–	IO = 100	216.0	24–240
	NaHCO3 + NAC	250	74	57	1.21	59	25		(450)		
Lee [36]	NS + NAC	189	67.5	71.4	1.50	79.9	100	46.0	IO = 100	116	24–48
	NaHCO3 + NAC	193	68.5	70.5	1.50	77.2	100	46.0	(382)		
Koc [37]	NS	101	62	48	1.00	60	100	36	LO = 100	90	48
	NaHCO3	94	62	54	1.00	66	100	23	(195)		
Klima [38]	NS	89	75	62	1.59	81	34	43.0	IO = 11	100	48
	‖NaHCO3	87	78	57	1.59	90	39	43.1	(29)		
	†NaHCO3	82	75	54	1.44	77	39	43.1	LO = 89 (229)		
Gomes [39]	NS	151	64.5	74.8	1.49	74.2	29.8	51.9	LO = 100	124.5	48
	NaHCO3	150	64.1	69.3	1.50	77.3	28.7	50.5	(301)		
Castini [40]	NS	51	72.7	84	1.49	20	78	49.5	IO = 100	194.5	24–120
	NS + NAC	53	70.5	94	1.57	26	83	48.8	(156)		
	NaHCO3	52	70	85	1.59	35	71	46.9			
Mahmoodi [41]	NS + NAC	175	64.48	59.4	1.17	–	–	64.1	LO = 100	–	48
	NaHCO3 + NAC	175	64.96	43.4	1.16	–	–	65.4	(350)		
Manari [42]	††NS	151	65	75	1.00	42	15	81.0	IO = 100	198.2	72
	‡NS	142	65.2	77	1.00	44	19	82.0	(592)		
	˙NaHCO3	145	63.9	72	1.03	39	16	80.0			
	¸NaHCO3	154	65.2	75	1.00	47	17	82.0			
Yeganehkhah [43]	NS	50	58.5	44	1.08	52	34	63.0	LO = 100	44.2	48
	NS+ NAC	50	58.1	50	1.17	52	44	64.3	(150)		
	NaHCO3	50	60.9	62	1.17	42	44	64.3			
Solomon [44]	NS	196	72	58	1.85	94	55	33.8	–	107	24–72
	NaHCO3	195	72	57	1.98	94	63	31.7			
ACT investigators [45]	NS	1136	68.1	40.7	1.20	85.9	59.7	69.0	IO = 2.9 (67) HO = 22.1 (509) LO = 73.9 (1705)	100	48–96
	NAC + NS	1172	68	42	1.20	86.5	61.2	69.3			
Albabtainl [46]	NS	66	59.8	81.8	1.22	53.1	79.7	74	LO = 100	87.6	120–144
	NAC	62	62	71	1.45	62.3	85.2	59.3	(243)		
Baskurt [47]	NS	72	67.1	56.9	1.30	59	33	51.5	LO = 100	119.1	48
	NAC	73	67.9	63	1.39	53	27	48.9	(217)		
Brigouri [48]	NS	91	64	89	1.50	72	32.5	54	LO = 100	197.0	48
	NS + NAC	92	64	84	1.50	72	43	56	(183)		
Azmus [49]	NS	201	67	58.2	1.27	–	50.7	60	HO = 95.7 (380) LO = 4.3 (17)	125.5	48
	NS + NAC	196	66	59.7	1.30	–	48.5	63			
Carbonell [50]	NS	109	60.7	72.5	0.96	57.8	27.5	88	LO = 100	188.0	48
	NS + NAC	107	63.1	80.4	0.94	52.3	39.3	86	(216)		
Coyle [51]	NS	69	63.3	68.1	1.10	87	100	76.0	–	93	48–96
	NS + NAC	68	66.7	61.8	1.16	91.2	100	70.0			
Ferrario [52]	NS	99	75	62	1.60	83	25	45	IO = 100	173.9	72
	NS + NAC	99	75	68	1.60	80	25	40	(200)		
Gomes [53]	NS	79	66.5	57	1.20	84.8	51.9	62	LO = 100	102.7	48

(continued on next page)

Table 1 (*continued*)

Studies	Groups	n	Mean age (year)	Men (%)	Baseline creatinine (mg/dL)	HTN (%)	DM (%)	*Baseline eGFR or CrCl	Contrast % (n)	Contrast volume (mL)	Adjudication time (hours)
	NS + NAC	77	63.8	61	1.40	87	51.9	59	(156)		
Holscher [54]	NS	127	–	–	–	–	–	–	–	192.6	72
	NS + NAC	128	–	–	–	–	–				
Kay [55]	NS	98	69	63	1.26	43	36	44	LO = 100	125	48
	NS + NAC	102	69	60	1.24	38	39	46	(200)		
Kim BJ [56]	NS	86	62	67	1.03	–	–	–	IO = 46.4	208.8	72
	NS + NAC	80	62	79	1.03	–	–	–	(77)		
									LO = 53.6		
									(89)		
Miner [57]	NS	85	69	66	1.40	77	67	44.1	LO = 100	347.0	72
	NAC + NS	95	71	68	1.40	72	68	46.3			
Shyu [58]	NS	61	70	65	2.80	67	64	–	LO = 100	117.0	48
	NAC + NS	60	70	70	2.80	70	63	–	(121)		
Thiele [59]	NS	125	68	66	0.80	74	33	86	LO = 100	170.0	72
	NAC + NS	126	68	71	0.90	71	25	85	(251)		
Brueck [60]	NS	198	74	62	1.50	94	51	42.0	LO = 100	111.0	72
	NAC + NS	199	75	65	1.50	94	43	40.0	(499)		
Webb [61]	NS	245	70	62	1.60	67.1	39.2	43.7	LO = 100	120.0	48–192
	NAC + NS	242	71	59	1.60	67.6	30.6	44.2	(487)		
Kumar [62]	NS	300	66	75	1.0	65	42	83.0	IO = 40.0	NR	48–72
	NAC	200	68	82	1.1	45	34	78.0	(200)		
									LO = 60.0		
									(300)		
Chong [63]	NAC + NS	157	69	72	1.5	90.5	49.7	48.3	LO = 100	116.0	48
	NaHCO3	153	68.4	77.8	1.60	85	45.1	47.3	(466)		
	NAC + NaHCO3	156	67	77.6	1.57	89.1	48.1	47.6			
Han [64]	NS	1500	61.44	66.1	1.07	72.7	100	74.4	IO = 100	115	48–72
	Rosuvastatin	1498	61.45	64.3	1.08	71.3	100	74.1	(2998)		
Jo SH [65]	Placebo	123	65.0	71.5	1.24	58.5	23.6	55.4	IO = 100	182.1	48
	Simvastatin	124	66.1	73.3	1.28	67.7	28.2	53.4	(247)		
Leoncini [66]	Placebo	252	66.1	65.5	0.96	54.8	22.6	82.6	IO = 100	144.0	72
	Rosuvastatin	252	66.2	65.9	0.95	56.7	19.8	82.5	(504)		
Li W [67]	NS	83	65.4	77.1	0.93	83.1	28.9	–	LO = 100	101.8	48
	Atorvastatin	78	66.3	74.4	0.93	78.2	26.9	–	(161)		
Patti [68]	Placebo	121	66	79	1.04	74	25	77.0	LO = 100	211.0	48
	Atorvastatin	120	65	76	1.04	76	30	79.8	(241)		
Quaintavalle [69]	Placebo	208	70	58	1.29	87.5	38.5	43.0	IO = 100	180.6	48
	Atorvastatin	202	70	51	1.32	85.5	44	42.0	(410)		
Bidram [70]	NS	100	60.4	92	1.14	–	0	70.2	IO = 100	NR	48
	Atorvastatin	100	60	89	1.18	–	0	68.0	(200)		
Abaci [71]	NS	105	67.7	73.4	1.40	87.6	47.6	51.3	LO = 100	128.3	48–72
	Rosuvastatin	103	67.5	64	1.30	88.3	51.4	52.8	(208)		
Shehta [72]	Placebo	65	57	53	2.00	52	100	48.0	LO = 100	276.0	72
	Atorvastatin	65	55	53	2.00	52	100	48.0	(130)		
Nijssen [4]	Placebo	332	72.6	64	1.33	–	33	47·59	LO = 100	90	44–144
	NS	328	71.9	59	1.34	–	32	47·30	(660)		
Weisbord [5]	NaHCO3	2511	70	94	1.50	–	81	50	IO = 56	85	72–120
	NS	2482	70	94	1.50	–	82	50	(5584)		
	NAC	2495	70	94	1.50	–	81	50	LO = 43		
	Placebo	2498	70	93	1.50	–	81	50	(4290)		

NaHCO3 (SUCRA, 0.72) (Fig. 4). There was a higher degree of statistical heterogeneity for CIAKI ($\tau^2 = 0.66$), while risk of hemodialysis and all-cause mortality were affected by moderate ($\tau^2 = 0.21$) and low degree of heterogeneity ($\tau^2 = 0.08$) respectively.

Subgroup analyses showed that when low osmolarity contrast was used for cardiac catheterization, statins were superior to NS alone (OR: 0.42; 95% CrI, 0.20–0.82) and placebo (OR: 0.41; 95% CrI, 0.23–0.74) in reducing the risk of CIAKI. The MCMC modeling showed that statins had the highest probability of reducing the risk of CIAKI in patients having low osmolarity contrast (SUCRA, 0.97) (S Fig. 1). The NMA did not show significant differences among the treatments in patients with iso-osmolarity contrast based procedures. The MCMC modeling demonstrated that NaHCO3 + NAC had the highest probability of being the best strategy to prevent CIAKI (SUCRA, 0.78), followed by NAC (SUCRA, 0.77) and statins (SUCRA, 0.64) (S Fig. 2).

In subgroups having elective cardiac catheterization, the NMA showed that risk of CIAKI was identical between all the treatments. The MCMC demonstrated that NaHCO3 had the highest probability of having the lowest risk of CIAKI (SUCRA, 0.80), followed by NAC (SUCRA, 0.66) and NaHCO3 + NAC (SUCRA, 0.61) (S Fig. 3). In patients undergoing emergent catheterization, the NMA showed that statins reduced the risk of CIAKI by 56% compared with placebo (OR: 0.42; 95% CrI, 0.210–0.87). The MCMC modeling demonstrated that statins had the highest probability of having the lowest rate of CIAKI in the setting of emergent cardiac catheterization (SUCRA, 0.88), followed by NAC (SUCRA, 0.74) and NaHCO3 + NAC (SUCRA, 0.56) (S Fig. 4).

4. Discussion

In this NMA of 49 RCTs including 28,063 patients, statins significantly reduced the relative risk of CIAKI compared with NS alone and placebo. These benefits were mainly driven by effects of statins in patients who received low osmolar contrast and patients who underwent emergent cardiac catheterization. There were no statistical differences between other treatments regarding the risk of CIAKI. In terms of risk of hemodialysis or all-cause mortality, all the treatment strategies

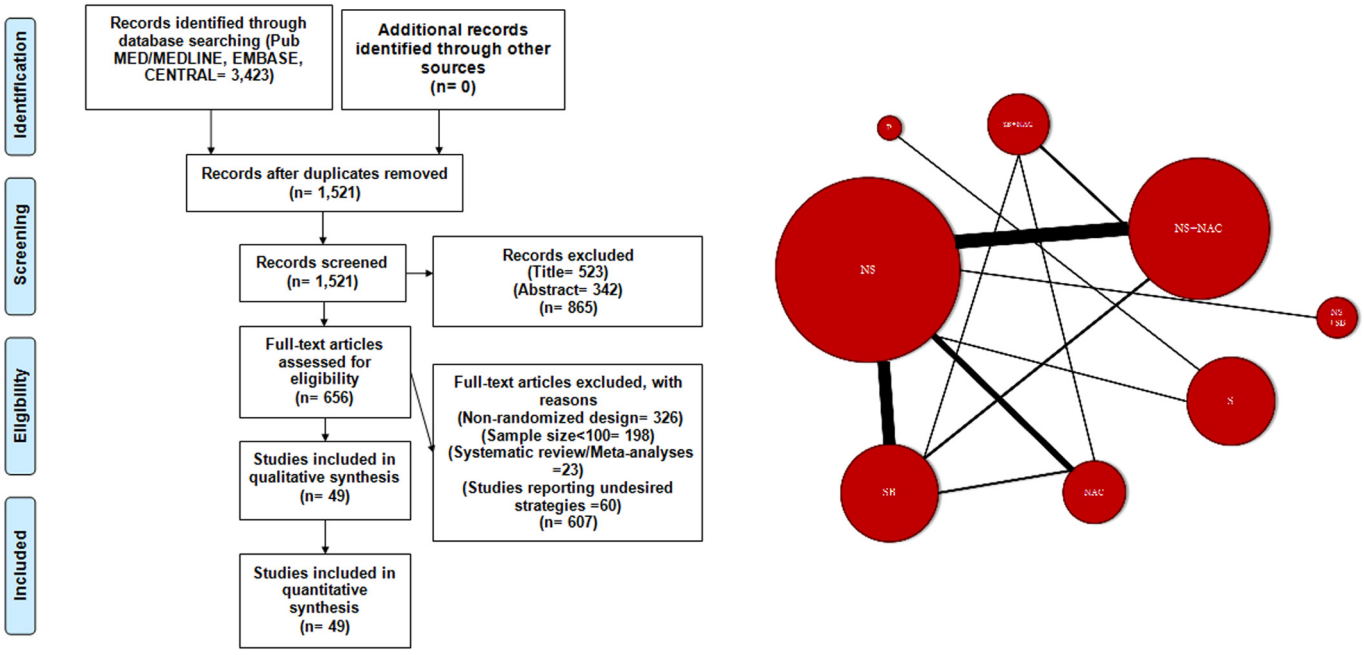

Fig. 1. Search strategy using PRISMA statement and network diagram. The size of circle represents sample size of the group. NS = Normal Saline, SB = Sodium Bicarbonate, NAC = N-Acetylcysteine, S = Statins, P = Placebo.

showed comparable outcomes. The MCMC modeling showed that statins had the highest probability of having the lowest risk of CIAKI, risk of hemodialysis and all-cause mortality.

The majority of meta-analyses on this topic were conducted via traditional methodology and compared one form of prophylaxis to other [16–18]. We are aware of at least one NMA by Giacoppo and colleagues, which had utilized the Bayesian approach to compare multiple interventions [10]. Giacoppo and colleagues reported that statin administration was associated with significant and sustained relative risk reduction compared with NS in patients undergoing PCI across various sensitivity analyses [10]. They further showed that xanthine, NAC, NaHCO3, NAC + NaHCO3, ischemic preconditioning and natriuretic peptide might have protective effects but the results were not consistent across sensitivity analyses. But in diabetic patients, none of the interventions reduced the risk of CIAKI. This NMA had certain shortcoming. First, this study assessed treatments which are not used in routine clinical practice (ascorbic acid, xanthine, dopaminergic agent, peripheral ischemic preconditioning and natriuretic peptide), and hence had relatively limited clinical applicability of the provided evidence. Second, the NMA focused only on CIAKI and did not assess the risk of hemodialysis or all-cause mortality, which represent more serious sequelae of contrast related renal complications. Third, due to inclusion of studies with small sample size, this NMA was potentially affected by reporting bias due to small study effects [19]. Finally, this NMA

Treatment	SUCRA
Statin	0.86
NAC	0.75
NaHCO3+NAC	0.64
NaHCO3	0.54
NS+NAC	0.45
NS+NaHCO3	0.29
NS	0.25
Placebo	0.22

Statin							
0.81(0.36 – 1.88)	**NAC**						
0.73(0.26 – 2.06)	0.90(0.37 – 2.16)	**NaHCO3+NAC**					
0.64(0.30 – 1.40)	0.79(0.44 – 1.41)	0.87(0.39 – 2.00)	**NaHCO3**				
0.59(0.27 – 1.29)	0.73(0.39 – 1.33)	0.81(0.39 – 1.69)	0.93(0.55 – 1.51)	**NS+NAC**			
0.39(0.06 – 2.42)	0.48(0.08 – 2.81)	0.54(0.08 – 3.44)	0.62(0.11 – 3.44)	0.66(0.12 – 3.74)	**NS+NaHCO3**		
0.50(0.25 – 0.99)	0.62(0.36 – 1.02)	0.68(0.31 – 1.48)	0.78(0.52 – 1.14)	0.85(0.58 – 1.22)	1.27(0.23 – 6.90)	**NS**	
0.44(0.24 – 0.83)	0.55(0.24 – 1.21)	0.61(0.22 – 1.70)	0.69(0.32 – 1.47)	0.75(0.35 – 1.62)	1.13(0.18 – 7.01)	0.89(0.45 – 1.76)	**Placebo**

Fig. 2. League table comparing different treatment strategies for CIAKI. OR < 1 means the treatment in the top left is more effective than other interventions. NAC = N-Acetylcysteine, NaHCO3 = sodium bicarbonate, NS = Normal Saline.

Treatment	SUCRA
Statin	0.88
NS	0.60
NAC	0.59
Placebo	0.51
NS+NAC	0.42
NaHCO3	0.42
NaHCO3+NAC	0.08

Statin						
0.49 (0.05 – 1.51)	NS					
0.52 (0.04 – 1.79)	0.99 (0.53 – 2.10)	NAC				
0.47 (0.03 – 1.46)	0.94 (0.45 – 2.12)	0.94 (0.45 – 2.08)	Placebo			
0.38 (0.03 – 1.95)	0.81 (0.36 – 1.68)	0.78 (0.27 – 2.06)	0.85 (0.29 – 2.21)	NS+NAC		
0.43 (0.02 – 1.49)	0.86 (0.48 – 1.57)	0.86 (0.44 – 1.69)	0.91 (0.43 – 2.00)	1.07 (0.45 – 3.00)	NaHCO3	
0.17 (0.02 – 1.02)	0.39 (0.11 – 1.28)	0.37 (0.09 – 1.41)	0.40 (0.09 – 1.60)	0.47 (0.17 – 1.33)	0.45 (0.11 – 1.71)	NaHCO3+NAC

Fig. 3. League table comparing different treatment strategies for risk of hemodialysis. OR < 1 means the treatment in the top left is more effective than other interventions. NAC = N-Acetylcysteine, NaHCO3 = sodium bicarbonate, NS = Normal Saline.

was published prior to AMACING [4] and PRESERVE [5] trials and thus lacked these contemporary data sets. Our up to date report has encountered these limitations via a strict inclusion/exclusion criteria which allowed us to include studies with relatively larger sample size, compare relevant treatment strategies and generate comprehensive assessment of contrast associated renal complications and mortality.

In another meta-analysis of 125 trials including >6000 patients, Sayegh et al., showed that statins reduced the risk of CIAKI by 55% compared with placebo (OR, 0.45, 95% confidence interval, 0.35–0.57) [20]. Meta-analysis by Subramaniam and colleagues included 86 RCTs comparing NAC, NaHCO3, statins, ascorbic acid and NS [21]. This study showed that low dose NAC plus NS and NAC plus NS significantly reduced the relative risk of CIN compared with NS alone. Moreover, greatest reduction in CIN was observed with NAC plus NS in patients receiving low osmolar contrast and with statins plus NAC plus NS. This was a pair-wise meta-analysis which essentially validates the impression that NS alone was not an optimal approach for prevention of CIN and groups receiving statins had significant benefit compared with

Treatment	SUCRA
Statin	0.81
NaHCO3	0.72
Placebo	0.60
NAC	0.49
NS	0.45
NS+NAC	0.37
NaHCO3+NAC	0.06

Statin						
0.72 (0.19 – 2.23)	NaHCO3					
0.66 (0.18 – 2.05)	0.93 (0.66 – 1.30)	Placebo				
0.63 (0.17 – 1.99)	0.88 (0.62 – 1.28)	0.95 (0.68 – 1.33)	NAC			
0.62 (0.17 – 1.87)	0.87 (0.64 – 1.19)	0.93 (0.71 – 1.23)	0.99 (0.73 – 1.33)	NS		
0.56 (0.15 – 1.80)	0.79 (0.46 – 1.35)	0.85 (0.52 – 1.37)	0.90 (0.53 – 1.54)	0.91 (0.58 – 1.45)	NS+NAC	
0.29 (0.06 – 1.26)	0.42 (0.15 – 1.11)	0.46 (0.17 – 1.15)	0.48 (0.18 – 1.25)	0.49 (0.18 – 1.24)	0.53 (0.20 – 1.31)	NaHCO3+NAC

Fig. 4. League table comparing different treatment strategies for risk of all-cause mortality. OR < 1 means the treatment in the top left is more effective than other interventions. NAC = N-Acetylcysteine, NaHCO3 = sodium bicarbonate, NS = Normal Saline.

groups without statins. Furthermore, interventions had more benefit in patients who received low osmolar contrast versus iso-osmolar contrast. However, because this study did not utilize Bayesian principles and therefore probability analyses could not be conducted. Our report can be considered an extension of these findings which ranked the treatments based on their efficacy suggesting that statins were most effective intervention followed by NAC while NS alone was ranked just above placebo on rankogram.

Theoretically, statins due to their "pleiotropic effects" can improve endothelial function, stabilize the atherosclerotic plaques and subsequently mitigate oxidative stress [22]. Statins can be highly effective in the state of profound inflammation and ultimately impede the process of contrast induced tubular cells apoptosis [23]. Perhaps, this is the reason that statins were more effective in emergent cardiac catheterization, which is a state of high inflammatory response.

There is significant body of evidence suggesting periprocedural hydration for the prevention of CIAKI in patients undergoing PCI [24, 25]. In recent PRESERVE trial, periprocedural intravenous NaHCO3 showed no benefit over NS in terms of risk of CIAKI or mortality. Moreover, there was no benefit of using oral NAC over placebo with respect to the risk of renal complications in patients undergoing angiography. These findings suggest that use of NaHCO3 or NAC can no longer be recommended in high risk patients receiving angiography and IV hydration with NS remains the mainstay of the prevention of CIN [5]. Conversely, a more recent meta-analysis (61 RCTs, 11,480 patients) suggested that in patients undergoing coronary angiography, use of NAC was associated with 26% relative risk reduction compared with control (RR, 0.74; $P = 0.0002$) [26]. On the same note, the AMACING trial suggested that withholding hydration in patients with eGFR > 29 mL/min/1.73 m^2 might be a safer approach in patients receiving contrast media [4]. It is important to note that ~48% patients receiving intra-arterial contrast underwent contrast enhanced computed tomography while only ~16% patients received coronary angiography or PCI in this study. Current NMA attempted to incorporate available quality data to provide a comprehensive summary of the evidence for prevention of CIN which is consistent with various former reports [10, 20, 21].

Our NMA has certain limitations. First, this study was conducted on study level information and due to lack of individual patient level data; various important subgroup analyses (age, comorbidities, contrast volume, baseline eGFR or CrCl etc.) could not be performed. Second, like former meta-analyses, there was a noticeable heterogeneity across the studies with respect to methodology, dosing of the treatments, contrast agents, their strength and volume, procedural setting, definition of CIAKI, adjudication timing of renal function and characteristics of the patients. Similarly, use of background volume expansion with concomitant use of oral NAC in certain studies might have generated a potential bias in the treatment effect. It is also possible that in statin trials, the population without statins could be sicker than patients in statin group. These differences could potentially bias the results in favor of statins arm. These variations resulted in high degree of statistical heterogeneity for the primary estimate. However, we used random effects model to account for any between study variability. Finally, since Bayesian approach generates evidence based on direct and indirect comparison, our NMA should be viewed as hypothesis generating.

In conclusion, our NMA suggests that in patients undergoing cardiac catheterization, statins were found to reduce the risk of CIAKI compared with NS alone. The use of NS, NaHCO3, NAC or combination of these agents provided no statistical differences in preventing CIAKI. Statins were shown to be more effective in patients receiving low osmolar contrast or requiring emergent cardiac catheterization. Neither of the strategies had significant superior protective effects on dialysis or all-cause mortality. However, probability analysis demonstrated that in addition to preventing CIAKI, statins had the highest probability of reducing the risk of dialysis and all-cause mortality. These findings do not contradict the role of background NS infusion rather suggest that a preventive strategy based only on NS infusion might not be highly effective. These observations carry important clinical value and should be further evaluated by conducting well-powered RCTs.

Acknowledgement

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carrev.2018.06.005.

References

[1] Azzalini L, Candilio L, McCullough PA, Colombo A. Current risk of contrast-induced acute kidney injury after coronary angiography and intervention: a reappraisal of the literature. Can J Cardiol 2017;33(10):1225–8.
[2] Thomsen HS, Morcos SK. ESUR guidelines on contrast media. Abdom Imaging 2006; 31(2):131–40.
[3] National Clinical Guideline C. National institute for health and clinical excellence: guidance. Acute kidney injury: prevention, detection and management up to the point of renal replacement therapy. London: royal college of physicians (UK) national clinical guideline centre; 2013.
[4] Nijssen EC, Rennenberg RJ, Nelemans PJ, Essers BA, Janssen MM, Vermeeren MA, et al. Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. Lancet (London, England) 2017;389(10076):1312–22.
[5] Weisbord SD, Gallagher M, Jneid H, Garcia S, Cass A, Thwin SS, et al. Outcomes after angiography with sodium bicarbonate and acetylcysteine. 2018;378(7):603–14.
[6] Ades AE, Sculpher M, Sutton A, Abrams K, Cooper N, Welton N, et al. Bayesian methods for evidence synthesis in cost-effectiveness analysis. Pharmacoeconomics 2006;24(1):1–19.
[7] Cochrane handbook for systematic reviews of interventions version 5.1.0: updated March 2011; 2011.
[8] Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015;162(11):777–84.
[9] Brar SS, Aharonian V, Mansukhani P, Moore N, Shen AY, Jorgensen M, et al. Haemodynamic-guided fluid administration for the prevention of contrast-induced acute kidney injury: the POSEIDON randomised controlled trial. Lancet (London, England) 2014;383(9931):1814–23.
[10] Giacoppo D, Gargiulo G, Buccheri S, Aruta P, Byrne RA, Cassese S, et al. Preventive strategies for contrast-induced acute kidney injury in patients undergoing percutaneous coronary procedures: evidence from a hierarchical Bayesian network Meta-analysis of 124 trials and 28 240 patients. Circ Cardiovasc Interv 2017;10(5).
[11] Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343.
[12] White IR, Barrett JK, Jackson D, Higgins JPT. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. Res Synth Methods 2012;3(2):111–25.
[13] Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane database of systematic reviews. Int J Epidemiol 2012;41(3):818–27.
[14] Hamra G, MacLehose R, Richardson D. Markov chain Monte Carlo: an introduction for epidemiologists. Int J Epidemiol 2013;42(2):627–34.
[15] Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 2011;64(2):163–71.
[16] Ali-Hassan-Sayegh S, Mirhosseini SJ, Rahimizadeh E, Ghodratipour Z, Sarrafan-Chaharsoughi Z, Dehghan AM, et al. Current status of sodium bicarbonate in coronary angiography: an updated comprehensive meta-analysis and systematic review. Cardiol Res Pract 2015;2015:690308.
[17] Lee JM, Park J, Jeon KH, Jung JH, Lee SE, Han JK, 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.
[18] Jang JS, Jin HY, Seo JS, Yang TH, Kim DK, Kim TH, 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):2255–65.
[19] Schwarzer G, Carpenter JR, Rücker G. Small-study effects in meta-analysis. Meta-analysis with R. Cham: Springer International Publishing; 2015; 107–41.
[20] Ali-Hasan-Al-Saegh S, Mirhosseini SJ, Ghodratipour Z, Sarrafan-Chaharsoughi Z, Rahimizadeh E, Karimi-Bondarabadi AA, et al. Strategies preventing contrast-induced nephropathy after coronary angiography: a comprehensive meta-analysis and systematic review of 125 randomized controlled trials. Angiology 2017;68(5): 389–413.
[21] Subramaniam RM, Suarez-Cuervo C, Wilson RF, Turban S, Zhang A, Sherrod C, et al. Effectiveness of prevention strategies for contrast-induced nephropathy: a systematic review and meta-analysis. Ann Intern Med 2016;164(6):406–16.

[22] Liao JK, Laufs U. Pleiotropic effects of statins. Annu Rev Pharmacol Toxicol 2005;45:89–118.
[23] Buyukhatipoglu H, Sezen Y, Yildiz A, Bas M, Kirhan I, Ulas T, et al. N-acetylcysteine fails to prevent renal dysfunction and oxidative stress after noniodine contrast media administration during percutaneous coronary interventions. Pol Arch Med Wewn 2010;120(10):383–9.
[24] Brar SS, Shen AY, Jorgensen MB, Kotlewski A, Aharonian VJ, Desai N, 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):1038–46.
[25] Navaneethan SD, Singh S, Appasamy S, Wing RE, Sehgal AR. Sodium bicarbonate therapy for prevention of contrast-induced nephropathy: a systematic review and meta-analysis. Am J Kidney Dis 2009;53(4):617–27.
[26] Xu R, Tao A, Bai Y, Deng Y, Chen G. Effectiveness of N-acetylcysteine for the prevention of contrast-induced nephropathy: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc 2016;5(9).
[27] Boucek P, Havrdova T, Oliyarnyk O, Skibova J, Pecenkova V, Pucelikova T, 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(3):303–8.
[28] Vasheghani-Farahani A, Sadigh G, Kassaian SE, Khatami SM, Fotouhi A, Razavi SA, 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):610–8.
[29] Thayssen P, Lassen JF, Jensen SE, Hansen KN, Hansen HS, Christiansen EH, 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):216–24.
[30] Tamura A, Goto Y, Miyamoto K, Naono S, Kawano Y, Kotoku M, 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):921–5.
[31] Pakfetrat M, Nikoo MH, Malekmakan L, Tabandeh M, Roozbeh J, Nasab MH, 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):629–34.
[32] Ozcan EE, Guneri S, Akdeniz B, Akyildiz IZ, Senaslan O, Baris N, 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):539–44.
[33] Motohiro M, Kamihata H, Tsujimoto S, Seno T, Manabe K, Isono T, 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):1604–8.
[34] Merten GJ, Burgess WP, Gray LV, Holleman JH, Roush TS, Kowalchuk GJ, et al. Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. JAMA 2004;291(19):2328–34.
[35] Maioli M, Toso A, Leoncini M, Gallopin M, Tedeschi D, Micheletti C, 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.
[36] Lee SW, Kim WJ, Kim YH, Park SW, Park DW, Yun SC, et al. Preventive strategies of renal insufficiency in patients with diabetes undergoing intervention or arteriography (the PREVENT trial). Am J Cardiol 2011;107(10):1447–52.
[37] Koc F, Ozdemir K, Altunkas F, Celik A, Dogdu O, Karayakali M, 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):872–7.
[38] Klima T, Christ A, Marana I, Kalbermatter S, Uthoff H, Burri E, 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):2071–9.
[39] Gomes VO, Lasevitch R, Lima VC, Brito Jr FS, Perez-Alva JC, Moulin B, et al. Hydration with sodium bicarbonate does not prevent contrast nephropathy: a multicenter clinical trial. Arq Bras Cardiol 2012;99(6):1129–34.
[40] Castini D, Lucreziotti S, Bosotti L, Salerno Uriarte D, Sponzilli C, Verzoni A, et al. Prevention of contrast-induced nephropathy: a single center randomized study. Clin Cardiol 2010;33(3):E63–8.
[41] 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):33–6.
[42] Manari A, Magnavacchi P, Puggioni E, Vignali L, Fiaccadori E, Menozzi M, et al. Acute kidney injury after primary angioplasty: effect of different hydration treatments. J Cardiovasc Med (Hagerstown) 2014;15(1):60–7.
[43] Yeganehkhah MR, Iranirad L, Dorri F, Pazoki S, Akbari H, Miryounesi M, 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):1217–23.
[44] Solomon R, Gordon P, Manoukian SV, Abbott JD, Kereiakes DJ, Jeremias A, 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):1519–24.
[45] 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):1250–9.
[46] 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):90–6.
[47] Baskurt M, Okcun B, Abaci O, Dogan GM, Kilickesmez K, Ozkan AA, et al. N-acetylcysteine versus N-acetylcysteine + theophylline for the prevention of contrast nephropathy. Eur J Clin Invest 2009;39(9):793–9.
[48] Briguori C, Manganelli F, Scarpato P, Elia PP, Golia B, Riviezzo G, et al. Acetylcysteine and contrast agent-associated nephrotoxicity. J Am Coll Cardiol 2002;40(2):298–303.
[49] Azmus AD, Gottschall C, Manica A, Manica J, Duro K, Frey M, et al. Effectiveness of acetylcysteine in prevention of contrast nephropathy. J Invasive Cardiol 2005;17(2):80–4.
[50] Carbonell N, Blasco M, Sanjuan R, Perez-Sancho E, Sanchis J, Insa L, et al. Intravenous N-acetylcysteine for preventing contrast-induced nephropathy: a randomised trial. Int J Cardiol 2007;115(1):57–62.
[51] 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.e9–1032.e12.
[52] Ferrario F, Barone MT, Landoni G, Genderini A, Heidemperger M, Trezzi M, et al. Acetylcysteine and non-ionic isosmolar contrast-induced nephropathy–a randomized controlled study. Nephrol Dial Transplant 2009;24(10):3103–7.
[53] Gomes VO, Poli de Figueredo CE, Caramori P, Lasevitch R, Bodanese LC, Araujo A, et al. N-acetylcysteine does not prevent contrast induced nephropathy after cardiac catheterisation with an ionic low osmolality contrast medium: a multicentre clinical trial. Heart 2005;91(6):774–8.
[54] Holscher 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):845–50.
[55] Kay J, Chow WH, Chan TM, Lo SK, Kwok OH, Yip A, 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):553–8.
[56] Kim BJ, Sung KC, Kim BS, Kang JH, Lee KB, Kim H, 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):239–45.
[57] Miner SE, Dzavik V, Nguyen-Ho P, Richardson R, Mitchell J, Atchison D, et al. N-acetylcysteine reduces contrast-associated nephropathy but not clinical events during long-term follow-up. Am Heart J 2004;148(4):690–5.
[58] 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):1383–8.
[59] Thiele H, Hildebrand L, Schirdewahn C, Eitel I, Adams V, Fuernau G, 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(20):2201–9.
[60] Brueck M, Cengiz H, Hoeltgen R, Wieczorek M, Boedeker RH, Scheibelhut C, 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(6):276–83.
[61] Webb JG, Pate GE, Humphries KH, Buller CE, Shalansky S, Al Shamari A, 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):422–9.
[62] Kumar A, Bhawani G, Kumari N, Murthy KS, Lalwani V, Raju Ch N. 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) (Hc03-7)e.
[63] Chong E, Poh KK, Lu Q, Zhang JJ, Tan N, Hou XM, 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;201:237–42.
[64] Han Y, Zhu G, Han L, Hou F, Huang W, Liu H, 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.
[65] Jo SH, Koo BK, Park JS, Kang HJ, Cho YS, Kim YJ, 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.e1–8.
[66] 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):71–9.
[67] Li W, Fu X, Wang Y, Li X, Yang Z, Wang X, 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.
[68] Patti G, Ricottini E, Nusca A, Colonna G, Pasceri V, D'Ambrosio 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.
[69] Quintavalle C, Fiore D, De Micco F, Visconti G, Focaccio A, Golia B, et al. Impact of a high loading dose of atorvastatin on contrast-induced acute kidney injury. Circulation 2012;126(25):3008–16.
[70] Bidram P, Roghani F, Sanei H, Hedayati Z, Golabchi A, Mousavi M, et al. Atorvastatin and prevention of contrast induced nephropathy following coronary angiography. J Res Med Sci 2015;20(1):1–6.
[71] Abaci O, Arat Ozkan A, Kocas C, Cetinkal G, Sukru Karaca O, Baydar O, 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):867–71.
[72] 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.