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Published in:
European Journal of Radiology

DOI:
10.1016/j.ejrad.2022.110368

Publication date:
2022

European Journal of Radiology 153 (2022) 110368

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Systematic review and *meta*-analysis of prophylaxis use with intravenous contrast exposure to prevent contrast-induced nephropathy

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ARTICLE INFO

Keywords:
Iodinated Contrast
Contrast induced nephropathy
Prophylaxis

ABSTRACT

Purpose: Iodinated radiographic contrast media has been associated with an acute deterioration in renal function, termed contrast induced nephropathy (CIN). This review aims to establish the efficacy of prophylaxis interventions used in adult patients prior to intravenous exposure to iodinated contrast to reduce the risk of CIN.
Methods: An electronic search for published peer-reviewed articles was performed, supplemented with manual review of references from previous systematic reviews and the National Institute for Health and Care Excellence guidelines. Risk of bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias. Random-effect *meta*-analyses were used to assess CIN incidence, need for kidney replacement therapy (KRT), mortality, fluid overload and persistent kidney dysfunction.
Results: 22 studies assessing a range of interventions were included in the qualitative analysis. The incidence of CIN was reduced by the use of N-acetylcysteine compared to a control group of saline (risk difference = -0.07, 95% CI −0.13 to −0.01) but not by sodium bicarbonate compared to control group of saline (risk difference = -0.02, 95% CI −0.04 to 0.01). Published studies give no indication that prophylactic interventions have significant impact on the need for KRT, mortality or persistent renal impairment.
Conclusion: Evidence for prophylaxis against CIN in patients receiving intravenous iodinated contrast is limited. There was an association with the use of NAC with reduced incidence of CIN following intravenous contrast but there was no impact on other clinical outcomes assessed. The clinical significance of these findings remains unclear and further research focusing on these clinical outcomes is required.

1. Introduction

Iodinated radiographic contrast media have been associated with an acute deterioration in renal function, commonly termed contrast induced nephropathy (CIN), defined as a rise in creatinine of ≥ 25% of baseline or 44 μmol/l from the pre-contrast value within 3 days of intravascular administration of a contrast medium [1]. Several clinical interventions aim to reduce the incidence of CIN, including volume expansion with intravenous (IV) or oral fluid, administration of N-Acetylcysteine (NAC), sodium bicarbonate, alprostadil and vitamin E[2,3].

The clinical relevance and presence of CIN following IV contrast, as typically used for computed tomography (CT) examinations, has increasingly become a topic of debate. Recent evidence suggests that the relationship between IV contrast and deterioration in renal function is not as clear as for intra-arterial (IA) contrast, and that risks appear to be previously overstated[4–7]. The American College of Radiology (ACR) has suggested that CIN (relating to when contrast has been specifically identified as causing the deterioration in renal function) be distinguished from post-contrast acute kidney injury (PC-AKI) (where there is coincidental AKI following contrast but likely not caused directly by the contrast), although they have acknowledged such distinction is not straightforward[8]. The latest consensus statements from the ACR and

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https://doi.org/10.1016/j.ejrad.2022.110368
Received 1 February 2022; Received in revised form 5 May 2022; Accepted 18 May 2022
Available online 23 May 2022

the National Kidney Foundation (NKF)[9] state that the true risk of CIN is unclear for patients with severe kidney impairment. Nevertheless, they recommend that prophylaxis is utilised for individuals who have AKI or an estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m^2 and considered for individuals with an eGFR 30–44 ml/min/1.73 cm^2 where other risk factors may exist. A recent retrospective study has demonstrated that the risk of AKI is increased following contrast-enhanced CT in patients with eGFR < 30 ml/min/1.73 m^2[10], which underscores the need to better identify interventions that might be effective in preventing CIN in this population.

While systematic reviews of contrast prophylaxis have been carried out before, these have largely included studies where intra-arterial (IA) contrast was administered with no distinction between outcomes in IV and IA contrast [2,3,11]. The indications for use of IV and IA contrast differ, with differences in the specific risk factors for AKI in the corresponding patient populations. Consequently, it is appropriate to evaluate the effectiveness of prophylaxis measures for IA and IV administration separately.

The aim of this review is to identify studies that provide evidence on the effectiveness of prophylaxis interventions used in adult patients prior to IV exposure of contrast media to reduce the risk of CIN.

2. Methods

This systematic review and *meta*-analysis were conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12].

This systematic review and *meta*-analysis were prospectively registered with PROSPERO (Registration Number: CRD42019128843). Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019128843.

A further systematic review relating to renal protection with IV fluids versus no renal protection prior to IV contrast exposure was also registered with PROSPERO (Registration Number: CRD42019129052). Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019129052.

2.1. Eligibility criteria

Controlled and observational studies involving adult patients, who received any intervention that aimed to reduce contrast-induced nephropathy compared with a control group, were eligible for inclusion. The control group was defined as patients receiving IV contrast who also received IV saline, oral hydration or no supplementary hydration. Studies were required to report the incidence of CIN, as per the individual study definition. Case reports and animal studies were excluded. Studies where route of contrast administration was unclear, where participants received only IA contrast, or studies where it was not possible to disaggregate outcomes for patients receiving IA versus IV contrast were also excluded.

2.2. Information sources and search strategy

An electronic search for published peer-reviewed articles was performed within MEDLINE, EMBASE and the Cochrane Library. Searches were restricted to those published in the English language only. Electronic database searches were supplemented with manual review of references from previous systematic reviews of contrast associated AKI and contrast induced nephropathy and the National Institute for Health and Care Excellence (NICE) guideline NG148 “Acute kidney injury: prevention, detection and management”[13]. Electronic databases were searched for all articles published up to 29th July 2020. A hand search of references was also carried out. The full MEDLINE search strategy is available in supplementary materials (Supplementary Table 1).

2.3. Data collection and analysis

Three reviewers (GG, HW and PT) independently screened article titles and abstracts to identify cases that were deemed to meet the inclusion criteria. These selected articles were then reviewed again independently, in full, by the same reviewers to confirm that they met the eligibility criteria. Any differences were resolved by consensus or discussion with another reviewer (SB). This was performed on the 5th of November 2021.

Data was extracted independently by two reviewers (GG and HW) and collated into a pre-defined data collection form which was entered into spreadsheet and electronic data manager (Review Manager 5.4) to allow for analysis.

Data recorded from each study comprised study characteristics (study design, setting, sample size, publication year), study methods (interventions and controls used, inclusion and exclusion criteria, CIN definition), patient characteristics (mean age, sex, presence of comorbidities, medications) and outcome measurement (incidence of CIN, need for kidney replacement therapy (KRT), failure of recovery of renal function following CIN, mortality and fluid overload). Where serum creatinine values were reported in mg/dl they were converted to μmol/l. Missing demographic data for the above variables were described for each included study as applicable.

2.4. Risk of bias

The Cochrane Collaboration’s RoB2 tool for assessing risk of bias was used to assess risk of bias for included studies by two independent reviewers (GG, HW, EL or PT)[14]. A risk of bias graph and summary table was generated to allow visualisation of bias within individual studies and across all included studies. Small sample bias was assessed visually using funnel plots and the presence of asymmetry was quantified using Egger’s statistical test of intercept. P-values < 0.05 were considered as significant evidence for asymmetry. Publication bias was also assessed using p-curve analysis which looks for p-hacking [15].

2.5. Summary measures and data synthesis

Outcomes were tabulated and *meta*-analysis performed where there were at least 3 studies comparing the same intervention where the outcome was measured to generate a risk difference.

All statistical analyses were performed using R software version 4.0.2 implementing random-effects models due to differences in the studied populations using the meta package. The Paule-Mandel estimator was used to generate effect sizes for continuous and dichotomous outcomes. The Paule-Mandel estimator is a classical estimation method that allows estimation of unknown between-study variance and was chosen for its low bias and superior performance as an estimator for both continuous and dichotomous outcomes[16].

3. Results

3.1. Study selection and characteristics of included studies

A total of 22 studies were included for qualitative synthesis in this systematic review, with 21 of these studies being feasible to include in the quantitative *meta*-analysis (one study resulted in two publications reporting outcomes at 35 days and 365 days). The study [17] that was excluded from *meta*-analysis was due to small study numbers in the control group preventing stratification by intervention. Fig. 1 shows a detailed flow diagram of the study selection process. Baseline study characteristics for the included studies are presented in Table 1. Study inclusion and exclusion criteria are presented in Supplementary Table 2 with definitions of CKD for each study presented in Supplementary Table 3. Nephrotoxic medication use is presented in Supplementary Table 4.

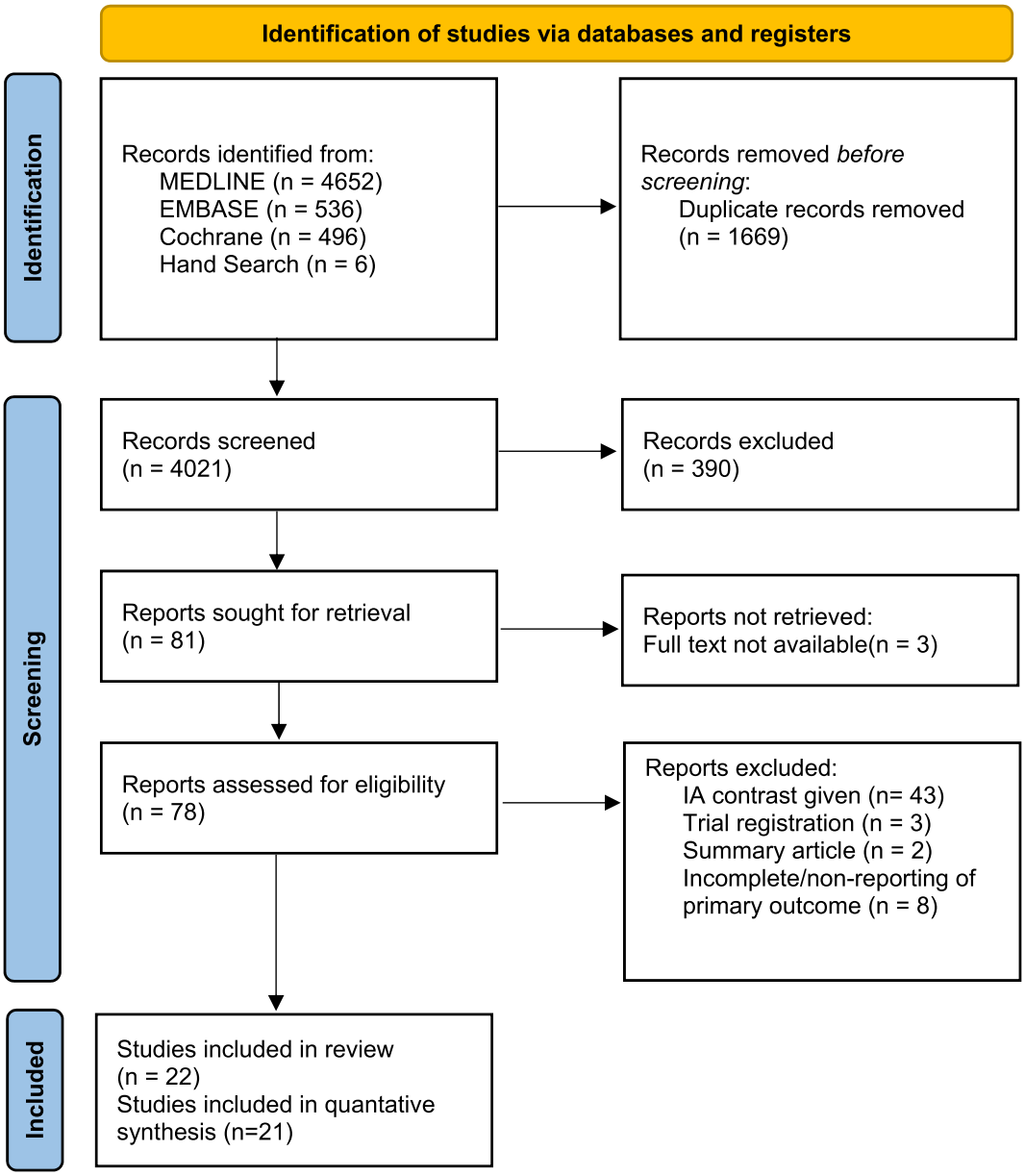

Fig. 1. Flow diagram of study selection.

Most studies assessed a single intervention against a control group receiving IV saline, with the exception of five studies; two used no hydration[18,19], one non-specific hydration[20], one oral hydration[21] and a single study compared saline as an intervention against no hydration[22,23]. Some studies assessed more than one intervention [20,24–26]. Ten studies compared the use of NAC with a control group of IV saline and four studies compared the use of sodium bicarbonate with a control group IV saline. Other interventions studied included IV saline [22,23], balanced salt solution[27], alprostadil[28,29], vitamin E [26], misoprostol[17], theophylline[17] and nifedipine[17].

Due to the low number of studies available, it was only possible to *meta*-analyse the outcomes of CIN and need for KRT for NAC and sodium bicarbonate. Other outcomes and treatments were lacking in the number of studies available.

Baseline kidney function (in the form of an eGFR measurement or creatinine clearance) was provided for nine studies. None of the populations of the studies that provided information on baseline measurement of kidney function had a mean eGFR of<30 ml/min^2 (Table 1).

Risk of bias was assessed with 15 of the 22 studies having a high risk of bias in at least one domain (Supplementary Figs. 1-2) with all of them relating to the blinding of participants or study team members to the randomised intervention. It was therefore not possible to evaluate the impact of blinding on the results in a sensitivity analysis.

3.2. Incidence of CIN

Of the 20 studies suitable for inclusion in the quantitative *meta*-analysis, twenty presented results of CIN in all treatment groups (see Table 2). The majority of studies used a "standard" change in creatinine of 44 μmol/l or > 25% from baseline with minor variation in the definition used for CIN – largely relating to the sampling time for the post-contrast sample, although one study incorporated cystatin C as well as creatinine into the diagnosis. However, only an absolute change in creatinine was included in one study and only a relative change in creatinine was used in two studies. Two studies used variations on the Kidney Disease Improving Global Outcomes (KDIGO) AKI definition with one using an increase in creatinine of ≥ 26.5 μmol/l or ≥ 20% and/or a decrease in eGFR ≥ 20% from baseline within 72 h of contrast to

Table 1
study demographics at baseline.

First author	Year	Country	Study Design	Intervention	No. of patients	Mean age (SD)	Sex – female n (%)	Hypertension n(%)	Diabetes n(%)	Baseline creatinine μmol/l (SD)	Baseline eGFR ml/min (SD)	CKD	Heart failure
Demir [17]	2008	Turkey	RCT	Intervention: oral NAC 600 mg/day for 3 days starting 1 day prior to procedure + 0.9% saline as per control group	20	62 (15.8)	9 (45)	–	Excluded	69 (16.8)	100.6 (39.6)	–	–
				Control: 2L 0.9% saline IV at least 24hrs prior and continuing 24hrs post contrast	20	58.2 (11.3)	5 (25)	–	Excluded	77.8 (20.3)	89.3 (36.9)	–	–
				Intervention: oral Misoprostol 400 mg/day for 3 days starting 1 day prior to contrast + 0.9% saline as per control group	20	56.5 (13)	11 (55)	–	Excluded	75.2 (16.8)	95.1 (31)	–	–
				Intervention: oral Theophylline 200 mg/day for 3 days starting 1 day prior to procedure + 0.9% saline as per control group	20	56.3 (13)	9 (45)	–	Excluded	74.3 (23.9)	113.4 (42.3)	–	–
				Intervention: oral Nifedipine 30 mg/day for 3 days starting 1 day prior to procedure + 0.9% saline as per control group	17	60.1 (10.7)	9 (52.9)	–	Excluded	72.5 (15)	90.2 (35.1)	–	–
Hsu [45]	2012	Taiwan	Case control	Intervention: IV NAC 600 mg in 0.9% saline 3 ml/kg (1.5 ml/kg with congestive pulmonary oedema) for 60 mins prior to contrast + 0.9% saline as per control group post contrast	106	79.7 (8.5)	28 (26.4)	70 (66)	31 (29.2)	123.8 (51.3)	–	32 (30.2)	18 (17)
				Control: 0.9% saline IV 3 ml/kg (1.5 ml/kg with congestive pulmonary oedema) for 60 mins prior to contrast + 0.9% saline 1 ml/kg/hr (or 0.5 ml/kg/hr) for 6 h post contrast	103	79.3 (11.1)	25 (24.3)	62 (60.2)	26 (25.2)	111.4 (38)	–	13 (12.6)	12 (11.7)
Kama [24]	2014	Turkey	RCT	Intervention: IV NAC 150 mg/kg in 1L 0.9% saline at rate of 350 ml/hr for 3 h (pre, during and post contrast)	36	69 (11.8)	15 (30.6)	–	15 (42)	–	–	–	14 (39)
				Intervention: IV sodium bicarbonate 150 mEq in 1L 0.9% saline at rate of 350 ml/hr for 3 h (pre, during and post contrast)	36	76 (11.8)	17 (34.7)	–	11 (31)	–	–	–	18 (50)
				Control: 1L 0.9% saline IV at rate of 350 ml/hr for 3 h (pre, during and post contrast)	35	67 (14.6)	16 (32.7)	–	9 (25.8)	–	–	–	6 (17)
Khalili [30]	2006	Iran	RCT	Intervention: oral NAC 1200 mg/day 1 day prior to contrast and day of contrast + 0.9% saline as per control group	35	59.8 (2)	15 (42.9)	–	14 (40)	126.4 (32.7)	56.5 (11.0)	35 (100)	–
				Control: 1L 0.9% saline IV 1 ml/kg/hr prior to contrast	35	55.9 (12.9)	13 (37.1)	–	11 (31.4)	99.9 (13.3)	59.2 (11.5)	35 (100)	–
Kitzler [26]	2012	Austria	RCT	Intervention: oral NAC granules 1200 mg + 540 mg placebo emulsion 4 doses (12hrs + 6hrs prior and 6hrs + 12 hrs post contrast) + 0.45% saline as per control group	10	76.6 (9.5)	8 (80)	–	–	121.1 (45.1)	56 (25)	10 (100)	–
				Intervention: oral vitamin E emulsion 540 mg + 1200 mg placebo granules 4 doses (12hrs + 6hrs prior and 6hrs + 12 hrs post contrast) + 0.45% saline as per control group	10	73.3 (11.9)	4 (40)	–	–	121.1 (17.7)	64 (24)	10 (100)	–
				Control: 0.45% saline IV 1 ml/kg/hr 12hrs prior and 12hrs post contrast + 1200 mg placebo granules + 540 mg placebo emulsion 4 doses (12hrs + 6hrs prior and 6hrs + 12 hrs post contrast)	10	74 (8.5)	5 (50)	–	–	117.6 (10.6)	63 (21)	10 (100)	–
Kooiman [33]	2014	Netherlands	RCT	Intervention: 250 ml 1.4% sodium bicarbonate IV 1hr prior to contrast	267	71.6 (9.8)	107 (40.1)	–	71 (26.6)	–	–	267 (100)	42 (15.7)
				Control: 2L 0.9% saline IV (1L prior + 1L post contrast, variable rate 83–250 ml/hr decided by treating physician)	281	72.5 (9.5)	110 (39.1)	–	76 (27)	–	–	281 (100)	48 (17.1)

(*continued on next page*)

Table 1 (*continued*)

First author	Year	Country	Study Design	Intervention	No. of patients	Mean age (SD)	Sex – female n (%)	Hypertension n(%)	Diabetes n(%)	Baseline creatinine μmol/l (SD)	Baseline eGFR ml/min (SD)	CKD	Heart failure
Kooiman 2 [19]	2014	Netherlands	RCT	Intervention: 250 ml 1.4% sodium bicarbonate IV 1hr prior to contrast	71	71.1 (13.3)	37 (52.1)	–	13 (14.9)	–	–	71 (100)	5 (7)
				Control: no hydration (unless clinical indication for IV fluid for volume expansion)	67	70 (12.4)	32 (47.8)	–	10 (18.3)	–	–	67 (100)	6 (9)
Martin-Moreno [20]	2015	Spain	RCT	Intervention: IV 1/6 M sodium bicarbonate 3 ml/kg/hr 1hr prior to contrast	43	59 (15.4)	13 (30.2)	–	–	79.6 (35.4)	–	–	NYHA III or IV
				Intervention: oral sodium citrate 1300 mg/l of sodium at a rate of 75 ml/10 kg divided into 4 doses (1 dose/hr) 4hr prior to contrast	43	56.6 (15.5)	18 (41.9)	–	–	70.7 (26.5)	–	–	excluded
				Control: no prophylaxis	44	56.8 (16.8)	18 (41)	–	–	79.6 (26.5)	–	–	–
Miao [28]	2013	China	RCT	Intervention: IV alprostadil 0.4 μg/kg/day in 100 ml 0.9% saline 48hrs prior to + 48hrs post contrast	154	79.1 (6.2)	34 (22.1)	118 (76.6)	49 31.8)	87.5 (24.8)	58.8 (16.8)	82 (53.2)	LVEF < 40%
				Control: 100 ml 0.9% saline IV 48hrs prior to + 48hrs post contrast	176	78.3 (6.6)	43 (24.4)	131 (74.4)	52 (29.5)	88.4 (23.9)	57.7 (16.5)	98 (55.7)	excluded
Nijssen [22,23]	2017	Netherlands	RCT	Intervention: long protocol intravenous 0·9% NaCl 1 ml/kg per h during 12 h before and 12 h aftercontrast administration OR intravenous0·9% NaCl 3–4 ml/kg per h during 4 h before and 4 h after contrast administration	152 (169 in ITT group)	*	*	*	*	*	*	*	*
				Control: No intravenous hydration	162 (172 in ITT group)	*	*	*	*	*	*	*	*
Palli [46]	2017	Greece	RCT	Intervention: 1200 mg NAC IV in 100 ml 0.9% saline + 2 g ascorbic acid IV in 100 ml 0.9% saline at 2hrs pre and 10hrs + 18hrs post contrast	60	51.3 (2.7)	14 (23.3)	18 (30)	9 (15)	71.6 (8.8)	–	6 (10)	–
				Control: 200 ml 0.9% saline IV at 2hrs pre and 10hrs + 18hrs post contrast	64	50.5 (2.7)	9 (14.1)	18 (28.1)	3 (4.7)	66.3 (5.3)	–	4 (6.3)	–
Park[27]	2020	South Korea	RCT	Intervention: balanced salt solution (Plasma solution A; CJ Healthcare) with 98 mEq/L of chloride at pH 7.4 at a rate of 3 ml/kg per hour for 1 h before and 1.5 ml/kg per hour for 4 h after the CE-CT	242	71.3 (10.4)	75 (31)	171 (70.7)	106 (43.8)	141.5 (53.1)	46.1 (13.1)	–	–
				Control: 0.9% saline solution with 154 mEq/L of chloride at pH 6.0 at a rate of 3 ml/kg per hour for 1 h before and 1.5 ml/kg per hour for 4 h after the CE-CT	251	70.6 (10.2)	73 (29.1))	200 (79.7)	135 (53.8)	141.5 (53.1)	45.2 (13.1)	–	–
Poletti [31]	2007	Switzerland	RCT	Intervention: 900 mg NAC IV in 50 ml 5% dextrose 1hr prior to contrast + 0.45% saline as per control group	50	69.5 (18.7)	18 (41)	–	9 (18)	145.9 (35.4)	–	50 (100)	Severe excluded
				Control: placebo 50 ml 0.9% saline IV 1hr prior to contrast + 0.45% saline IV 5 ml/lg 1hr prior to contrast and 1 ml/kg over 12hrs post contrast	50	72.7 (17.2)	14 (33)	–	6 (12)	147.7 (36.3)	–	50 (100)	
Poletti[38]	2013	Switzerland	RCT	Intervention: 600 mg NAC IV in 100 ml 0.45% saline given over 1hr prior to contrast	55	78.1 (12)	27 (49.1)	–	15 (27)	132.6 (34.5)	42.7 (1.2)	55 (100)	–
				Control: 100 ml 0.45% saline given over 1hr prior to contrast	59	78.2 (11.8)	30 (50.8)	–	11 (19)	133.5 (34.5)	41.7 (1.2)	59 (100)	–
Sar[47]	2010	Turkey	RCT	Intervention: 1200 mg/day NAC oral 1hr prior to contrast and each day post contrast for 2 days + 0.9% saline IV as per control group	25	60 (11.3)	9 (45)	–	25 (100)	73.4 (13.3)	90.9 (25.1)	–	Excluded
				Control: 0.9% saline IV 1 ml/kg 12hrs pre + 24hrs post contrast	20	53.5 (9.9)	12 (48)	–	20 (100)	71.6 (15)	97.8 (28.6)	–	

(*continued on next page*)

Table 1 (*continued*)

First author	Year	Country	Study Design	Intervention	No. of patients	Mean age (SD)	Sex – female n (%)	Hypertension n(%)	Diabetes n(%)	Baseline creatinine μmol/l (SD)	Baseline eGFR ml/min (SD)	CKD	Heart failure
Sebastià [21]	2021	Spain	RCT	Intervention: IV sodium bicarbonate 166 mmol/l 3 ml/kg/hour 1 h before and 1 ml/kg/hour for 1 h after contrast exposure	114	76 (range 35–96)	35 (30.7)	89 (78.1)	52 (45.6)	150 (range 106–195)	36.0 (range 25.0–44.0)	–	–
				Control: 500 ml water two hours before and 2000 ml in the 24 h post-contrast exposure	114	74 (range 35–96)	40 (35.1)	78 (68.4)	43 (37.7)	141 (range 97–195)	39.0 (range 28.0–44.0)	–	–
Tepel [32]	2000	Germany	RCT	Intervention: 600 mg/day NAC oral 1 day prior + post contrast + 0.45% saline as per control group	41	66 (11)	17 (41.5)	–	13 (32)	221.1 (114.9)	–	41 (100)	–
				Control: 0.45% saline 1 ml/kg/hr 12hrs pre + post contrast	42	65 (15)	19 (45.2)	–	14 (33)	212.2 (114.9)	–	42 (100)	–
Timal [18]	2020	Netherlands	RCT	Intervention: 250 ml 1.4% sodium bicarbonate IV 1hr pre contrast	261	73 (-)	95 (36.4)	–	104 (39.8)	124.7 (23)	–	261 (100)	43 (16.5)
				Control: No hydration	262	74 (-)	92 (35.1)	–	103 (39.3)	126.4 (23.9)	–	262 (100)	39 (14.9)
Traub [48]	2013	USA	RCT	Intervention: 3 g NAC IV in 500 ml 0.9% saline 30mins pre contrast, 200 mg/hr NAC IV in 1L 0.9% saline post contrast for minimum 2hrs – infusion stopped when patient discharged, by caring clinician, after 24 h or any adverse reactions	185	61.5 (15.3)	124 (62)	153 (77)	65 (33)	88.4 (24.8)	–	18 (9)	10 (5)
				Control: 500 ml 0.9% saline IV 30mins pre contrast + 0.9% saline OV 67 ml/hr post contrast given for minimum 2 h - infusion stopped when patient discharged, by caring clinician, after 24 h or any adverse reactions	172	59.7 (15.9)	113 (57)	148 (74)	64 (32)	87.5 (23.9)	–	7 (4)	8 (4)
Turedi [25]	2016	Turkey	RCT	Intervention: 3 g NAC IV in 1L 0.9% saline 3 ml/kg for 1hr pre contrast + 1 ml/kg for minimum 6hrs maximum 24hrs post contrast	85	76 (18.5)	44 (51.8)	–	11 (12.9)	80.5 (38.9)	88.9 (69.8)	9 (10.6)	8 (9.4)
				Intervention: 132 mEq sodium bicarbonate IV in 1L 0.9% saline 3 ml/kg for 1hr pre contrast + 1 ml/kg for minimum 6hrs maximum 24hrs post contrast	85	77 (20.9)	42 (49.4)	–	14 (16.5)	80.5 (40.7)	85 (62.6)	6 (7.1)	8 (9.4)
				Control: 0.9% saline IV 3 ml/kg for 1 hr pre contrast + 1 ml/kg post contrast for minimum 6hrs maximum 24hrs post contrast	87	74 (6.8)	41 (47.1)	–	6 (13.8)	90.2 (37.1)	73.8 (135.6)	10 (11.5)	8 (9.2)
van Mourick [49]	2018	Netherlands	RCT	Intervention: 1.4% sodium bicarbonate IV 3 ml/kg/hr for 1hr pre contrast	39	81.2 (-)	19 (48.7)	32 (82.1)	14 (35.9)	117.6 (37.1)	–	39 (100)	24 (68.6)
				Control: 0.9% saline IV 1 ml/kg/hr 8hrs pre contrast + 16hrs post contrast	35	83 (-)	22 (62.9)	26 (74.3)	9 (25.7)	109.6 (32.7)	–	35 (100)	29 (74.4)

* Study demographics were provided for participants who received IV and IA contrast

Table 2
Studies reporting incidence of study-defined CIN.

Paper	Definition Used	Intervention Received	Events in Intervention Group	Size of Intervention Group	Absolute Risk
Demir 2008[17]	An elevation of serum creatinine by ≥ 44 μmol/l or ≥ 25% within three days of RCA injection	NAC	1	20	0.05
		Misoprostol	0	20	0
		Theophylline	4	20	0.20
		Nifedipine	0	17	0
		Control IV saline	0	20	0
Hsu 2012[45]	Increase in SCr ≥ 44 μmol/l or ≥ 25% from baseline within 48–72 h of contrast	NAC	12	106	0.11
		Control IV saline	20	103	0.19
Kama 2014[24]	Increase in SCr ≥ 44 μmol/l or ≥ 25% from baseline within 48–72 h of contrast	NAC	7	36	0.19
		Sodium Bicarbonate	4	36	0.11
		Control IV saline	5	35	0.14
Khalili 2006[30]	Increase in SCr ≥ 25% from baseline within 48–72 h of contrast	NAC	5	35	0.14
		Control IV saline	12	35	0.34
Kitzler 2012[26]	Increase in SCr > 25% from baseline within 48 h of contrast	NAC	0	10	0
		Sodium Bicarbonate	0	10	0
		Control IV saline	0	9	0
Kooiman 2014 [33]	Increase in SCr ≥ 44 μmol/l or > 25% from baseline within 48–96 h of contrast	Sodium Bicarbonate	8	264*	0.03
		Control IV saline	14	274*	0.05
Kooiman2 2014 [19]	Increase in SCr ≥ 44 μmol/l or > 25% from baseline within 48–96 h of contrast	Sodium Bicarbonate	5	70*	0.07
		Control no hydration	6	65*	0.09
Martin-Moreno 2015[20]	Increase in SCr ≥ 25% from baseline within 24 h of contrast	Sodium Bicarbonate	3	43	0.07
		Oral Sodium Citrate	5	43	0.12
		Control no hydration	4	44	0.09
Miao 2013[28]	Increase in SCr ≥ 44 μmol/l or > 25% from baseline within 72 h of contrast	Alprostadil	14	154	0.09
		Control IV saline	39	176	0.22
Nijssen 2017 [22,23]	Increase in serum creatinine by>25% or ≥ 44 μmol/l within 2–6 days of contrast exposure	IV fluid	2	152*	0.01
		Control no hydration	2	162*	0.01
Palli 2017[46]	Increase in SCr ≥ 25% from baseline within 120 h of contrast	NAC and ascorbic acid	11	60	0.18
		Control IV saline	10	64	0.16
Park 2020[27]	Serum creatinine level elevation ≥ ≥44 μmol/l or ≥ 25% from baseline at the follow-up visit 48 to 72 h after CE-CT	Balanced Salt Solution	10	242	0.04
		Control IV saline	17	251	0.07
Poletti 2007[31]	Increase in SCr or cycstatin C ≥ 25% from baseline within 48–96 h of contrast	NAC	2	44*	0.05
		Control IV saline	9	43*	0.21
Poletti 2013[38]	Increase in SCr ≥ 44 μmol/l or ≥ 25% from baseline within 72 h of contrast	NAC	8	52*	0.15
		Control IV saline	10	58*	0.17
Sar 2010[47]	Increase in SCr ≥ 26.5 μmol/l or ≥ 20% and/or a decrease in eGFR ≥ 20% from baseline within 72 h of contrast	NAC	0	25	0
		Control IV saline	3	20	0.15
Sebastià 2021 [21]	Increase in serum creatinine ≥ 0.3 mg/dl (26.5 μmol/l) or ≥ 1.5 times baseline level occurring within 48–72 h of intravascular administration of iodinated contrast media	Sodium Bicarbonate	6	114	0.05
		Control oral hydration	5	114	0.04
Tepel 2000[32]	Increase in SCr ≥ 44 μmol/l from baseline within 48 h of contrast	NAC	1	41	0.02
		Control IV saline	9	42	0.21
Timal 2020[18]	Increase in SCr ≥ 44 μmol/l or > 25% from baseline within 48–120 h of contrast	Sodium Bicarbonate	4	261	0.02
		Control no hydration	7	262	0.03
Traub 2013[48]	Increase in SCr ≥ 44 μmol/l or ≥ 25% from baseline within 48–72 h of contrast	NAC	14	185	0.08
		Control IV saline	12	172	0.07
Turedi 2016[25]	Increase in SCr ≥ 44 μmol/l or ≥ 25% from baseline within 48–72 h of contrast	NAC	20	85	0.24
		Sodium Bicarbonate	18	85	0.21
		Control IV saline	23	87	0.26
van Mourick 2018[49]	Increase in SCr ≥ 44 μmol/l or > 25% from baseline within 48–120 h of contrast	Sodium Bicarbonate	0	39	0
		Control IV saline	0	35	0

* The number of participants includes only those who had a post-contrast creatinine level checked for assessment of CIN (not all that were randomised)

define CIN and the other using an increase in creatinine of ≥ 26.5 μmol/l or ≥ 1.5 times baseline level occurring within 48–72 h of contrast media administration.

Ten studies compared the use of NAC with a control group of IV saline and four studies compared the use of sodium bicarbonate with a control group IV saline. Pooled estimates indicate that use of NAC was

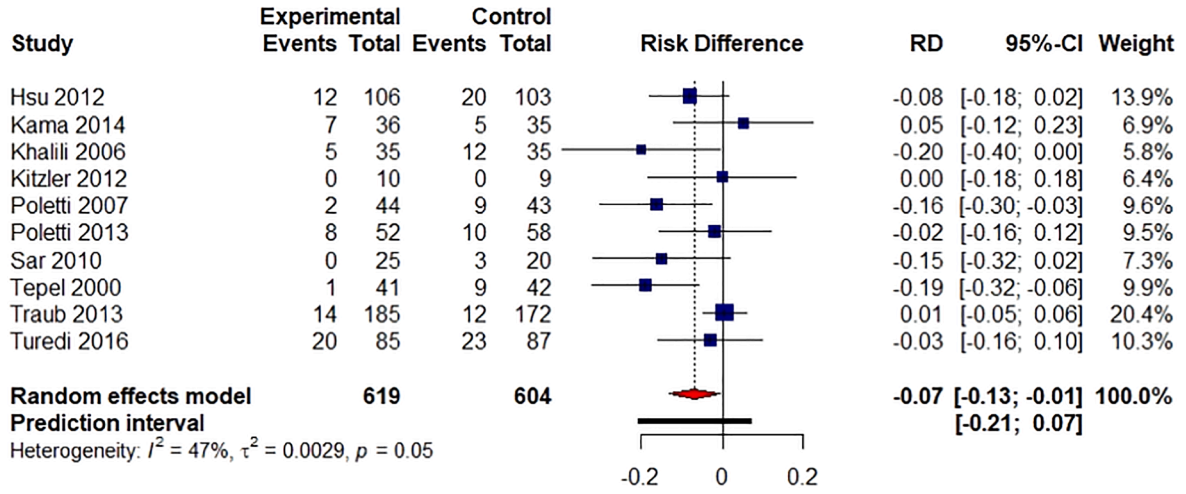

Fig. 2. Forest Plot displaying Risk Difference for CIN in participants treated with NAC.

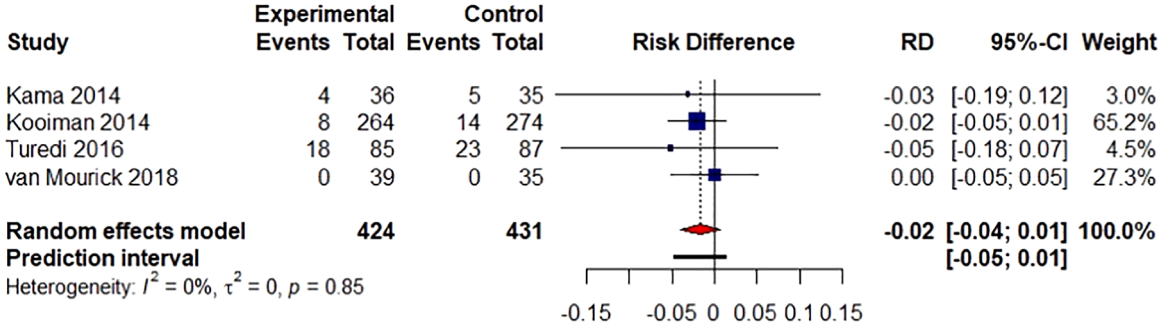

Fig. 3. Forest Plot displaying Risk Difference for CIN in participants treated with sodium bicarbonate.

associated with a reduced rate of CIN (risk difference = -0.07, 95% CI −0.13 to −0.01), whereas use of sodium bicarbonate was associated with a non-significant reduction (risk difference = -0.02, 95% CI −0.04 to 0.01), as represented in Figs. 2 and 3. The absolute risk of CIN in the control groups in NAC studies ranged from 0 to 0.34 and ranged from 0 to 0.26 in the sodium bicarbonate studies.

Within the NAC group, three of the ten studies[30–32] had a statistically significant outcome favouring the use of NAC. The rates of CIN within the control group were amongst the four highest reported rates of CIN within the control groups (Table 2).

Two studies compared the use of sodium bicarbonate against no hydration[18,19] and one compared the use of sodium bicarbonate against a control group of non-specific hydration[20], all found no significant difference in incidence of CIN between intervention and control groups. A further single study reported on CIN incidence comparing sodium bicarbonate against oral hydration and similarly found no significant difference between the two groups[21].

3.3. Need for kidney replacement therapy

Twelve studies reported the need for KRT, five studies compared the use of NAC with a control group IV saline and four compared the use of sodium bicarbonate with a control group of IV saline (Table 3). Use of NAC was not associated with a reduction in the need for KRT (risk difference −0.00, 95% CI −0.05 to 0.04, Supplementary Fig. 3). Use of sodium bicarbonate was also not associated in a reduction in the need for KRT (risk difference = 0.00, 95% CI −0.03 to 0.03, Supplementary Figure 4). One study[23] compared the effect of IV saline hydration prior to IV contrast with no hydration on need for KRT at 365 days following IV contrast administration and found no significant difference between the hydration and no hydration groups. Another study[27] compared the use of a balanced salt solution against normal saline and found no significant difference in the need for KRT between the groups. The two studies[18,33] comparing sodium bicarbonate with a control of no hydration and the study[21] comparing sodium bicarbonate against oral hydration all found no difference between the groups need for KRT. The timeframe for initiation of KRT was not defined in seven studies and there was significant variation in the timeframes for initiation of KRT that were reported.

3.4. Mortality

Seven studies reported on mortality following IV contrast administration (Table 4). Three of the seven studies investigated the effect of sodium bicarbonate but only one of these was compared to a control group of IV saline. Two of the seven studies investigated the effect of NAC with a control group of IV saline. None of the studies investigating the effect of sodium bicarbonate reported any significant impact of mortality. Neither of the studies investigating NAC demonstrated any significant difference in mortality. Two further studies reported effects of prophylactic treatments on mortality with no significant difference seen with either hydration alone[22] or use of a balanced salt solution [27].

3.5. Failure of recovery of kidney function

Three studies reported frequency of failure of recovery of kidney function, all using sodium bicarbonate, only one of these was against a control group of IV saline (Supplementary Table 5). None of the studies demonstrated any significant effect on the frequency of failure to

Table 3
Studies reporting need for KRT.

Paper	Timeframe given	Intervention Received	Events in Intervention Group	Size of Intervention Group
Hsu 2012[45]	No timeframe defined	NAC	0	106
		Control IV saline	1	103
Kama 2014[24]	No timeframe defined	NAC	3	36
		Sodium Bicarbonate	2	36
		Control IV saline	0	35
Kooiman 2014[33]	No timeframe defined	Sodium Bicarbonate	0	267
		Control IV saline	0	281
Kooiman2 2014[19]	Within 365 days	Sodium Bicarbonate	0	70
		Control no hydration	0	65
Nijssen 2017[22,23]	10 days post-contrast administration	IV fluid	0	169
		Control no hydration	2	172
Palli 2017[46]	10 days	NAC and ascorbic acid	3	60
		Control IV saline	4	64
Park 2020[27]	No timeframe defined	Balanced Salt Solution	1	236
		Control IV saline	0	244
Sebastià 2021[21]	1 month	Sodium Bicarbonate	0	114
		Control oral hydration	0	114
Tepel 2000[32]	No timeframe defined	NAC	0	41
		Control IV saline	0	42
Timal 2020[18]	1 year	Sodium Bicarbonate	0	261
		Control no hydration	0	262
Traub 2013[48]	No timeframe defined	NAC	0	185
		Control IV saline	0	172
Turedi 2016[25]	No timeframe defined	NAC	8	85
		Sodium Bicarbonate	9	85
		Control IV saline	15	87
van Mourick 2018[49]	No timeframe defined	Sodium Bicarbonate	0	39
		Control IV saline	0	35

Table 4
Studies reporting mortality.

Paper	Timeframe used	Intervention Received	Events in Intervention Group	Size of Intervention Group
Hsu 2012[45]	All-cause inpatient mortality	NAC	8	106
		Control IV saline	13	103
Kooiman2 2014[19]	Within 24 h of CTPA	Sodium Bicarbonate	1	70
		Control no hydration	0	65
Nijssen 2017[22,23]	Within 365 days	IV fluid	24	169
		Control no hydration	32	172
Palli 2017[46]	Within ICU stay	NAC and ascorbic acid	15	60
		Control IV saline	11	64
Timal 2020[18]	1 year	Sodium Bicarbonate	25	261
		Control no hydration	26	262
Turedi 2016[25]	During hospitalisation	NAC	11	85
		Sodium Bicarbonate	10	85
		Control IV saline	12	87

recover kidney function

3.6. Fluid overload

Three studies reported fluid overload, all using sodium bicarbonate, one against a control of no hydration and two with a control group of IV saline (Supplementary Table 6). One reported a statistically significant difference favouring sodium bicarbonate, one reported no significant difference, and in the third no participants developed volume overload. Due to likely confounding relating to the volumes of fluid given and heterogeneity in definition of fluid overload, no *meta*-analysis was performed.

4. Discussion

The most significant limitation and finding of this review was the lack of evidence available. In our search we found no other studies relating to only IV contrast that assessed oral hydration versus no hydration or other intervention. There was a non-inferiority study[22] comparing no hydration against IV saline hydration which found that withholding hydration was non-inferior but IV prophylactic hydration was associated with increased costs and complications. This paucity of published studies comparing prophylaxis with no hydration emphasises the lack of evidence relating to IV contrast administration and the benefits of hydration (either IV or oral). The *meta*-analysis demonstrated an association between use of NAC compared with saline and a reduced frequency of CIN. This apparent reduction in CIN was not accompanied by any reduction in mortality, need for KRT or persistent decline in kidney function. It is not clear whether this is because no causal relationship exists or because these outcomes were not universally reported. Sodium bicarbonate use was not associated with a reduction in CIN or need for KRT with a lack of studies reporting on other outcomes preventing further *meta*-analyses for these. No other potential renoprotective treatments were able to be *meta*-analysed.

The fact that there are very few published studies investigating the effect of prophylactic methods on CIN with IV contrast administration makes interpretation of these results challenging – particularly given that many of these studies feature a low incidence of CIN and small study populations. It is conceivable that if a higher number of larger studies were performed in higher-risk populations that a treatment effect might be demonstrated for sodium bicarbonate or other prophylactic treatments. Conversely it is also possible that larger studies would

demonstrate a lack of effect of NAC. There was a significant degree of heterogeneity between studies in terms of their effect size and in the frequency of CIN within their control groups.

It is not clear why use of NAC would be associated with a lower incidence of CIN compared to sodium bicarbonate. Although biologically plausible explanations for NAC and sodium bicarbonate to reduce the incidence of CIN exist, these mechanisms differ. The mechanisms for NAC reducing the incidence of CIN are thought to be its action as an antioxidant, induction of glutathione synthesis and as a vasodilator[34]. Sodium bicarbonate has been thought to reduce CIN by reduction of free radical generation by increasing tubular pH in a dose-dependent manner [35]. It is possible that either the dose of sodium bicarbonate used in the included studies was insufficient to produce an effect on CIN or that sodium bicarbonate is ineffective at preventing CIN in the context of intravenous contrast administration.

A previous *meta*-analysis including both IA and IV contrast demonstrated that a fall in serum creatinine was observed in patients given NAC[36]. This was investigated further by an *in vitro* study demonstrating that adding NAC to waste blood plasma samples resulted in a lower measurement of serum creatinine when serum creatinine was analysed using an enzymatic method as opposed to the Jaffe method [37]. This raises the prospect that the impact of NAC on CIN is purely artefactual, which would explain why no impact on mortality or need for KRT are seen. Of the studies investigating the effect of NAC on incidence of CIN, only three detailed the method of serum creatinine measurement [26,31,38], all of which used the Jaffe method.

One of the most striking findings from this review was that the vast majority of studies investigating prophylaxis in patients given IV contrast took place in patient groups where the mean eGFR was above the 30 ml/min/1.73 m^2 cut-off recommended by current guidance for saline prophylaxis. There was also significant heterogeneity in reporting of baseline renal function with studies variously reporting eGFR, creatinine clearance and creatinine values. These limits alter the applicability to the patients at highest risk of both CIN and a reluctance to administer contrast due to lack of evidence in this population. The potential hesitancy to administer contrast to patients with advance kidney disease can be extrapolated to the term "renalism" which has been used to describe lower than expected rates of coronary angiography in patients with advanced kidney disease[39]. It is not unreasonable to think that patients with advanced kidney disease may be denied "gold standard" imaging due to concerns about risk of CIN. From the evidence available it is not possible to identify mitigation strategies that would be effective in this cohort of patients.

The current definition of CIN was developed prior to the widespread adoption of universal AKI definitions (most recently the KDIGO definition[40]). Although the CIN definition is similar to the KDIGO AKI definition in that it uses both an absolute and relative change in creatinine, it has a lower threshold for the identification of renal impairment in people with a baseline creatinine of 104 μmol/l or lower and a higher threshold for the identification of renal impairment in people with a baseline creatinine of 104 μmol/l or higher. This adds a layer of confounding to any comparison between post-contrast AKI, CIN and AKI in general. Further complicating matters is the fact that despite a consensus definition for CIN[1], five different definitions were used for CIN across 20 studies (not including small differences in the timing of the post-contrast sample). Previous work has demonstrated that the application of the KDIGO definition of AKI is also inconsistent[41]. As the timing of the "insult" in CIN is known much of the inconsistency should be avoided.

Although observational studies have shown an association between CIN and mortality and need for KRT[42–44], the clinical utility of prophylactic treatments remains unclear at preventing need for KRT and mortality. Prophylactic treatments are not without cost: there is a financial cost, a small but non-zero risk of side effects and the additional inconvenience to patients receiving a prolonged infusion of IV fluid. One of the studies included in this review[33] included a cost estimate of €224 for a one hour infusion of 250 ml sodium bicarbonate and €683 for two litres of 0.9% saline infused over 8–24 h. Prophylactic IV infusions represent a potential burden on patients in terms of time spent on an infusion and potential side effects.

Our work presents a comprehensive review of the literature around IV contrast administration. Given the subject matter and debate around CIN following IV contrast there is a high possibility of negative studies that may not have been published. However, there was no evidence to suggest this when assessing publication bias for the primary outcome of CIN (Supplementary Fig. 5-6).

In addition to the lack of studies surrounding no hydration compared with IV or oral hydration a further limitation was that studies where both IV and IA contrast were excluded if there was no reporting of outcomes by route of administration which limited the number of studies available to be included. This evidence was particularly limited for patients with CKD stages 4 and 5, who are at the highest risk.

This review highlights the lack of hard evidence around the use of contrast prophylaxis in preventing the important clinical outcomes of mortality, need for KRT and progression of CKD. Further research is needed to determine whether prophylaxis with either IV hydration alone or with adjuvant therapies (such as NAC and sodium bicarbonate) are of benefit in patients with an eGFR of < 30 ml/min. Future studies should report important clinically relevant outcomes (mortality, need for KRT and progression of CKD) in a consistent manner as well as reporting the incidence of CIN and AKI using consistent definitions.

5. Conclusion

There is a paucity of published studies, and therefore a lack of evidence comparing hydration (either IV or oral) with a control of no hydration. Future studies should focus on exploring if hydration is superior to no hydration. This *meta*-analysis has observed that use of NAC appears to be associated with a reduced incidence of CIN while sodium bicarbonate does not appear to have an impact on the incidence of CIN. However, the impact on important clinical outcomes (such as mortality, need for KRT and persistent impairment of kidney function) is not clear. The majority of available evidence studied patients with eGFR > 30 ml/min and therefore limits the applicability of these conclusions to other patient groups. Other areas to be considered in future research include clear and consistent reporting of important clinical outcomes, including reporting timeframes, as well as using a consistent definition for CIN. Ideally the KDIGO definition for AKI should be employed to allow for clearer comparisons in outcome between CIN and AKI of other causes. This would establish whether the risk of administering contrast media for CT scanning outweigh the benefits.

6. Summary statement

Evidence for prophylaxis against contrast induced nephropathy in patients receiving intravenous iodinated contrast is limited. N-acetylcysteine following IV contrast was found to be associated with a slight reduction in the incidence of contrast-induced nephropathy but there was no impact on other clinical outcomes, therefore the clinical significance of these findings remains unclear.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejrad.2022.110368.

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