Health Technology Assessment Report

N-Acetylcysteine In The Prevention Of Contrast-Induced Acute Kidney Injury (CIAKI)

DISCLAIMER

This Health Technology Assessment has been developed from analysis, interpretation and synthesis of scientific research and/or technology assessment conducted by other organizations. It also incorporates, where available, Malaysian data, and information provided by experts to the Ministry of Health Malaysia. While effort has been made to do so, this document may not fully reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion of the review. This report is subjected for external reviewers.

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EXECUTIVE SUMMARY

Background

Acute kidney injury (AKI) is one of health problems that affects kidney structure and function. It is common, harmful and potentially treatable. Even a minor acute reduction in kidney function has an adverse prognosis. Contrast-induced acute kidney injury (CIAKI) is uncommon among people with normal kidney function. It is accepted that, in patients with normal renal function; even in the presence of diabetes, the risk for CIAKI is low (1 – 2%). Usually it is defined as a rise in serum creatinine (srCr) of ≥ 0.5mg/dl (≥ 44µmol/l) or a 25% increase from baseline value, assessed at 48 hours after a radiological procedure. This definition was based on the observation that creatinine elevation after contrast administration typically peaks within three days.

There are several approaches for CIAKI prevention, either pharmacological strategies (N-acetylcysteine (NAC), theophylline, fenoldopam, statins and ascorbic acid) or non-pharmacological (haemodialysis or haemofiltration and hydration). N-acetylcysteine is a treatment of choice in CIAKI prevention, as it is inexpensive and appears to be safe; many studies did show potential benefits of NAC towards reducing CIAKI incidence especially among high risk patient.

Currently, there is no standard operating procedure for the prevention of CIAKI during and after radio-contrast procedure in Ministry of Health (MOH). This review was requested by Pharmacist from Hospital Selayang in order to determine the efficacy or effectiveness of NAC in prevention of CIAKI.

Technical features

N-acetylcysteine is an acetylated derivative of the amino acid cysteine. The chemical formula is $C_5H_9NO_3S$, with molecular mass of 163.2g/mol. The drug can be administered via oral, intravenous (i.v) or respiratory routes. N-acetylcysteine is known as an antioxidant. In active reaction the NAC will reacts with and deactivate hydroxyl radicals. In human body, any antioxidant effects of NAC will be indirect. Theoretically, the NAC will induce glutathione synthesis. Glutathione plays a central role in the body's defences against cellular oxidative damage.

Policy Question

Should NAC be used for prevention of CIAKI in patient undergoing i.v iodinated contrasted procedure?

Objectives

i) To assess the efficacy/effectiveness of NAC in the prevention of CIAKI
ii) To assess the safety of NAC in the prevention of CIAKI
iii) To assess the economic implications related to NAC in the prevention of CIAKI
iv) To assess the ethical, legal, and organizational implications related to NAC in the prevention of CIAKI

Methods

Major electronic databases such as MEDLINE, EMBASE and Cochrane Database were searched up to September 2016. No limits were applied to the search. Additional studies were identified from reviewing the references of retrieved articles. Retrieved records were screened for relevance. Potentially relevant papers were retrieved and independently checked against predefined criteria for inclusion by two reviewers. Included reviews and primary papers were critically appraised and data were extracted and narratively presented.

Results

A total of 538 titles were identified. After removal of 139 irrelevant titles, a potential of 399 relevant titles were screened for abstracts. Out of 399 abstracts, only 185 abstracts were retrieved for full text articles. Of these, 39 full texts could not be retrieved and 146 articles were appraised. Although the full text of 39 relevant abstracts could not be retrieved, the abstracts showed that the results reported were not much different from the study retrieved. Ten relevant full text articles were identified from references of retrieved articles and while updating the search. After critically appraised and discussion with second reviewer and expert committees only 10 articles were included in the review. The included articles consisted of seven systematic reviews (SRs) with meta-analysis (MAs), one systematic review (SR) and two randomised controlled trials (RCTs).

The findings of this review were concluded as follows:

Efficacy
- In patients with renal insufficiency, oral NAC may reduce CIAKI incidence compared with placebo. However, the optimum dose of NAC required cannot be determined.
- In diabetes patients, use of NAC has no significant effects in CIAKI prevention
- In patients undergoing cardiac angiography, the role of NAC in CIAKI prevention was inconsistent. However, high dose NAC seems to be more effective compared to low dose NAC
- Use of NAC with LOCM showed better outcome in CIAKI prevention compared to NAC with IOCM
- NAC single use has no significant difference in prevention of CIAKI compared to combination of NAC with other alternatives

Safety
- No adverse events were reported with the use of oral NAC but i.v NAC was associated with mild adverse events such as itching, flushing and rash

Cost
- No retrievable evidence on cost-effectiveness
- Local price of NAC injection (200mg/ml of 10ml vial) is about RM11.29 and in tablet formulation of 100mg, 200mg and 600mg is about RM2.00 to RM 5.00 per tablet

Ethical, legal and Organizational
- No standard guideline for CIAKI prevention in MOH
- In Malaysia, NAC is not indicated for CIAKI prevention. The off label use for CIAKI prevention require approval from the Director General of Health.
- Oral NAC is not listed in MOH Drug Formulary thus patients buy their own oral NAC tablet from a retail pharmacy
- Adverse events which may occur pertaining to off-label use of NAC for CIAKI prevention may have legal implications

Conclusion

Good level of evidences was retrieved to show the effects of NAC in CIAKI prevention. However patients underlying problems, NAC dose and type of contrast media use may influence the overall effects of NAC in CIAKI preventions.

Recommendation

Based on the available evidence, oral NAC may be used in prevention of CIAKI in renal insufficiency patients. Other factors that may influence CIAKI incidence should be considered in patients undergoing radio-contrast procedure such as types of contrast media and patients' hydration status.

LIST OF ABBREVIATIONS

ACS	Acute coronary syndrome
AKI	Acute kidney injury
ARF	Acute renal failure
CASP	Critical Appraisal Skills Programme
CHF	Congestive heart failure
CI	Confidence interval
CIAKI	Contrast induced acute kidney injury
CIN	Contrast induced nephropathy
CKD	Chronic kidney disease
COM	Combination
CrCl	Creatinine clearance
CT-scan	Computed tomography scan
eGFR	Estimated glomerular filtration rate
GFR	Glomerular filtration rate
HOCM	High osmolar contrast media
IA / i.a	Intra-arterial
IHD	Ischaemic heart disease
IOCM	Iso-osmolar contrast media
IV / i.v	Intravenous
KIM-1	kidney injury molecule 1
LOCM	Low molecular weight contrast media
MA	Meta-analysis
MOH	Ministry of Health
NAC	N-acetylcysteine
NaCl	Sodium chloride
NaHCO3	sodium bicarbonate
NGAL	Neutrophil gelatinase-associated lipocalin
NS	Normal saline
OR	Odds ratio
PCI	Percutaneous coronary intervention
RCT	Randomised controlled trial
RR	Relative risk
SOB	sodium bicarbonate
SR	Systematic review
srCr	Serum creatinine
STEMI	ST segment elevation myocardial infarction
U.S	United State

Contents

N-ACETYLCYSTEINE (NAC) IN PREVENTION OF CONTRAST-INDUCED NEPHROPATHY (CIAKI)

1.0 BACKGROUND

Acute kidney injury (AKI) is one of the health problems that affect kidney structure and function. It is common, harmful and potentially treatable. Even a minor acute reduction in kidney function has an adverse prognosis. Early detection and treatment of AKI may improve outcomes. Acute kidney injury is defines as any of the following:-[1]

i) Increase in srCr by ≥ 0.3mg/dL (≥ 26.5µmol/L) within 48 hours or
ii) Increase in srCr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior seven days; or
iii) Urine volume < 0.5ml/kg/h for six hours

Contrast-induced acute kidney injury (CIAKI) is uncommon among people with normal kidney function. Even in the presence of diabetes, the risk for CIAKI is low (1 – 2%). However, its frequency increases with declining kidney function, ranging from 5% in those with mild kidney impairment to 50% in those with diabetes and severe renal insufficiency.[1, 2] Contrast-induced acute kidney injury was described as the third most common cause of new AKI in hospitalised patients (after decreased renal perfusion and nephrotoxic medications) and was responsible for 11% of cases.[1]

The rate of CIAKI incidence as a complication of radiographic diagnostic and interventional studies varies markedly, depending on the definition used and on other variables such as the type of radiology procedure performed, the dose and type of contrast agent administered, the differing patients populations in regard to number and type of risk factors and the length of patient follow-up.[3] Usually CIAKI is defined as a rise in srCr of ≥ 0.5mg/dl (≥ 44µmol/l) or a 25% increase from baseline value, assessed at 48 hours after a radiological procedure.[1, 4] This definition was based on the observation that creatinine elevation after contrast administration typically peaks within three days.[4]

The US Food and Drug Administration has reported that the overall incidence of CIAKI following contrast administration from 1990 to 1994 ranged from 1.22 to 2.35/million examinations and from 0.6% to 2.3% of all reported reactions. Most occurrences of CIAKI develop following diagnostic examination. Reported incidence of CIAKI was 11%, 9% and 4% following outpatient computed tomography (CT), peripheral angiography, and intravenous pyelography respectively. Contrast-induced acute kidney injury incidence following CT among hospitalised cancer patients was 20%. In this population, CIAKI developed more often in patients who had undergone chemotherapy recently. In patients undergoing percutaneous coronary intervention for coronary heart disease, the incidence of CIAKI was 3.3% overall and approximately 25% in patients with baseline SCr > 2.0 mg/dL (176.8 µmol/L).[5]

Iodinated contrast agents are known to cause CIAKI. There are three types of contrast agents available. Namely high osmolar contrast media (HOCM), low osmolar contrast media (LOCM) and iso-osmolar contrast media (IOCM). Several studies did demonstrate that LOCM results in substantially less contrast-induced nephropathy than HOCM in patients with pre-existing renal dysfunction but no benefit in those without renal dysfunction. Although, there was no proven decrease in contrast-induced nephropathy in normal populations, better tolerability and fewer side effects of LOCM have largely resulted in their supplanting HOCM in routine clinical practice.[5] High-osmolar contrast media were described in the 1970s as the third most frequent cause of CIAKI, behind surgery and hypotension, in hospitalisation patients. More than 20 years later, a similar incidence of CIAKI

secondary to contrast administration was reported. With increasing use of computed tomography scan (CT-scan), the risk of CIAKI remains a clinical concern.[4]

Actually many factors have been reported as risk to the CIAKI. The risk factors can be divided as either non-modifiable factors or modifiable factors.[2, 3] The most important non-modifiable risk factors for contrast-induced nephropathy include pre-existing renal insufficiency, older age, diabetes mellitus, reduced left ventricular systolic function, advanced congestive heart failure, acute myocardial infarction, cardiogenic shock, hypertension, cardiac diastolic dysfunction, procedural bleeding and kidney transplantation.[2] Meanwhile, the modifiable risk factors include types and dose or volume of contrast media, anaemia, dehydration, low serum albumin level (< 35 g/L), use of certain medicine such as angiotensin-converting enzyme inhibitors, frusemide and non-steroidal anti-inflammatory drugs.[2]

There are several approaches for CIAKI prevention, either pharmacological or non-pharmacological (haemodialysis or haemofiltration and hydration). Pharmacological strategies include N-acetylcysteine, theophylline, fenoldopam, statins, and ascorbic acid.[1] The available evidence on these strategies are conflicting and inconclusive for CIAKI prevention.[1, 2] N-acetylcysteine becomes the treatment of choice in CIAKI prevention due to its low cost and appears to be safe. However, the actual effects are uncertain.[1, 5, 6]

There is no standard operating procedure for prevention of CIAKI during and after radio-contrast procedure in Ministry of Health Malaysia (MOH) at present. This review was requested by a Pharmacist from Hospital Selayang in order to determine the role of NAC in prevention of CIAKI.

2.0 TECHNICAL FEATURES

N-acetylcysteine is an acetylated derivative of the amino acid cysteine. The chemical formula is $C_5H_9NO_3S$, with molecular mass of 163.2g/mol. The drugs can be administered via oral, intravenous (i.v) or respiratory routes. In oral routes, very small quantities of oxidised drug were detected in circulation, with no free drug detectable. Bioavailability was <5%, because of extensive first-pass hepatic metabolism. In i.v user, the NAC is highly bound to plasma and tissue proteins, forming various disulphide compounds. Only small amounts of NAC are found in circulation despite the i.v route.[7]

N-acetylcysteine is a medication used to treat paracetamol overdose and to loosen thick mucus such as in cystic fibrosis or chronic pulmonary disease.[8]

N-acetylcysteine is also known as an antioxidant. In vitro, NAC is very effective in neutralizing certain free radicals. In active reaction NAC will reacts with and deactivate hydroxyl radicals. In human body, any antioxidant effects of NAC will be indirect. Theoretically, NAC will induce glutathione synthesis. Glutathione plays a central role in the body's defences against cellular oxidative damage. Another property is vasodilatory effects. By stabilising nitric oxide, NAC may have a vasodilatory effect for renal protection.[7]

There are several regimes of NAC practiced in different MOH hospitals for CIAKI prevention, as there is no standard guidelines. Examples of the regimes are obtained from four hospitals and are stated in table 1.

Table 1: Various NAC Regimens for CIAKI Preventions in MOH Hospitals*

NAC ROUTES	NAC PRE - DOSE	NAC POST - DOSE	TOTAL NAC TABLETS / IV DOSES
Oral	600 mg six hours before contrast procedure and 600 mg two hours just before contrast procedure	600 mg two hours just after contrast procedure and 600 mg six hours after contrast procedure	Four (4) tablets of 600mg NAC tablet
	1.2 g six hours before contrast procedure and 1.2 g two hours just before contrast procedure	1.2 g two hours after contrast media and 1.2 g six hours just after contrast procedure	Eight (8) tablets of 600mg NAC tablet
	600 mg twice daily for 3 days		Six (6) tablets of 600mg NAC tablet
Intravenous	1.2 g infuse over four hours (six hours before contrast procedure) 1.2 g infuse over 4 hours (two hours before contrast procedure)	1.2 g infuse over four hours (two hours before contrast procedure) 1.2 g infuse over four hours (six hours after procedure)	Four (4) iv doses
	150 mg/kg in 500 ml normal saline (NS) over 30 minutes prior to contrast procedure	Followed by 150 mg/kg in 500 ml NS over 4 hours	
	If CrCl < 30 ml/min Hydration 12 hours with NS 1 ml/kg/hr 150 mg/kg in 500 ml NS over two hours (two hours before contrast procedure)	If CrCl < 30ml/min Hydration 12 hours with NS 1 ml/kg/hr 50 mg/kg in 500 ml	

*Data received from Drug Information Services Pharmacist from Selayang Hospital, Klang Hospital, Labuan Hospital and Banting Hospital

3.0 POLICY QUESTION

Should NAC be used for prevention of CIAKI in patient undergoing iodinated contrasted procedure?

4.0 OBJECTIVES

i) To assess the efficacy/effectiveness of NAC in prevention of CIAKI
ii) To assess the safety of NAC in prevention of CIAKI
iii) To assess the economic implications related to NAC in prevention of CIAKI
iv) To assess the ethical, legal, and organizational implications related to NAC in prevention of CIAKI

4.1 Research Questions

i) Is NAC safe and effective in prevention of CIAKI among patients undergoing iodinated contrasted procedure?
ii) What is the economics, ethical, legal, and organizational implications using NAC in prevention of CIAKI?

5.0 METHODS

5.1 Literature search strategy

Studies were identified by searching electronic databases. The following databases were searched through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present. Parallel searches were run in PubMed and EMBASE. Appendix 2

shows the detailed search strategies. No limits were applied to the search. The last search was run in September 2016. Additional studies were identified from reviewing the references of retrieved articles.

5.2 Study Selection

Based on the inclusion and exclusion criteria, study selection was carried out independently by two reviewers. The titles and abstracts of all studies were assessed for the above eligibility criteria by first reviewer. If it was absolutely clear from the title and / or abstract that the study was not relevant, it was excluded. If it was unclear from the title and / or the abstract, the full text article was retrieved. The selected articles were assessed by first reviewer and second reviewer verified the content of the articles. Any disagreement and issues were resolved by discussion.

5.3 Inclusion criteria

a. Population : Patients undergoing iodinated contrasted procedure

b. Intervention : Intravenous or oral N-acetylcysteine / i.v or oral NAC

c. Comparators : As listed below:-
   - i) Other drugs (diuretic, calcium channel blocker, adenosine antagonist, endotheline receptor blocker, and prostaglandin)
   - ii) Other procedures (hydration or non-drug)
   - iii) Choice of contrast
   - iv) No comparator

d. Outcome : Efficacy/Effectiveness (prevention of CIAKI), safety, economic impact, organizational, legal and ethical implications

e. Study design : Systematic reviews (SRs), and randomised controlled trials (RCTs)

f. Others : Full text articles published in English

5.4 Exclusion criteria

a. Animal study
b. Narrative review
c. Experimental study
d. N-acetylcysteine used for other indication except for prevention of contrast-induced nephropathy

5.5 Quality assessment strategy

The methodological quality of all the relevant full text articles retrieved was assessed using the Critical Appraisal Skills Programme (CASP) tool by one reviewer. The CASP checklist is as in Appendix 3. All full text articles were graded based on guidelines from the U.S./Canadian Preventive Services Task Force (Appendix 2).

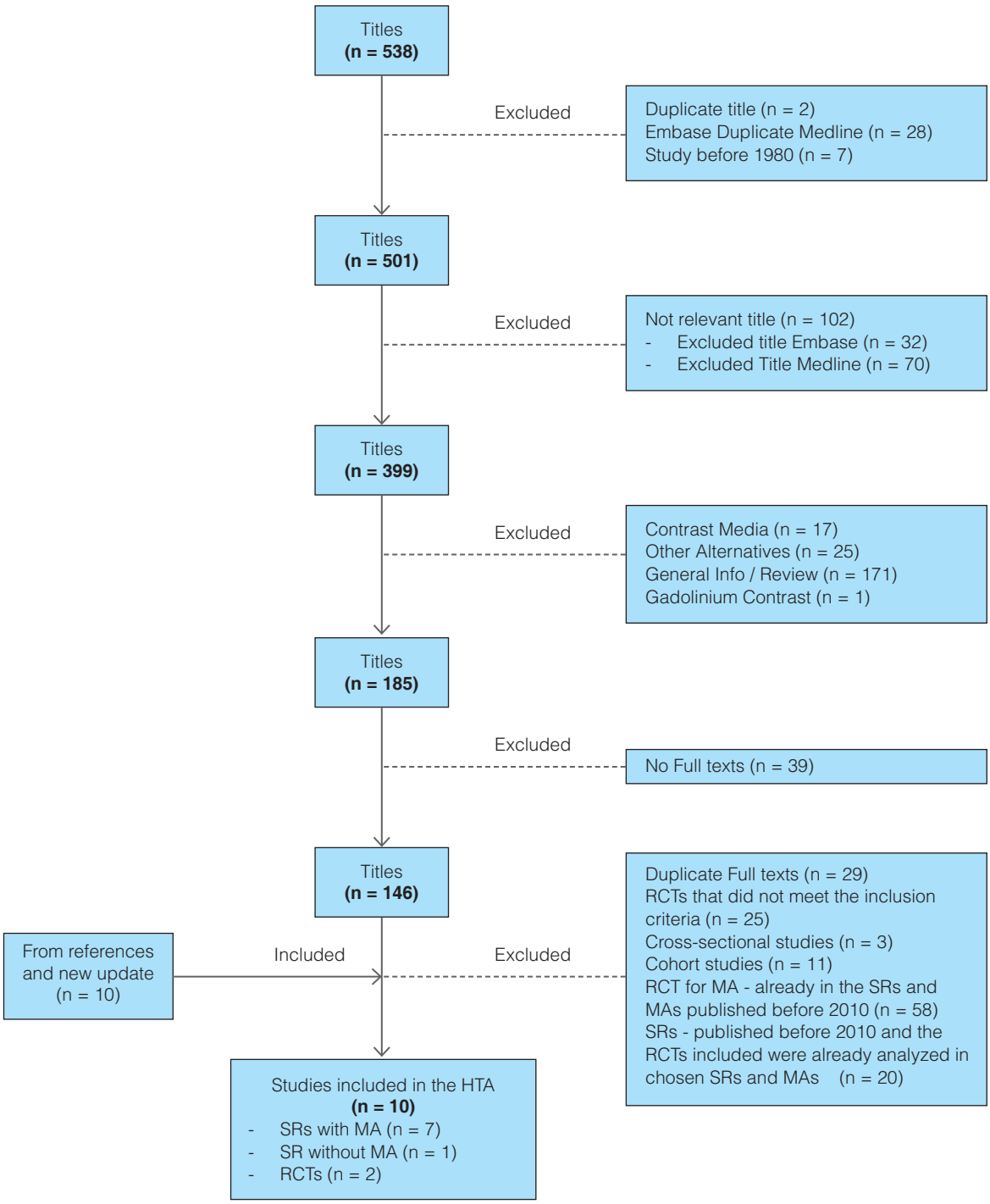

Figure 1: Flowchart of Retrieved Articles Used in the HTA

5.6 Data extraction strategy

Data were extracted from the included studies by a reviewer using a pre-designed data extraction form (evidence table as shown in Appendix 6) and checked by second reviewer. Disagreements were resolved by discussion with third reviewer. Details on: (1) methods including study design and study selection characteristics for systematic review and meta-analysis, (2) study population characteristics including gender, age, medical history, and underlying health problems (3) type of intervention and dosage information, (4) comparators and dosage information, (5) type of outcome measures either primary or secondary outcomes including: a) p-value, b) odd ratio (OR), c) relative risk (RR), d) biochemical indicators, e) economic evaluation, and f) organizational issues were extracted. Other information on author, journal and publication year, and study objectives were also extracted. The evidence table were presented and discussed with the expert committee. Upon discussion with the expert committee any suggestion of study exclusion were considered and only the final chosen studies were reported and analysed.

5.7 Methods of data synthesis

Data on the safety, efficacy and cost implication of N-acetylcysteine to prevent contrast-induced acute kidney injury were presented in tabulated format with narrative summaries. No meta-analysis was conducted for this review.

6.0 RESULTS

6.1 Overall Search Results

A total of 538 titles were identified through the Ovid interface: MEDLINE (R) In-process and other Non-Indexed Citations and Ovid MEDLINE (R) 1948 to present, Embase 1988 to present and PubMed. After removal of 37 duplicates and studies before 1980, 501 titles were intensively screened. Out of 501 titles, 102 titles were excluded. A total of 399 relevant abstracts were screened. From the abstracts, 214 were not related to the objective of the HTA and thus, were excluded. The remaining 185 abstracts were retrieved for full text articles. Of these, 39 full texts could not be retrieved and 146 articles were appraised. Although the full text of 39 relevant abstracts could not be retrieved, the abstracts showed that the results reported were not much different from the study retrieved. Ten relevant full text articles were identified from references of retrieved articles and while updating the search. After critically appraised and discussion with second reviewer and expert committee only 10 articles were included in the review. The excluded studies were listed in Appendix 3. The characteristics of included studies are discussed in the next section. A simplified flow diagram showing the numbers of articles identified is shown in the Figure 1.

6.2 Characteristics of Included Studies

This section will discuss on the characteristic of the included studies under sub-sections below.

6.2.1 Study Design

Ten studies were included in this review, where seven of the studies were systematic reviews (SRs) with meta-analysis (MA), one SR and two randomised controlled trials (RCTs). Both RCTs were not included in any of the SR.

The SRs with MA were by Subramaniam RM et al. 2016[9], Wang N et al. 2016[10], Ali-Hassan-Sayegh S et al. 2016[11], Zhao SJ et al. 2016[12], Kang X et al. 2015[13], Wu MY et al. 2013[14], and Sun Z et al.

2013[15]. One SR without MA was by Busch SVE et al. 2013[16]. The two RCTs were by Habib M et al. 2016[17], and Poletti PE et al. 2013[18]. Details of each study will be discussed in other sub-sections of this section accordingly.

6.2.2 Participants

Five SRs with MA included patients with renal insufficiency or nephropathies.[9, 12-14] Most of the RCTs in the SRs with MA defined the nephropathies as an increase in serum creatinine levels of 25% and more or 44.2µmol/L and more from baseline. Two SRs with MAs included patients with cardiac problems undergoing CT-scan for cardiac catheterisation and peripheral angiography or coronary angiography.[11, 15] Meanwhile the only SR without MA involved patients with STEMI undergoing percutaneous coronary intervention (PCI).[16]

For the RCTs, the target population varies based on study outcome. The RCT by Habib M et al. 2016 included high-risk patients which were characterized as having at least one risk factor for CIAKI (age > 70 years, baseline creatinine level > 1.5mg/dL, heart failure, diabetes mellitus or contrast media volume > 300mL) and undergoing elective cardiac catheterisation.[17] Another RCT by Poletti PA et al. 2013 included patients with renal insufficiency and requested for an urgent contrast CT.[18]

6.2.3 Intervention

Studies using NAC in prevention of CIAKI used either in high dose or low dose with any route of administrations; intravenous, or oral were included in this review.

6.2.4 Comparators

NAC was compared with a combination of NAC and other preventions: drugs, placebo, hydration or other alternatives.

6.2.5 Types of Contrast Media

The included studies used low osmolar contrast media (LOCM) and iso-osmolar contrast media (IOCM). Table 2 described the types of the contrast media.

Table 2: Types of Contrast Media

Types of Contrast Media	Low-Osmolality Contrast Media (LOCM)	High-Osmolality Contrast Media (HOCM)
Definition	3 types of LOCM[19] i) Non-ionic monomers: tri-iodinated benzene ring with hydrophilic hydroxyl group, lack of carboxyl group and not ionize in solution ii) Ionic Dimers: consisted of two ionic monomers and eliminate one carboxyl group iii) Non-ionic Dimers/iso-osmolar contrast media (IOCM): consists of two joined non-ionic monomers and has lowest osmolality of all the contrast agents. Highly viscous and have limited clinical usefulness. Iso-osmolar with plasma.	Consisted of tri-iodinated benzene ring with 2 organic side chains and a carboxyl group[19]
Example	i) Iohexol, iopamidol, ioversol and iopromide ii) Ioxaglate iii) Iotrol and iodixanol	Diatrizoate Iothalamate

6.2.6 Outcome Measures

The outcome measures assessed in the studies included primary outcome and secondary outcome. Most of the studies defined CIAKI as primary outcome. Meanwhile, secondary outcome varied depending on the objective of each study. Definition of primary and secondary outcome for each study was described in the Table 3.

Table 3: Definitions of Outcome Measures

Source	Primary Outcome	Secondary Outcome
Subramaniam RM et al 2016[9]	Increase in serum creatinine levels ≥ 25% or 44.2µmol/L (0.5mg/dL)	Requirement for renal replacement therapy, cardiac events and mortality
Wang N et al 2016[10]	Increase in serum creatinine levels ≥ 25% or 44.2µmol/L (0.5mg/dL)	Not Mentioned
Ali-Hassan-Sayegh S et al 2016[11]	Increase in serum creatinine levels ≥ 25% and/or ≥ 0.5mg/dL from its baseline	Haemodialysis requirement
Zhou SJ et al 2016[12]	Increase of 25% of creatinine from baseline	Not mentioned
Kang X et al 2015[13]	Increase in serum creatinine levels ≥ 25% or 44.2µmol/L (0.05mg/dL)	Not mentioned
Wu MY et al 2013[14]	Increase of 0.3 – 0.5mg/dL and/or increase of 20-25% over baseline creatinine at 2-5 days after administration of contrast media	Requirement for renal replacement therapy, changes in creatinine clearance and cystatin C
Sun Z et al 2013[15]	Increase in serum creatinine levels ≥ 25% or 44.2µmol/L (0.5mg/dL)	Requirement for renal replacement therapy, mortality, length of hospital stay
Busch SV et al 2013[16]	Increase in serum creatinine levels > 25% or > 0.5mg/dL from baseline within 72 hours	Changes in cystatin C, mortality, adverse clinical events, additional markers of kidney damage and/or function (serum creatinine and eGFR)
Habib M et al 2016[17]	Increase in serum creatinine concentration of 0.5mg/dL or ≥25% of the baseline value within 48 hrs after administration of contrast media	Comparison of the creatinine level, urea and creatinine clearance after administration of contrast media
Poletti PA et al 2013[18]	Incidence of CIAKI at day 2, 4 or 10 with increase of at least 25% or 44µmol/L in serum creatinine level or increase in cystatin C levels at day 2, 4 or 10 compared to day 0	Mean increases in creatinine and cystatin C concentrations on days 2, 4 and 10 along with the maximum increase during the time periods from day 2 to day 10 (peak increase)

6.2.7 Country

The RCT by Habib et al. was conducted in European Gaza Hospital, Gaza, and Palestine.[17] Randomised controlled trial by Poletti et al was conducted at University Hospital of Geneva, Switzerland.[18] Other studies consisted of several RCTs which were conducted and involved samples from United Stated of America, Europe, and Asia including India, China, Taipei, Singapore, and Malaysia.

6.2.8 Risk of Bias

Two reviewers assessed the risk of bias of the included RCTs. For the MAs and SR, the authors did mention the bias of their included RCTs. Overall the authors of the MAs and SR found that the quality of the RCTs were fair to good. The quality of the study depended on the samples size and other bias that might occur within the RCTs. One MA categorized the findings as moderate or low strength of evidence due to limitations of quality of the included RCTs and inconsistency in the results of the RCTs.

6.2.9 Overlapped Trials

The RCTs included in the seven SRs with MAs and one SR in this review were overlapping. The difference was in the way the authors analysed the results. The findings will be further discussed in Section 6.3. Table 4 showed the list of RCTs included in the SRs.

Table 4: Lists of RCTs Included in the SRs

BIL	RCTs	SYSTEMATIC REVIEWS							
		Subramaniam RM et al 2016	Wang N et al 2016	Ali-Hassan-Sayegh S et al 2016	Zhao SJ et al 2016	Kang X et al 2015	Wu et al 2013	Sun et al 2013	Busch et al 2013
1	ACT Investigator 2011	+	-	+	-	+	-	-	-
2	Adamian et al 2002	-	-	-	-	-	-	-	-
3	Agrawal et al 2004	-	+	-	-	-	-	-	-
4	Albabtain et al 2013	+	-	+	-	-	-	-	-
5	Alessandri N 2013	-	-	+	-	-	-	-	-
6	Alioglu et al 2013	+	+	-	-	-	-	-	-
7	Allaqaband et al 2002	+	+	-	-	+	-	-	-
8	Amini et al 2009	+	+	+	-	-	-	-	-
9	Arabmomeni M 2015	-	-	+	-	-	-	-	-
10	Aslanger et al 2012	-	+	-	-	-	-	Ex	+
11	Awal et al 2011	+	+	-	-	-	-	-	-
12	Azmus et al 2005	+	+	+	-	-	-	-	-
13	Baker et al 2003	-	+	+	-	+	-	+	-
14	Balderramo et al 2004	+	+	-	-	-	-	-	-
15	Baskurt et al 2009	-	+	+	-	+	-	-	-
16	Berwanger O 2013	-	-	+	-	-	-	-	-
17	Boccalandro et al 2003	+	-	-	-	-	-	-	-
18	Brar SS et al 2008	-	-	-	+	-	-	-	-
19	Briguori et al 2007	-	-	-	+	-	-	-	-
20	Briguori et al 2002	+	+	+	-	-	-	-	-
21	Brueck et al 2013	+	+	+	-	+	-	-	-
22	Burns et al 2010	-	-	-	-	-	+	-	-
23	Calabroo P 2011	-	-	+	-	-	-	-	-
24	Carbonell et al 2007	+	+	+	-	-	-	+	-
25	Carbonell et al 2010	+	-	+	-	+	-	+	-
26	Castini et al 2010	+	-	+	-	-	-	-	-
27	Chong E 2015	-	-	+	+	-	-	-	-
28	Coyle et al 2006	-	+	+	-	+	-	-	-
29	Demir et al 2008	-	+	-	-	-	-	-	-
30	Diaz-Sandoval et al 2002	+	-	+	-	-	-	-	-
31	Drager et al 2004	-	-	-	-	-	-	-	-
32	Droppa et al 2011	-	-	-	-	-	-	-	+
33	Durham et al 2002	+	+	+	-	+	-	-	-
34	Efrati et al 2003	-	-	-	-	-	-	-	-
35	El Mahmoud et al 2003	-	-	-	-	-	-	-	-
36	Erickson et al 2002	-	-	-	-	-	-	-	-

BIL	RCTs	SYSTEMATIC REVIEWS							
		Subramaniam RM et al 2016	Wang N et al 2016	Ali-Hassan-Sayegh S et al 2016	Zhao SJ et al 2016	Kang X et al 2015	Wu et al 2013	Sun et al 2013	Busch et al 2013
37	Erturk et al 2014	+	-	-	-	-	-	-	-
38	Ferrario et al 2009	+	-	+	-	+	-	-	-
39	Fung et al 2004	-	+	+	-	+	-	-	-
40	Goldenberg et al 2004	+	+	+	-	-	-	-	-
41	Gomes et al 2005	+	+	+	-	-	-	-	-
42	Gulel et al 2005	+	+	+	-	-	-	-	-
43	Gunebakmaz et al 2012	+	-	+	-	-	-	-	-
44	Hafiz AM et al 2012	-	-	-	+	-	-	-	-
45	Heguilen et al 2013	+	-	-	+	-	-	-	-
46	Heng AE 2008	-	-	+	-	-	-	-	-
47	Holscher et al 2008	+	-	+	-	-	-	-	-
48	Hsu CH et al 2007	+	-	-	-	-	-	-	-
49	Hsu TF et al 2012	+	-	-	-	-	+	-	-
50	Inda-Filho 2014	-	-	+	+	-	-	-	-
51	Izani et al 2008	+	+	-	-	-	-	-	-
52	Jaffery et al 2012	+	+	+	-	+	-	+	+
53	Kahlon et al 2002	-	-	-	-	-	-	-	-
54	Kama et al 2014	+	-	-	-	-	-	-	-
55	Kay et al 2003	+	+	+	-	+	-	-	-
56	Kefer et al 2003	+	+	+	-	-	-	+	-
57	Khalili et al 2006	+	-	-	-	-	-	-	-
58	Kim et al 2010	+	-	+	-	-	-	-	-
59	Kimmel et al 2008	+	-	-	-	+	-	-	-
60	Kinbara et al 2010	+	+	+	-	-	-	-	-
61	Kitzler et al 2012	-	-	-	-	-	+	-	-
62	Koc et al 2012	-	+	+	-	+	-	+	-
63	Koo TY et al 2011	-	-	-	+	-	-	-	-
64	Kotlyar et al 2005	+	+	-	-	-	-	Ex	-
65	Kumar A 2004	-	-	+	-	-	-	-	-
66	Le Feuvre et al 2003	-	-	-	-	-	-	-	-
67	Lee SW et al 2011	-	-	-	+	-	-	-	-
68	Loutrianakis et al 2003	-	-	-	-	-	-	-	-
69	MacNeil et al 2003	+	+	+	-	-	-	-	-
70	Mahmoodi K et al 2014	-	-	-	+	-	-	-	-
71	Maioli M et al 2008	-	-	-	+	-	-	-	-
72	Marenzi et al 2006	+	+	-	-	-	-	Ex	+
73	Miner et al 2004	+	+	+	-	+	-	-	-
74	Mouhayar et al 2002	-	-	-	-	-	-	-	-
75	Namgung et al 2005	-	-	-	-	-	-	-	-
76	Nguyen-Ho et al 2003	-	-	-	-	-	-	-	-
77	Nogareda et al 2003	-	-	-	-	-	-	-	-
78	Ochoa et al 2004	+	+	+	-	+	-	-	-

BIL	RCTs	SYSTEMATIC REVIEWS							
		Subramaniam RM et al 2016	Wang N et al 2016	Ali-Hassan-Sayegh S et al 2016	Zhao SJ et al 2016	Kang X et al 2015	Wu et al 2013	Sun et al 2013	Busch et al 2013
79	Oldemeyer et al 2003	+	+	+	-	+	-	-	-
80	Ozcan et al 2007	+	+	-	-	-	-	-	-
81	Pate et al 2003	-	-	-	-	-	-	-	-
82	Poletti et al 2007	+	-	-	-	+	+	+	-
83	Rashid et al 2004	+	-	-	-	+	-	+	-
84	Ratcliffe et al 2009	+	+	+	+	-	-	Ex	-
85	Recio-Mayoral A et al 2007	-	-	-	+	-	-	-	-
86	Reinecke 2007	+	+	-	-	-	-	-	-
87	Sadat et al 2011	+	-	-	-	-	-	-	-
88	Sandhu et al 2006	-	-	-	-	-	-	-	-
89	Sar et al 2010	-	-	-	-	-	+	-	-
90	Seyon et al 2007	+	+	+	-	+	-	-	-
91	Shyu et al 2002	+	+	+	-	-	-	-	-
92	Sinha et al 2007	-	-	-	-	-	-	-	-
93	Tadros et al 2003	-	-	-	-	-	-	-	-
94	Tanaka et al 2011	+	+	-	-	-	-	-	+
95	Tepel et al 2000	+	-	-	-	-	+	-	-
96	Thayssen et al 2014	+	+	+	+	-	-	-	-
97	Thiele et al 2010	+	+	+	-	-	-	+	+
98	Traub 2013	+	-	-	-	-	-	-	-
99	Vallero et al 2002	-	-	-	-	-	-	-	-
100	Wang JH 2008	-	-	+	-	-	-	-	-
101	Webb et al 2004	-	+	+	-	+	-	+	-
102	Yang et al 2014	-	+	-	+	-	-	-	-
103	Yeganehkhah et al 2014	+	+	+	-	-	-	-	-

*'+' refer to RCT that included in the SR
* '-' refer to RCT that not included in the SR
*'Ex' refer to RCT that being excluded from the SR

6.3 Efficacy / Effectiveness

The results will be described based on the factors that may affect the effectiveness of NAC to prevent CIAKI. The main factor was patients underlying problems. This was further divided into other factors which were dosage and administration routes of NAC and combination of NAC with other preventions. The other factor was contrast media type. Some of the RCTs reported in the SRs were overlapped. However, the way the authors reported the final outcome depended on their objectives.

6.3.1 Patients Underlying Problems

6.3.1.1 Renal Insufficiency

Overall results

Kang X et al. conducted SR and MA to identify the effects of NAC for CIAKI prevention in patients with pre-existing renal insufficiency or diabetes. The study included 21 RCTs where a total of 3,581

patients with pre-existing renal insufficiency and 725 patients with diabetes were studied. The authors performed subgroup analysis of pre-existing renal insufficiency. The effects of NAC on CIAKI incidence in pre-existing renal insufficiency patients showed that an overall pooled OR of 0.76 (95% CI: 0.61,0.93), p = 0.008, which indicated lower incidence of CIAKI in patients who received NAC.[13, level 1]

Wu MY et al. conducted SR and MA to assess the effectiveness of NAC in CIAKI prevention in patients undergoing contrast-enhanced CT-scan. Only six RCTs were included with a total of 496 patients. The analysis was based on renal profile of the patients which was grouped under high risk (srCr above 1.2mg/dL) or low risk (srCr below 1.2mg/dL). In high risk patients, there was significant difference between treatment group and control group; more patients in the control group experience greater CIAKI incidence compared to treatment group with RR of 0.20, (95% CI: 0.07,0.57). In the low-risk patients there was no significant difference between the treatment group and control groups with RR of 0.46, (95% CI: 0.21,1.02).[14, level 1]

Dose of NAC

Subramaniam RM et al. in their systematic review with meta-analysis assessed / evaluated the effectiveness of prevention strategies for CIAKI among patients with diabetes and renal insufficiency. Other than NAC, they also reviewed other prevention strategies such as sodium hydrocarbonate ($NaHCO_3$), statins and ascorbic acid. There were 86 RCTs included and 55 RCTs were mainly for NAC and the rest were for the other preventions. Most of the RCTs used placebo as a control. The pooled results for high-dose NAC revealed that there was small effect in reducing CIAKI risk but the reduction was not statistically significant. The high-dose NAC was administered either intra-arterial (i.a) or intravenous (i.v). The pooled risk ratio (RR) for high dose i.a NAC was 0.78 (95% CI: 0.55,1.12) and for high dose i.v NAC was 0.55 (95% CI: 0.12,2.62). For low-dose NAC, the clinically important effect on CIAKI prevention was borderline; pooled RR for CIAKI either by i.a NAC or i.v NAC was 0.77 (95% CI: 0.66,0.91) and 0.62 (95% CI: 0.18,2.10) respectively.[9, level 1]

Kang et al. also analysed the results based on NAC dose, only NAC dose of 2.4 gram ± 2.0 gram was included. The result showed that with such dose the NAC was effective to prevent CIAKI in pre-existing renal insufficiency patient with OR 0.76 (95% CI: 0.60,0.95, p = 0.02 but not in diabetes mellitus patients OR 0.99 (95% CI: 0.64,1.53, p = 0.96).[13, level 1]

Poletti PA et al. conducted a RCT to determine whether ultra-high dose intravenous NAC (6 gram) is efficient to prevent CIAKI after emergency contrast CT-scan in patients admitted to the emergency department with elevated creatinine levels. One hundred and twenty (120) patients were randomised to high-dose NAC group or placebo group. However, only 110 patients were analysed; 52 patients in NAC group and 58 patients in placebo group. Nevertheless irrespective of definition of CIAKI, there was no significant difference in CIAKI incidence between both groups.[18, level 1]

Route of NAC Administrations

Sensitivity analyses by Subramaniam RM et al. revealed imprecise estimates of the pooled RR for CIN, when stratified by route of administration. A comparison between oral and i.v routes of NAC showed that the oral NAC plus i.v saline had a small effects in reducing CIAKI with RR of 0.77 (95% CI: 0.65,0.92) and for i.v NAC plus i.v saline, RR of 0.90 (95% CI: 0.72, 1.12).[9, level 1]

Wang N et al. conducted SR and MA to assess the effects of NAC on the incidence of CIAKI. The RCTs included used either i.v or oral NAC as study treatment and placebo or i.v saline as a control. The pooled results showed that oral NAC had significantly lowered CIAKI incidence with odds ratio (OR) of 0.645, (95% CI: 0.489, 0.851), I^2 = 29.15%; p = 0.002). In i.v routes of NAC, although the CIAKI rate was lower compared to placebo, the difference was not statistically significant; OR

0.737, (95% CI: 0.530, 1.025); I^2 = 43.85%; p = 0.070. However, there was no significant difference in comparing between i.v and oral route; p = 0.472.[10, level 1]

Kang X et al. also assessed at the effects of NAC routes of administration either by i.v or oral. In pre-existing renal insufficiency patients, they found that i.v NAC showed significant difference in CIAKI occurrence with OR 0.67 (95% CI: 0.50, 0.91), p = 0.008. In oral route for pre-existing renal insufficiency patients, the OR was 0.85 (95% CI: 0.64, 1.13, p = 0.26).[13, level 1]

SR with MA by Sun et al, involved 10 RCTs and a total of 1,914 patients which included patients with chronic kidney disease and normal kidney function. Although i.v NAC was associated with reduction in CIAKI incidence when compared to hydration alone, it was only borderline statistically significant; P = 0.06.[15, level 1]

Single Use NAC versus Combination of NAC with Other Alternatives

Zhao SJ et al. conducted SR and MA to compare the efficacy of combination therapy with each individual therapy of NAC and $NaHCO_3$. The review assessed the combination therapy of NAC and $NaHCO_3$ (COM group) versus either single therapy of NAC (NAC group) or $NaHCO_3$ (SOB group). Out of 16 RCTs included, 14 RCTs reported CIAKI incidence in patients allocated to COM group or NAC group. However, only 13 studies were included for further analysis which involved 2,874 patients. The overall CIAKI incidence was 10.9% (157/1,436) in COM group and 12.8% (184/1,438) in the NAC group. The findings showed that there was no significant reduction of CIN in COM group compared with NAC group with RR 0.85 (95% CI: 0.70, 1.03), p = 0.10. A subgroup analysis among patients with renal insufficiency was also reported. Eight out of 14 RCTs were included and the results revealed that there was also no significant reduction in CIAKI incidence in combination group compared with NAC group (RR 0.89, 95% CI: 0.70,1.14, p = 0.37).[12, level 1]

6.3.1.2 Diabetes Mellitus (DM)

Overall Results

Wang N et al. conducted SR and MA to assess the effects of NAC on the incidence of CIAKI. The author included 43 RCTs which involved a total of 3,277 patients. Twenty seven (27) RCTs evaluated the effect of NAC on patients with diabetes, and without diabetes regardless of their renal status. The overall pooled results of CIAKI incidence in patients with diabetes were similar between NAC versus placebo with OR 0.74, (95% CI: 0.53,1.02), p = 0.070. In patients without DM, there was a significant reduction in CIAKI incidence with OR, 0.65, 95% CI: 0.49,0.85), p = 0.002). However, in comparing both diabetes and non-diabetes patients, the results showed no significant difference (p = 0.580).[10, level 1]

Kang X et al. reported that, the overall pooled OR of CIAKI incidence in diabetes patients with NAC used was 0.87 (95% CI: 0.58, 1.30), p = 0.50, which was not statistically significant.[13, level 1]

Dose of NAC

As stated previously, Kang et al. found that NAC dose of 2.4 gram ± 2.0 gram was not effective to prevent CIAKI in diabetes mellitus patients, OR of 0.99 (95% CI: 0.64,1.53, p = 0.96).[13, level 1]

Routes of NAC Administration

Sub-analysis of diabetes mellitus patients by Kang X et al. found that both routes of administration did not show any significant effects towards CIAKI occurrence; i.v NAC with OR 0.73 (95% CI: 0.43, 1.23, p = 0.24) and oral NAC with OR 1.21 (95% CI: 0.60, 2.09, p = 0.72).[13, level 1]

Single Use NAC versus Combination of NAC with Other Alternatives

Zhao SJ et al. performed sub-analysis to evaluate the effect of NAC in diabetes patients. Out of

14 RCTs that compared combination group and single use of NAC, four studies (621 patients) reported CIAKI incidence in diabetes patients. The incidence of CIAKI was 11.3% (34/311) in the combination group and 9.7% (30/310) in the NAC group. The analysis showed that there was no significant benefit in combination group compared to NAC group in reducing CIAKI incidence with RR 1.11, (95% CI: 0.71,1.75), p = 0.65.[12, level 1]

6.3.1.3 Cardiac Problems (Acute Coronary Syndrome (ACS) and ST-Segment Elevation Myocardial Infraction (STEMI))

Overall Results

Wang N et al. in their MAs included eight RCTs that assessed the use of NAC in patients with ACS. The authors found that in ACS patients that received NAC treatment, the trend of CIAKI incidence was towards a lower rate but the finding was not significant; OR of 0.758 (95% CI: 0.54,1.07), p = 0.111. On the other hand, in patients without ACS, there was significantly lower CIAKI rate in the group taking NAC compared to control; OR = 0.64 (95% CI: 0.49, 0.83), p = 0.001. Another five RCTs included patients with STEMI and non STEMI. The assessment found that the CIAKI incidence rate in patients with STEMI undergoing PCI, was towards lower trend though not significant with OR 0.56 (95% CI: 0.31, 1.01), p = 0.056. In non STEMI subgroups, there was lower CIAKI rate in the NAC group with OR 0.69 of (95% CI: 0.55, 0.89), p = 0.004.[10, level 1]

Ali-Hassan-Sayegh S et al. conducted SR and MA to determine the strength of evidence for the effects of hydration (NaHCO3 and NaCl) and, supplementations (NAC and vitamin C and other common drugs) on the incidence of CIAKI and requirement for haemodialysis after coronary angiography. Out of 125 RCTs, 49 RCTs were included for NAC versus placebo with total patients of 11,446. Overall findings showed that the average CIAKI incidence was 13.1% ranging from 0% to 29.8%; 11.7% in NAC group and 14.4% in placebo group. Pooled treatment effect analysis revealed that NAC could significantly decreased the incidence of CIAKI compared with placebo; OR 0.79 (95% CI: 0.70, 0.88, p = 0.001). As for haemodialysis requirement, pooled analysis found that NAC therapy could not significantly decreased the incidence of haemodialysis with OR of 1.18 (95% CI: 0.60, 2.3, p = 0.6).[11, level 1]

Sun Z et al. conducted SR and MA to evaluate the efficacy of i.v NAC for CIAKI prevention in patients undergoing cardiac catheterization peripheral angiography (9 RTCs) and patients undergoing CT-scan (1 RCT) with a total of 1,914 patients. The overall pooled RR of CIAKI using random effects model was 0.68 (95% CI: 0.45, 1.02, p = 0.06) which indicated a non-significant trend towards benefit in patients who received NAC. Secondary outcomes which included dialysis requirement, and in-hospital mortality were not significant; p = 0.72, and p = 0.67 respectively. The findings indicated that the role of i.v NAC was inconclusive due to insufficient data on secondary outcome and statistically significant borderline result in prevention of CIAKI incidence.[15, level 1]

Dose of NAC

Busch SV et al conducted SR which included nine RCTs in order to assess preventions of CIAKI in STEMI patients undergoing primary percutaneous coronary intervention (PCI). Six RCTs were included for NAC and the other three studies were for the other preventions. Five RCTs in the SR showed no significant difference in CIAKI incidence compared to placebo. Only one study showed that CIAKI incidence was significantly lowered in high dose NAC compared with low dose NAC. In addition, they also found that high dose NAC significantly decreased in hospital mortality. The high dose of NAC was equivalent to i.v bolus of 1,200mg before primary PCI and 1,200mg NAC iv BD for 48 hours after procedure or 200mg/hr for 24 hours.[16, level 1]

Habib M et al. conducted a RCT to evaluate the effect of high dose NAC plus hydration, low dose NAC plus ascorbic acid and hydration or hydration alone on the prevention of CIAKI in high-risk

patients undergoing elective coronary artery intervention. Patients were randomised into three groups; Group A were 30 patients who received high-dose oral NAC 1200 mg every 12 hours for two days, Group B were 30 patients who received low-dose NAC 600 mg orally every 12 hours for two days and Group C were 45 patients who received placebo. The primary outcome of the RCT was CIAKI incidence which was defined as an increase in srCr concentration of 0.5 mg/dL or 25% and more of the baseline value within 48 hours after procedure. The secondary outcome was comparison of creatinine level, urea and creatinine clearance between those groups. After 48 hours of exposure to contrast media, the incidence of CIAKI was detected in 6.66% patients in Group A, 16.66% in Group B and 17.77% in Group C. The difference between Group A versus Group B and Group A versus Group C was highly significant; p = 0.001. Meanwhile the difference between Group B and Group C was not statistically significant; p = 0.37. For secondary outcome, the difference of plasma urea level between Group A and Group B was statistically significant; p = 0.029. As for creatinine clearance, the difference was statistically significant between Group A and Group C; p = 0.045. While comparing between Group B and Group C, the difference was not statistically significant with respect to creatinine clearance or serum creatinine before and after interventions. This study showed that high doses of NAC with hydration provide better protection against CIAKI than combination therapy of NAC and ascorbic acid or hydration alone.[17, level 1]

Single Use NAC versus Combination of NAC with Other Alternatives

Zhao SJ et al. also conducted subgroup analysis to compare the effect of combination therapy with single use of NAC in CIAKI incidence among patients undergoing PCI. Out of 14 RCTs included, four studies were analysed which involved 893 patients. The incidence of CIAKI was 13.2% (59/447) in the combination group and 17.0% (76/446) in the NAC group, which indicated that there was no significant benefit in the combination group compared to NAC group in the reduction of CIAKI incidence (RR 0.76, (95% CI: 0.70, 1.14), p = 0.37).[12, level 1]

6.3.2 Contrast Media Used

Systematic review with meta-analysis by Subramaniam RM et al. assessed the effect of NAC when different types of contrast media were used. The used of LOCM with NAC showed clinically important benefit to reduce CIAKI; with pooled RR of 0.69 (95% CI: 0.58,0.84). Meanwhile, the used of IOCM with NAC did not have clinically important benefit to reduce CIAKI RR: 1.12 (95% CI 0.74,1.69).[9, level 1]

6.4 Safety

Some studies reported several adverse events due to administration of NAC in CIAKI prevention. No adverse event was reported for oral use of NAC. The specific adverse events reported which was directly related to administration of i.v NAC were the incidence of high rate transient itching, flushing and rash. These adverse events were considered mild and treated with hydrocortisone and stop the NAC therapy.[15] One RCT reported no side effects attributed to NAC injection throughout the study.[18]

6.5 Economic Evaluation

There was no retrievable evidence on cost-effectiveness of NAC to prevent CIAKI. In the Ministry of Health Drug Formulary, only N-Acetylcysteine 200mg/ml injection is listed. The estimated price of N-acetylcysteine 200mg/ml injection of 10 ml per vial is about RM 11.29. The oral NAC tablet was not listed in MOH Formulary and the price range in the retail pharmacy is about RM2.00 to RM5.00 per tablet of 100mg, 200mg and 600mg.

6.6 Organizational, Ethical and Legal Consideration

Currently MOH did not have any standard operating procedure for the prevention of CIAKI. Although NAC is a common drug, in MOH Malaysia NAC has being used off-label for CIAKI prevention and requires approval from the Director General of Health. The oral formulation of NAC is not available in MOH Formulary. Thus patients will have to buy it on their own. For injection route by either i.v or i.a, the procedure will be conducted in the hospital under health care supervision. However, for oral route, the first dose will be taken by the patients themselves. Nevertheless, legal implications may arise if patient develop complications due to the off-label use.

7.0 DISCUSSION

This review identified sufficient number of good level evidence on the effectiveness of NAC for CIAKI prevention. Seven SRs with MAs were included in this review and four of the studies were published in 2016. Although the initial plan was to conduct another meta-analysis, this review was conducted as an overview of the reviews due to the available recent meta-analysis.

The overall results showed that although NAC have small effects in reducing CIAKI incidence, the results were not consistent. In determining the better routes of NAC administration for CIAKI prevention, the evidence was inconclusive as patients underlying disease did play a role. The evidence indicated that NAC has potential in reducing CIAKI incidence in patients with pre-existing renal insufficiency. In this group of patients the routes of administration did not significantly affect the outcome. Meanwhile in diabetes patients, the use of NAC for CIAKI prevention was not associated with significant reduction in CIAKI regardless of routes of NAC administration.

As for patients with cardiac problems namely ACS and STEMI, regardless of the contrast procedure involved, NAC did not significantly reduce the rate of CIAKI incidence, although the incidence rate was towards a lower trend. In some practices, combination treatments have been used as well. The evidence showed that combination therapy has no significant effect in reducing CIAKI incidence compared with NAC single treatment.

Different NAC dosages have been used for CIAKI prevention; the evidence showed that the effects of NAC dose for prevention of CIAKI were inconsistent. Although the effects were towards a lower trend of CIAKI incidence, the trend was not statistically significant. Only one study from one SR showed that high dose NAC significantly reduced CIAKI incidence among STEMI patients as well as reducing hospital mortality. In addition, in diabetes patients with renal insufficiency, high dose of NAC may also significantly reduced CIAKI incidence when compared with diabetes patients without renal insufficiency.

There was also possibility that the effectiveness of NAC in CIAKI prevention was attenuated based on type of contrast agent used. Evidence showed that the use of NAC along with LOCM had clinically important benefit in reducing CIAKI incidence compared with it usage with IOCM.

There was variation of practice in MOH hospitals; certain hospital did not use NAC as a preventive measure. Instead of pharmacological preventive measures, hydration either parenterally with normal saline or orally by encouraging patients to drink plenty of water before and after procedure is widely used. The evidence showed, there was no significant difference in CIAKI occurrence when NAC usage was compared with hydration. There is also practice that use different type of contrast media along with NAC.

However, with many other alternatives for CIAKI prevention during radio-contrast procedure, it is important to remember that there are many other factors that may contribute to CIAKI incidence. Besides pre-existing kidney disease with renal function impairment, other factors such as diabetes, cardiac problems, hypertension, advanced age, volume depletion, haemodynamic instability, use of concurrent nephrotoxic medications and large volume or high osmolality of the contrast agent may contribute to the CIAKI incidence.[1]

7.1 Limitations

This review has some limitations which should be considered. The focus of the review was to assess the effects of NAC in CIAKI prevention, thus this review did not consider other alternatives including combination of NAC with other alternatives, unless the studies compared the alternatives with single use of NAC. Another limitation that needs to be considered was that the studies included were on NAC used in CIAKI prevention and did not really evaluate the other important outcomes such as morbidity, mortality and cost. Besides, the dose of NAC varied from one study to another and was not base on any standard procedures or guidelines. There was also no standardised protocol for hydration which is also one of the important alternatives for CIAKI prevention in all studies. All studies included involved hydrations protocols before and after radio-contrast procedures.

8.0 CONCLUSION

Good level of evidence retrieved on the effects of NAC in CIAKI prevention. The evidence showed that patients underlying problems, NAC dose and type of contrast media used may influence the overall effects of NAC in CIAKI preventions.

In patients with renal insufficiency, oral NAC may reduce CIAKI incidence while compared with placebo. However, the optimum dose of NAC required cannot be determined. On the other hand, in diabetes patients, use of NAC brought no significant effects in CIAKI prevention. As for patients undergoing cardiac angiography, role of NAC in CIAKI prevention was inconsistent. However, high dose NAC seems to be more effective compared to low dose.

The choice of contrast media has an effect in reducing CIAKI incidence, where use of NAC with LOCM showed better outcome compared to NAC with IOCM. Besides that, NAC single use showed no significant different with combination of NAC with alternatives. On safety, there was no adverse events reported for oral NAC but intravenous NAC did show some adverse events such as itching, flushing and rash.

9.0 RECOMMENDATION

Based on the available evidence, oral NAC may be used in prevention of CIAKI in renal insufficiency patients. Other factors that may influence CIAKI incidence should be considered in patients undergoing radio-contrast procedure such as types of contrast media and patients' hydration status

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11.0 APPENDIXIES

APPENDIX 1: HTA PROTOCOL

HEALTH TECHNOLOGY ASSESSMENT (HTA) PROTOCOL: N-ACETYLCYSTEINE (NAC) IN PREVENTION OF CONTRAST-INDUCED ACUTE KIDNEY INJURY (CIAKI)

1.0 BACKGROUND INFORMATION

Contrast-induced acute kidney injury (CIAKI) is defined as acute renal failure occurring within 48 hours of exposure to intravascular radiographic contrast material that is not attributable to other causes. It also known as contrast-induced nephropathy (CIN).[1] In KDIGO (Kidney Disease, Improving Global Outcomes) guidelines the term contrast-induced acute kidney injury (CIAKI) is used.[2] Based on serum creatinine levels; CIAKI is defined as 0.5 mg/dl or more increase in serum creatinine (SCr) from baseline after 48 hours or a 25% or more increase in SCr from baseline after 48 hours.[1,2,3]

Contrast-induced acute kidney injury is uncommon among people with normal kidney function. However, its frequency increases with declining kidney function, ranging from 5% in those with mild kidney impairment to 50% in those with diabetes and severe renal insufficiency.[2] However, the rate of incidence of CIAKI as a complication of radiographic diagnostic and interventional studies varies markedly, depending on the definition used and on other variables such as the type of radiology procedure performed, the dose and type of contrast agent administered, the differing patients populations in regard to number and type of risk factors and the length of patient follow-up.[1]

The US Food and Drug Administration has reported that the overall incidence of CIAKI following contrast administration from 1990 to 1994 ranged from 1.22 to 2.35/million examinations and from 0.6% to 2.3% of all reported reactions. Most occurrences of CIAKI develop following diagnostic examination. Reported incidence of CIAKI is 11%, 9% and 4% following outpatient computed tomography (CT), peripheral angiography, and intravenous pyelography respectively. Contrast-induced acute kidney injury incidence following CT among hospitalised cancer patients was 20%. In this population, CIAKI developed more often in patients who had undergone chemotherapy recently. In patients undergoing percutaneous coronary intervention for coronary heart disease, the incidence of CIAKI was 3.3% overall and approximately 25% in patients with baseline SCr > 2.0 mg/dL (176.8 µmol/L).[2]

There are three types of contrast agents available. Namely high osmolar contrast media (HOCM), low osmolar contrast media (LOCM) and iso-osmolar contrast media (IOCM). Several studies did demonstrate that LOCM results in substantially less contrast-induced nephropathy than HOCM in patients with pre-existing renal dysfunction but no benefit in those without renal dysfunction. Although, there was no proven decrease in contrast-induced nephropathy in normal populations, better tolerability and fewer side effects of LOCM have largely resulted in their supplanting HOCM in routine clinical practice.[4]

Many factors have been reported as risk to the CIAKI. The risk factors can be divided as either non-modifiable factors or modifiable factors.[1,2] The most important non-modifiable risk factors for contrast-induced nephropathy include pre-existing renal insufficiency, older age, diabetes mellitus, reduced left ventricular systolic function, advanced congestive heart failure, acute myocardial infarction, cardiogenic shock, hypertension, cardiac diastolic dysfunction, procedural bleeding and kidney transplantation.[2] Meanwhile, the modifiable risk factors include types and dose or volume of contrast media, anaemia, dehydration, low serum albumin level (< 35 g/L), use of certain medicine

such as angiotensin-converting enzyme inhibitors, frusemide and non-steroidal anti-inflammatory drugs.[2]

Several approaches has been used in the attempt to prevent CIAKI. These approaches include providing adequate hydration peri-procedure, choice of contrast media, used of certain drugs such as diuretics, calcium channel blocker, adenosine antagonist, endotheline receptor blockers, prostaglandin as well as N-acetylcysteine and performing haemodialysis or haemofiltration.[1] N-acetylcysteine is an acetylated derivative of the amino acid cysteine. The chemical formula is $C_5H_9NO_3S$, with molecular mass of 163.2 g/mol. The drug can be administered via oral, intravenous, or through respiratory routes.[6] The potential mechanism of N-acetylcysteine for contrast-induced nephropathy prophylaxis includes both antioxidant and vasodilatory effects. Use of N-acetylcysteine as prophylaxis of contrast-induced nephropathy is extensive, however, the efficacy of the practice is inconclusive.[3,4]

Currently in Ministry of Health, there is no national standard procedure on the prophylaxis of CIAKI. However, N-acetylcysteine has been used off-label in prevention of CIAKI. Thus, this health technology assessment was requested by Pharmacist from Selayang Hospital to assess the efficacy, safety and cost-effectiveness of the practice due to high demand on N-acetylcysteine as a prophylaxis of CIAKI.

2.0 POLICY QUESTION

2.1 Should N-acetylcysteine be used for the prevention of CIAKI in patient undergoing intravenous iodinated contrasted procedure?

3.0 OBJECTIVE

3.1 To assess the safety of N-acetylcysteine in prevention of contrast-induced acute kidney injury

3.2 To assess the efficacy/effectiveness of N-acetylcysteine in prevention of contrast-induced acute kidney injury

3.3 To assess the economic implications related to N-acetylcysteine in prevention of contrast-induced acute kidney injury

3.4 To assess the ethical, legal, and organizational implications related to N-acetylcysteine in prevention of contrast-induced acute kidney injury

Research Questions

iii) Is N-acetylcysteine safe and effective in prevention of contrast-induced acute kidney injury among patients undergoing intravenous iodinated contrasted procedure?

iv) What is the economics, ethical, legal, and organizational implications using N-acetylcysteine in prevention of contrast-induced acute kidney injury?

4.0 METHODS

4.1. Search Strategy

4.1.1 Electronic databases will be searched for published literatures pertaining to NAC as prophylaxis of CIN. The databases are MEDLINE, PubMed, and EBM Reviews-Cochrane Database of Systematic Review, EBM-Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-Cochrane Methodology

Register, EBM Reviews-NHS Economic Evaluation Database, Database of Abstracts of Reviews of Effects (DARE), Horizon Scanning, INAHTA Database, HTA database and FDA database.

4.1.2 Additional literatures will be identified from the references of the related articles.

4.1.3 General search engine will also be used to get additional web-based information.

4.1.4 There will be no limitation applied in the search such as year and language.

4.1.5 The search strategy will be included in the appendix.

4.2 Inclusion and exclusion criteria

4.2.1 Inclusion criteria

a. Population : Patients undergoing intravenous iodinated contrasted procedure

b. Intervention : Intravenous or oral N-acetylcysteine / i.v or oral NAC

c. Comparators : As listed below:-

   i. Other drugs (diuretic, calcium channel blocker, adenosine antagonist, endotheline receptor blocker, and prostaglandin)

   ii. Other procedures (hydration or non-drug)

   iii. Choice of contrast

   iv. No comparator

d. Outcome : Efficacy/Effectiveness (prevention of CIAKI), safety, economic impact, organizational, legal and ethical implications

e. Study design : Health technology assessment (HTA) reports, systematic reviews (SRs), randomised controlled trials (RCTs), cohorts, case-control study, pre- and post- intervention and economic evaluation studies

f. : Full text articles published in English

4.2.2 Exclusion criteria

a. Animal study

b. Narrative review

c. Experimental study

d. N-acetylcysteine used for other management except for prevention of contrast-induced nephropathy

Based on the above inclusion and exclusion criteria, study selection will be carried out independently by two reviewers. Disagreement will be resolved by discussion.

4.3 Critical Appraisal of Literature

The methodology quality of all retrieved literatures will be assessed using the relevant checklist of Critical Appraisal Skill Programme (CASP)

4.4 Analysis and Synthesis of Evidence

4.4.1 Data extraction strategy

The following data will be extracted:

a. Details of methods and study population characteristics.

b. Detail of intervention and comparators if any

c. Details on outcomes for effectiveness, safety and cost associated with N-acetylcysteine as CIN prophylaxis

d. Details on organizational, ethical and legal issues related to the practice

Data will be extracted from selected studies by a reviewer using a pre-designed data extraction form and checked by another reviewer. Disagreements will be resolved by discussion.

4.4.2 Methods of Data Synthesis

Data on the efficacy/effectiveness, safety and cost-effectiveness of N-acetylcysteine as CIN prophylaxis will be presented in tabulated format with narrative summaries.

5.0 Report writing

6.0 References

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APPENDIX 2: DESIGNATIONS OF LEVELS OF EVIDENCE

HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

APPENDIX 3: CASP CHECKLIST FOR SYSTEMATIC REVIEW

10 questions to help you make sense of a review

How to use this appraisal tool

Three broad issues need to be considered when appraising the report of a systematic review:

- **Are the results of the review valid?** **(Section A)**
- **What are the results?** **(Section B)**
- **Will the results help locally?** **(Section C)**

The 10 questions on the following pages are designed to help you think about these issues systematically.
The first two questions are screening questions and can be answered quickly. If the answer to both is "yes", it is worth proceeding with the remaining questions.

There is some degree of overlap between the questions, you are asked to record a "yes", "no" or "can't tell" to most of the questions. A number of prompts are given after each question. These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.
These checklists were designed to be used as educational tools as part of a workshop setting
There will not be time in the small groups to answer them all in detail!

(A) Are the results of the review valid?

Screening Questions

1. Did the review address a clearly focused question? ❒ Yes ❒ Can't tell ❒ No

HINT: An issue can be 'focused' in terms of
- The population studied
- The intervention given
- The outcome considered

2. Did the authors look for the right type of papers? ❒ Yes ❒ Can't tell ❒ No

HINT: 'The best sort of studies' would
- Address the reviews question
- Have an appropriate study design (usually RCTs for papers evaluating interventions)

Detailed questions

3. Do you think all the important, relevant studies were included? ❒ Yes ❒ Can't tell ❒ No

HINT: Look for
- Which bibliographic databases were used
- Follow up from reference lists
- Personal contact with experts
- Search for unpublished as well as published studies
- Search for non-English language studies

4. Did the review's authors do enough to assess the quality of the included studies? ❒ Yes ❒ Can't tell ❒ No

HINT: The authors need to consider the rigour of the studies they have identified. Lack of rigour may affect the studies' results. ("All that glisters is not gold" Merchant of Venice – Act II Scene 7)

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5. If the results of the review have been combined, was it reasonable to do so? ❒ Yes ❒ Can't tell ❒ No

HINT: Consider whether

- The results were similar from study to study
- The results of all the included studies are clearly displayed
- The results of the different studies are similar
- The reasons for any variations in results are discussed

(B) What are the results?

6. What are the overall results of the review?

HINT: Consider

- If you are clear about the review's 'bottom line' results
- What these are (numerically if appropriate)
- How were the results expressed (NNT, odds ratio etc)

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7. How precise are the results?

HINT: Look at the confidence intervals, if given

(C) Will the results help locally?

8. Can the results be applied to the local population? ❒ Yes ❒ Can't tell ❒ No

HINT: Consider whether

- The patients covered by the review could be sufficiently different to your population to cause concern
- Your local setting is likely to differ much from that of the review

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9. Were all important outcomes considered? ❒ Yes ❒ Can't tell ❒ No

HINT: Consider whether

- Is there other information you would like to have seen

---

10. Are the benefits worth the harms and costs? ❒ Yes ❒ Can't tell ❒ No

HINT: Consider

- Even if this is not addressed by the review, what do you think?

APPENDIX 4: SEARCH STRATEGIES USED IN THE MAJOR ELECTRONIC BIBLIOGRAPHIC DATABASE

MEDLINE/EMABSE/PubMED

1. Contrast Media/
2. (contrast adj (agent* or material* or media)).tw.
3. ((radiocontrast or radiopaque) adj (agent* or media)).tw.
4. Iohexol/
5. exypaque.tw.
6. iohexol 350.tw.
7. iohexol.tw.
8. nycodenz.tw.
9. omnipaque.tw.
10. Injections, Intravenous/
11. intravenous injection*.tw.
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. Acetylcysteine/
14. acetylcysteine sodium.tw.
15. sodium, acetylcysteine.tw.
16. acetylcysteine.tw.
17. n acetyl l cysteine.tw.
18. n acetylcysteine.tw.
19. n-acetyl-l-cysteine.tw.
20. n-acetylcysteine.tw.
21. nac al.tw.
22. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. 12 and 22
24. limit 23 to humans

APPENDIX 5: LIST OF EXCLUDED STUDIES

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APPENDIX 6

EVIDENCE TABLE
(SR & MA: EFFICACY OF NAC TO PREVENT CIAKI)

Evidence Table : Effectiveness of N-acetylcysteine in prevention of contrast-induced nephropathy among patients undergoing radiocontrast procedure

Question : Is N-acetylcysteine effective in prevention of contrast-induced nephropathy among patients undergoing radiocontrast procedure?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
1. Subramaniam RM, Suarez-Cuerzo C, Wilson RF, Turban S,Zhang A, Sherrod C, Aboagye J, Eng J,Choi MJ, Hutfless & Bass EB. Effectiveness of Prevention Strategies for Contrast-Induced Nephropathy. A Systematic Review and Meta-analysis. 2016; 164: 406-416	SR and MA Contrast Media: iso-osmolar or low osmolar via IV or IA Graded the SOE using grading scheme recommended in Methods Guide of the Evidence-Based Practice Center Following guidance of GRADE, authors rated evidence as precise if : a) Total number of patients exceeded an optimum information size and 95% CI excluded a risk ratio (RR) of 1.0 b) Number of patients exceeded the optimum information size and CI did not excluded the possibility of clinically important benefit or harm (RR<0.75 or >1.25)	1	86 RCTs included All ages of patients Renal dysfunction at baseline (srCr level >106.08µmol/L [>1.2mg/dL] (in 35 studies) RCTs included: administration of NAC (55), NaHCO3 (19), NaCl, statins (20) or ascorbic acid (8) to prevent CIN **55 RCTs on NAC:** • ACT investigators 2011 • Alioglu E 2013 • Allaqaband S 2002 • Amini M 2009 • Aslanger E 2012 • Awal A 2011 • Azmus AD 2005 • Baskurt M 2009 • Boccalandro F 2003 • Briguori C 2002 • Brueck M 2013 • Carbonell N 2007 • Carbonell N 2010 • Castini D 2010 • Demir M 2008 • Durham JD 2002 • Erturk M 2014 • Ferrario F 2009 • Goldenberg I 2004 • Gomes VO 2005 • Gulel O 2005 • Gunebakmaz 2012 • Holscher B 2008 • Hsu CH 2007 • Hsu TF 2012 • Izani WM2008 • Jaffery Z 2012 • Kama A 2014 • Kay J 2003 • Kefer JM 2003 • Khalili H 2006 • Kim BJ 2008 • Kimmel M 2008 • Kinbara T 2010 • Kotlyar E 2005 • MacNeill BD 2003 • Marenzi G 2006 • Miner SE 2004 • Ochoa A 2004 • Oldemeyer JB 2003 • Ozcan EE 2007 • Poletti PA 2007 • Rashid ST 2004 • Ratcliffe JA 2009 • Reinecke H 2007 • Sadat U 2011 • Seyon RA 2007 • Shyu KG 2002 • Tanaka A 2011 • Tepel M 2000 • Thayssen P 2014 • Thiele H 2010 • Traub SJ 2013 • Yeganehkhah MR 2014 • Heguilen RM 2013	NAC $NaHCO_3$ Statins Ascorbic Acid	iv placebo with or without placebo		Primary outcome: - Relative Risk (RR) reduction of CIN Secondary Outcome: - Renal replacement therapy - Cardiac events - Mortality **N-Acetylcysteine** ✓ *NAC + iv saline vs iv saline* • 55 RCTs included (comparator: none or placebo) • 35 studies: study pts had renal dysfunction at baseline (SrCr >106.08µmol/L [>1.2mg/dL]) • Pooled RRs and CIs for subgroups by high and low dose NAC and type of routes and type of contrast were stated in Table 1 (refer article) • **High-dose** NAC + iv saline had a **small effect** on reducing CIN risk (**not statistically significant**) • **Low-dose** NAC + iv saline had **borderline** clinically important effect on CIN prevention • Both comparison had low strength of evidence (SOE) • **Orally**: NAC + iv saline had **small effect** on reducing CIN risk that was clinically unimportant but **statistically significant** with low SOE • Contrast type **LOCM**: NAC + iv saline **had clinically** important benefit to reduce CIN but with moderate SOE • Contrast type **IOCM**: NAC + iv saline **not have** clinically important benefit to reduce CIN but with moderate SOE (refer Figure 1) *Table 1.* Pooled RRs for CIN With NAC Compared With IV Saline Pooled Group / Studies, n / Pooled RR for CIN (95% CI) High-dose NAC 18 0.78 (0.59-1.03) IA administration 16 0.78 (0.55-1.12) IV administration 2 0.55 (0.12-2.62) Low-dose NAC 35 0.75 (0.63-0.89) IA administration 30 0.77 (0.66-0.91) IV administration 5 0.62 (0.18-2.10) Oral NAC 40 0.77 (0.65-0.92) IV NAC 14 0.90 (0.72-1.12) NAC when LOCM are used 40 0.69 (0.58-0.84) NAC when IOCM are used 7 1.12 (0.74-1.69) CIN = contrast-induced nephropathy; IA = intra-arterial; IOCM = iso-osmolar contrast media; IV = intravenous; LOCM = low-osmolar contrast media; NAC = N-acetylcysteine; RR = risk ratio. ✓ *NAC + iv saline vs $NaHCO_3$* • 7 RCTs that comparing NAC and $NaHCO_3$ were included • Varied in administration, and contrast type • **Pooled RR, 1.11 [CI, 0.51 to 2.41] – no clinically important benefit to reduce CIN risk in 1 intervention over the other** • The CI was wide → insufficient SOE to conclude about the potential difference between the interventions in any outcome evaluated ✓ *Statins added to NAC and iv saline with NAC + iv saline or NaHCO3* • Clinically **important and statistically significant reduction in CIN (RR, 0.52 [CI, 0.29 to 0.93])** and low SOE • Secondary outcomes → insufficient SOE ✓ *Ascorbic acid vs NAC* • 3 RCTs included, 2 excluded for MA because NAC were used in both groups • The difference was **clinically unimportant and statistically insignificant (RR, 0.89 [CI, 0.34 to 2.30]** → low SOE and insufficient for secondary outcomes	

Evidence Table : Effectiveness of N-acetylcysteine in prevention of contrast-induced nephropathy among patients undergoing radiocontrast procedure
Question : Is N-acetylcysteine effective in prevention of contrast-induced nephropathy among patients undergoing radiocontrast procedure?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
2. Wang N, Qian P, Kumar S, Yan TD & Phan K. The Effect of N-Acetylcysteine on the Incidence of Contrast-Induced Kidney Injury: A Systematic Review and Trial Sequential Analysis. International Journal of Cardiology. 2016;319-327	SR and Trial Sequential Analysis a) Traditional MA b) Trial Sequential Analysis (TSA) Studies Criteria: • Age at randomization N18 years, • Randomized allocations to treatment groups, • Prospective studies of patients with NAC compared to one or more control groups (either no NAC or placebo • Pre-procedure administration, and • Incidence of contrast induced acute kidney injury (AKI) reported as an endpoint post procedure. • When institutions published duplicate studies with accumulating numbers of patients or increased lengths of follow-up, only the most complete reports were included for quantitative assessment at each time interval. All publications included were limited to those involving human subjects and the English language	1	43 RCTs (3277 pts) • Agrawal M 2004 • Albabtain MA 2013 • Allaqaband S 2002 • Amini M 2009 • Aslanger E 2012 • Awal A 2011 • Azmus AD 2005 • Baker CS 2003 • Balderramo DC • Baskurt M 2009 • Briguori C 2002 • Brueck M 2013 • Carbonell N 2007 • Coyle LC 2006 • Diaz-Sandoval LJ 2002 • Durham JD 2002 • Fung JW 2004 • Goldenberg I 2004 • Gomes VO 2005 • Gulel O 2005 • Izani ZD 2008 • Jaffery Z 2015 • Kay J 2003 • Kefer JM 2003 • Kinbara T 2010 • Koc F 2012 • Kotlyar E 2005 • MacNeil BD 2003 • Marenzi G 2006 • Miner SE 2004 • Ochoa A 2004 • Oldemeyer JB 2003 • Ozcan EE 2007 • Ratcliffe JA 2009 • Reinecke J 2007 • Seyon RA 2007 • Shyu KG 2002 • Tanaka A 2011 • Thayssen P 2014 • Thiele H 2010 • Webb JG 2004 • Yang K 2014 • Yeganehkhah MR 2014	IV and oral NAC	Placebo Orange drink IV NS 154mEq/L of NaCL		CIN Definition Increase in SrCR levels ≥ 25% or 44.2µmol/L (0.0.5md/dL) **POOLED RESULTS (USING TRADITIONAL MA)** Outcome of AKI - Significantly lower rate of AKI in NAC group compared to control group (**OR 0.666; 95% CI, 0.532-0.834; I^2 = 40.11%; p = 0.004** • Treatment arm: 358 CIN out of 3277 (10.9%) • Control arm: 495 CIN out of 3277 (15.1%) Subgroups Analysis - Was conducted to determine whether any factors were particularly associated with lower AKI rates with NAC use ➢ Patient with ACS vs no-ACS - **8 RCTs with ACS** pts only (Aslanger, Carbonell, Jaffery, Marenzi, Seyon, Tanaka, Thayssen, Thiele) → trend towards lower AKI rates in NAC group but not significance **(OR 0.758; 95% CI, 0.538-1.066; I2 = 38.56%; p = 0.111)** • In no-ACS subgroups, there was significantly lower AKI rate in groups taking NAC compared to controls (OR, 0.642; 95% CI, 0.492-0.838; I2 = 3.73%; p = 0.001) • No significant interaction found between these subgroups (p = 0.525) ➢ Patients with STEMI vs no STEMI - **5 RCTs with STEMI pts undergoing PCI** (Aslanger, Marenzi, Tanaka. Thayssen, Thiele), there was **trend toward lower AKI rates in NAC group (OR, 0.556; 95% CI, 0.305 – 1.014; I2 = 69.91%; p = 0.056)** • In no STEMI subgroups, there was lower AKI rates in the NAC group (OR, 0.698; 95% CI, 0.546 – 0.891; I2 = 33.09; p = 0.004) ➢ Age Effect - Age: significantly lower AKI rates for NAC group in both age groups • ≥65 years (OR, 0.721; 95% CI, 0.547-0.950; I^2 = 37.74%; p = 0.02) • <65 years (OR, 0.579; 95% CI, 0.392-0.856; I^2 = 43.51%; p = 0.006) ➢ Type of contrast agents LOCM • Iopamidol: significantly lower AKI rates in NAC cohorts (OR, 0.392; 95% CI, 0.164-0.938; I^2 = 42.19%; **p = 0.035**) • Iohexol: significantly lower AKI rates in NAC cohorts (OR, 0.329; 95% CI, 0.137-0.793; I^2 = 59.88; **p = 0.013**) • Iopromide: not significantly lower AKI rates in NAC groups (OR, 0.815; 95% CI, 0.611 – 1.087; I^2 = 0%; p = 0.165) IOCM • Iodixanol: not significantly lower AKI rates in NAC groups (OR, 0.652; 95% CI, 0.176-2.413; I^2 = 56.39%; p = 0.522) ➢ Patients with DM and/or renal insufficiency (RI) vs no DM and/or RI - 27 RCTs included - Pooled AKI rates were similar between NAC and placebo groups (OR, 0.737; 95% CI; 0.530-1.025; I^2 = 43.85%; p = 0.070) - Significant reduction in AKI rates without DM and/or RI (Or, 0.645; 95% CI, 0.489-0.851; I^2 = 29.15%; p = 0.002) - No statistically significant difference between DM and/or RI vs no DM and/or RI subgroups (p = 0.580) ➢ Types of Administration Routes (pooled results) - IV NAC: non-significant trend for lower AKI rates with NAC (OR, 0.737; 95% CI, 0.530-1.025; I2 = 43.85%; p = 0.070) - Oral NAC: significance difference (OR, 0.645; 95% CI, 0.489-0.851; I2 = 29.15%; **p = 0.002**) - No significant difference between IV vs oral NAC subgroups (p = 0.472) Meta-Regression Analysis To determine any association between contrast dose and AKI rates in: - No significant association (p = 0.461) amongst all studies - No significant association (p = 0.720) among study included iv NAC only - No significant association (p = 0.199) among study included oral NAC only	

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							TRIAL SEQUENTIAL ANALYSIS - D2-adjusted required information size is ✓ 32,190 participants with RRR of 10% ✓ 14,056 participants with RRR of 15% ✓ 7,692 participants with RRR of 20% ✓ 3,257 participants with RRR of 30% - The cumulative Z-curve demonstrate inconclusive evidence to support or refute NAC vs control for AKI when RRR was 10% - With RRR 15%,20% or 30%, TSA demonstrate conclusive evidence in the support of NAC as cumulative Z-curve does cross the trial sequential boundaries CONCLUSION NAC was beneficial to reduce rate of CIN amongst patients undergoing coronary angiography TSA suggested that no further RCTs were required to investigate the benefit of NAC for a RRR of 15%	

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3. Ali-Hassan-Sayegh S, Mirhosseini SJ, Ghodratipour Z, Sarrafab-Chaharsoughi Z, Rahimizadeh E, Karimi-Bondarabadi AK, Haddad F, Shahidzadeh A, Dehghan H, Ghanei A, Lotfaliani M, Weymann A, Zeriouh M, Popov AF, & Sabashnikov A. Strategies Preventing Contrast-Induced Nephropathy After Coronary Angiography: A Comprehensive Meta-Analysis and Systematic Review of 125 Randomized Controlled Trials. Angiology. 2016; 1-25	SR with MA **Obj**: to determine the strength of evidence for the effects of hycration (NaHCO3 and NaCl), supplementations (NAC and vitamin C), and further common drugs (adenosine antagonists, statins, loop diuretics and angiotensin-converting enzyme inhibitors (ACEIs) on the incidence of CIN and requirement for hemodialysis after coronary angiography **Methods** CIN Definition: ≥ 25% and/or ≥ 0.5mg/dL increase in creatinine from its baseline Study Selection - Effects of 7 therapeutics strategies (normal saline vs NaHCO3, NAC vs placebo, citamin C vs placebo, statin vs placebo, amino acid vs placebo, loop diuretic vs placebo and ACEI or ARB vs lacebo - Reorting data on clinical outcomes based on the authors' review checklist Statistical Analysis/ Publication Bias - OR <1 favoured study groups - OR >1 favoured control groups - P < 0.1 for Q test or I2 > 50% indicated significant heterogeneity among the studies Meta-regression		125 RCTs 49 RCTs included for NAC vs Placebo With total patients of 11,446 (5724 in NAC group and 5722 in placebo group) • ACT Investigator 2011 • Albabtain MA 2013 • Alessandri N 2013 • Amini M 2009 • Arabmomeni M 2015 • Azmus AD 2005 • Baker CS 2003 • Baskurt M 2009 • Berwanger O 2013 • Briguori C 2002 • Brueck M 2013 • Calabro P 2011 • Carbonell N 2007 • Carbonell N 2010 • Castini D 2010 • Chong E 2015 • Coyle LC 2006 • Diaz-Sandoval LJ 2002 • Durham JD 2002 • Ferrario F 2009 • Fung JW 2004 • Goldenberg I 2004 • Gomes VO 2005 • Gulel O 2005 • GunebakmazO 2012 • Heng AE 2008 • Holscher B 2008 • Inda-Filho 2014 • Jaffery Z 2012 • Kay J 2003 • Kefer JM 2003 • Kim BJ 2010 • Kinbara T 2010 • Koc F 2012 • Kumar A 20014 • MacNeill BD 2003 • Miner SE 2004 • Ochoa A 2004 • Oldemeyer JB 2003 • Ratcliffe JA 2009 • Ratcliffe JA 2009 • Seyon RA 2007 • Shyu KG 2002 • Thayssen P 2014 • Thayssen P 2014 • Thiele H 2010 • Wang JH 2008 • Webb JG 2004 • Yeganekhah MR 2014	NAC NaHCO3 Vitamin C Statins Adenosine Antagonist Loop Diuretics Angiotensin-Converting System	Placebo NaCl Placebo Placebo Placebo Placebo Placebo		**N-Acetylcysteine** - 49 RCTs with toal of 11446 patients - Patients population ranged from 30 to 2308 - 5724 were allocated to NAC group and 5722 to the placebo group CIAKI Incidence in NAC - Overall : 13.1% ranging from 0% to 29.8% (11.7% in NAC group and 14.4% in placebo group) - Pooled treatment effect analysis revealed that NAC could significantly decrease the incidence of CIN compared with placebo with OR of 0.79 (95% CI: 0.70-0.88; P = 0.001) – fixed-effects model - No significant heterogeneity among the studies (X^2 = 71.68, I^2 = 34.4%) - No publication bias and risk of small study effects among the included RCTs (Begg Test, P = 0.445 Haemodialysis - Out of 49 studies on NAC vs placebo, 24 RCTs reported data of the incidence of the need for haemodialysis (overall haemodialysis incidence 2.07%: 1.9% in NAC group and 2.18% in placebo group) - 13 of the 21 comparisons did not present any haemodialysis in 2 comparative arms; therefore the remaining 11 RCTs were used to perform the MA - Pooled analysis = NAC therapy could not significantly decrease the incidence of haemodialysis with OR of 1.18 (95% CI: 0.60-2.3; P = 0.6) – fixed effects model - No heterogeneity among the studies **Normal saline vs NaHCO3** - 33 RCTs with total of 6984 patients - Patients populations ranged from 34 to 502 - 3485 were allocated to SB group and 3499 to the NS group CIAKI incidence - Overall: 10.7% ranging from 3.4% to 20.9% (9.3% in NaHCO3 group and 12.11 % in normal saline group) - Pooled treatment effect analysis revealed that NaHCO3 could significantly decrease the incidence of CIN compared with NS with an OR of 0.73 (95% CI: 0.56-0.94; P = 0.01) – random effects model - Some heterogeneity among studies analysed (X2 = 68.44, I2 = 53.2%) - No publication bias and risk of small study effects among the included RCTs (Begg Test, P = 0.878) - Subgroup analysis: NaHCO3 compared with NS was associated with stronger preventive effects on incidence of CIAKI after coronary angiography using LOCM rather than IOCM or HOCM (OR = 0.59; 95% CI 0.47-0.74;; P = 0.001) and emergency coronary angiography rather than elective angiography (OR = 0.62; 95% CI 0.46-0.84; P = 0.002) Haemodialysis - 21 RCTs reported data on haemodialysis requirement - Overall haemodialysis incidence: 0.77%; 0.82% in NaHCO3 and 0.73% in NS group - 11 of the 21comparison did not present any haemodialysis in 2 comparative arms; therefore only 10 RCTs were used to perform the MA - Pooled analysis indicated that incidence of haemodialysis was similarly distributed between NaHCO3 and NS groups with OR of 1.11 (95% CI: 0.58-2.09; P = 0.7) – fixed-effects model	

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4. Zhao SJ, Zhong ZS, Qi GX & Tian W. The Efficacy of N-acetylcysteine plus Sodium Bicarbonate in the Prevention of Contrast-Induced Nephropathy after Cardiac Catheterization and Percutaneous Coronary Intervention: A Meta-Analysis of Randomized Controlled Trials. International Journal of Cardiology. 2016; 221:251-259	SR with MA Obj: To compare the efficacy of combination therapy with individual therapy of NAC and SOB Methods Study Selection - Inclusion criteria i. RCT ii. Combination NAC and NaHCO3 was administered and compared with individual use of NAC or NaHCO3 (NAC and NaHCO3) iii. Reporting data of CIAKI incidence during catheterization and PCI Data abstraction and quality assessment - Incidence of CIAKI: increase of 25% or absolute elevation of 0.5mg/dL of Cr from baseline after contrast application Statistical Analysis - Treatment effect was expressed as pooled risk ratios (RRs) and studies with no CIAKI incidence was discarded - Heterogeneity in I2 test and a value of I2>50% indicated significant heterogeneity among studies - If heterogeneity remains , a random effects model (RE) would be used - Publication bias based on funnel plots with Begg's Test - P < 0.05 was considered as statistically significant Quality Assessment - 12 RCTs reported random effects - 12 RCTs reports duration of follow-up3 RCTs used double-blind approach - 3 RCTs reported allocation concealments in detail	1	16 RCTs were included - Involved a total of 4432 cases (1835 in COM group, 1536 in NAC group and 1061 in NaHCO3 group) Group i. Combination of NAC and NaHCO2 = COM group ii. Single use of NAC = NAC group iii. Single use of NaHCO3 = NaHCO3 group • Chong E et al 2016 • Thayssen O et al 2014 • Yang K et al 2014 • Inda-Filho AJ et al 2014 • Mahmoodi K et al 2014 • Heguilen RM et al 2013 • Hafiz AM et al 2012 • Lee SW et al 2011 • Koo TY et al 2011 • Ratcliffe JA et al 2009 • Maioli M et al 2008 • Brar SS et al 2008 • Recio-Mayoral A et al 2007 • Briguori C et al 2007	NAC	Combination of NAC and NaHCO3		**RESULTS** <u>Results of COM group vs NAC group</u> *CIAKI in total patients* - 14 RCTs reported the CIAKI incidence which were allocated to COM group or NAC group → significant heterogeneity (I2 = 54.7%, P = 0.01) - After sensitivity analysis: excluded 1 study then the heterogeneity become non-significant I2 = 41.5%, P = 0.06) → 13 studies (1436 patients) were included for meta-analysis using fixed effects model - CIAKI incidence: a) COM group = 10.9% (157/1436) b) NAC group =12.8% (184/1438) - No significant reduction of CIAKI in COM group (RR 0.85, 95% CI 0.70 to 1.03, P = 0.10) *CIAKI in Diabetes Patients* - 4 RCTs with total of 621 patients reported CIAKI incidence in diabetes patients without evidence of publication bias - Heterogeneity was not significant among studies: I2 23.1%, P = 0.27 → used fixed effects - CIAKI incidence was a) COM group: 11.3% (35/311) b) NAC group: 9.7% (30/310) - No significant benefit in COM group compared to NAC group in CIAKI incidence reduction (RR 1.11, 95% CI 0.71 to 1.75, P = 0.65) *CIAKI in Patients Performing PCI* - 4 RCTS with total of 893 patients reported the incidence of CIAKI in patients performing PCI without evidence of publication bias - Heterogeneity was significant (I2 = 65.8%, P = 0.03) → used the random effects without sensitivity and subgroup analysis - CIAKI incidence was: a) COM group: 13.2% (59/447) b) NAC group: 17.0% (76/446) - No significant benefit in COM group compared to NAC group in CIAKI incidence reduction (RR 0.76, 95% CI 0.39 to 1.47, P = 0.41) *CIAKI in Patients with Baseline Renal Dysfunction* - 8 RCTs reported CIAKI incidence in patients with baseline renal dysfunction (eGFR < 60ml/min/1.73m2) - No significant heterogeneity across the studies (I2 = 41.3%, P = 0.10) → Fixed effects were used - CIAKI incidence was a) COM group: 11.2% (102/912) b) NAC group: 12.6% (115/914) - No significant reduction in CIAKI incidence in COM group (RR 0.89, 95% CI 0.70 to 1.17, P = 0.37) <u>Results of COM vs NaHCO3</u> *CIAKI in Total Patients* - 10 RCTs with total of 1997 patients reported the CIAKI incidence with no publication bias evidence - No significant heterogeneity across the studies (I2 = 1.4%, P = 0.43)→ fixed effect model was used - CIAKI incidence was: a) COM group: 10.9% (104/957) b) NaHCO3 group: 11.8% (123/1040) - No significant CIAKI incidence reduction in COM group (RR 0.91, 95% CI 0.71 to 1.16, P = 0.45) *CIAKI in Patients Performing PCI* - 2 RCTs reported the incidence of CIAKI in PCI patients - No heterogeneity across the studies (I2 = 0.0%, P = 0.50) and no publication bias → fixed effects model was used - CIAKI incidence was: a) COM group: 17.3% (42/243) b) NaHCO3 group: 18.1% (45/248) - No significant benefit in COM group compared to NaHCO3 group in reduction of CIAKI incidence (RR 0.96, 95% CI 0.65 to 1.40, P = 0.81) *CIAKI in Patients with Baseline Renal Dysfunction* - 6 RCTs reported the incidence of CIN in a total of 1048 patients with baseline renal dysfunction (eGFR < 60ml/min/1.73m2) - Non-significant heterogeneity (I2 = 50.0%, P = 0.08) - After fixed-effects model was applied = CIAKI incidence was a) COM group: 10.2% (50/489) b) NaHCO3 group: 10.7% (60/559)	

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							- No significant reduction of CIAKI incidence in COM group (RR 0.95, 95% CI 0.67 to 1.36, P = 0.79) Conclusion No significance difference between combination and individual use of NAC and/or NaHCO3 in CIAKI incidence even in high risk patients with diabetes, baseline renal dysfunction or undergoing PCI procedure	

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5. Kang X, Hu DY, Li CB, Ai ZS & Peng A. N-Acetylcysteine for the Prevention of Contrast-Induced Nephropathy in Patients with Pre-Existing Renal Insufficiency or Diabetes: a Systematic Review and Meta-Analysis. Ren Fail.2015; 37(10):297-303	SR and MA Studies Criteria Studies were limited to prospective, RCTs investigating the efficacy of the administration of NAC in preventing CIN, in which at least some subjects with pre-existing renal insufficiency or diabetes and at least one of the treatment groups received NAC, administered orally or intravenously at any dose, for any length of time. Renal insufficiency was defined as elevation of SCr or decrease of evaluated glomerular filtration rate (eGFR) or creatinine clearance rate (eCrCl).	1	21 RCTs (3466 subjects) Pre-existing renal insufficiency / diabetes mellitus Pts scheduled for coronary angiography/ cardiac catheterization • ACT Investigators 2012 • Allaqaband S 2002 • Baker CS 2003 • Baskurt M 2009 • Brueck M 2013 • Carbonell N 2010 • Carbonell N 2007 • Coyle LC 2006 • Durham JD 2002 • Ferrario F 2009 • Fung JW 2004 • Jaffery Z 2012 • Kay J 2003 • Kimmel M 2008 • Koc F 2012 • Miner SE 2004 • Ochoa A 2004 • Oldemeyer JB 2003 • Poletti PA 2007 • Rashid ST 2004 • Seyon RA 2007 • Webb JG 2004 Pre-existing renal insufficiency : 20 RCTs Diabetes : 9 RCTs	NAC	Placebo Orange drink IV NS 154mEq/L of NaCl iv NAC bolus		➢ **Effects of NAC on Outcomes in Population with Pre-Existing Renal Insufficiency (Incidence of CIN)** - NAC group ranged from 3.9% to 27.6%with average of **10.2%** - Control group ranged from 5.9% to 33.3% with an average of **15.9%** - **Overall pooled OR of CIN** using fixed effects model was **0.76 (95% CI, 0.61-0.93, p = 0.008)** → significant trend toward benefit in patients who received NAC - No significant heterogeneity in analysis comparing the occurrence of CIN across studies (p = 0.07; I^2 = 34%) Subgroup studies - In **IV NAC: OR, 0.67 (95% CI, 0.50-0.90, p = 0.008)**; heterogeneity p = 0.07; I^2 = 46% - In **oral NAC: OR, 0.85 (95% CI, 0.64 – 1.13; p = 0.26)**; heterogeneity p = 0.19; I^2 = 26% ➢ **Effects of NAC on Outcomes in Population with Diabetes (Incidence of CIN)** - NAC group ranged from 6.7% to 42.1% with an average of **16.5%** - Control group ranged from 1.5% to 35.3% with an average of 16.9% - **Overall pooled OR of CIN was 0.87 (95% CI, 0.58-1.30, p = 0.50)** → no significant trend toward benefit in patient with NAC - Slight heterogeneity (p = 0.40; I^2 = 5%) Subgroup studies - In **IV NAC: OR, 0.73 (95% CI, 0.43-1.23, p = 0.24)**; heterogeneity p = 0.86; I^2 = 0.% - In **oral NAC: OR, 1.21 (95% CI, 0.60-2.09, p = 0.72)** → heterogeneity p = 0.14; I^2 = 43% ➢ **Sensitivity Analyses** - In pre-existing renal insufficiency (study by Poletti was removed) → **OR 0.78** (95% CI, 0.63-0.96, p = 0.02); heterogeneity p = 0.19; I^2 = 29% - In DM (studies by Carbonell, Coyle and Rashid were removed) → **OR, 0.74** (95% CI, 0.47-1.016, p = 0.19; heterogeneity p = 0.54, I^2 = 0 ✓ **No benefit of NAC to prevent CIN in pts with both diabetes and renal impairment** - NAC dose: study with dosage of 2.4 ±2.0 gram were included • In Pre-existing renal insufficiency: OR, 0.76(95% CI, 0.60-0.95, p = 0.02) and • In DM: OR 0.99 (95% CI, 0.64-1.53, p = 0.96) CONCLUSION NAC effective to reduce the incidence of CIN in patients with pre-existing renal insufficiency For DM : inconclusive findings	

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6. Wu MY, Hsiang HF, Wong CS, Yao MS, Li YW, Hsiang CY, Bai CH, Hsu YH, Lin YF, & Tam KW. The Effectiveness of N-acetylcysteine in Preventing Contrast-Induced Nephropathy in Patients Undergoing Contras-Enhanced Computed Tomography: a Meta-Analysis of Randomized Controlled Trials. Int Urol Nephrol. 2013; 45:1309-1318	SR and Meta-Analysis Studies Criteria RCTs that have evaluated the efficacy of acetylcysteine, administered orally or intravenously, versus a control group with hydration alone to prevent CIN in patients undergoing contrast-enhanced CT	1	6 trials (496 pts) – to prevent CIN in CT scan in CT scan procedure Diabetes / renal insufficiency Burns et al (2010) Hsu et al (2012) Kitzler et al (2012) Poletti et al (2007) Sar et al (2010) Tepel et al (2000 <u>Characteristics of the trials (6 trials)</u> - 4 trials (Burns, Poletti, Tepel, Kitzler) evaluated pts with history of chronic renal insufficiency and with serum creatinine concentration above 1.2mg/l (106µmol/l) - 1 trial (Sar) with type 2 diabetic patients with normal renal function (mean serum creatinine <1.2mg/l) - 3 trials (Poletti, Tepel, Kitzler) with pts underwent CT with a nonionic low-osmolality (iopromide ultravist) radiographic contrast agent - 1 trial (Sar) with iv contrast media (iohexol) for abdominal CT - Baseline characteristics were balance between the 2 treatment groups in the 6 trials - 1 trial (Kitzler) randomized the pts either to vitamin E, NAC or control groups - Administration route of NAC varies : oral (Sar, Tepel, Kitzler) and i.v (Burns, Poletti, Hsu) - NAC dosages and hydration were adjusted according to various protocols - All the studies underwent quality / bias risk assessment)	Oral and iv NAC	Hydration only Saline	2 – 5 days after procedure	<u>Incidence of CIN within Trials</u> - Authors conducted subgroup analysis on populations with serum creatinine above or below 1.2mg/dL • In **high risk**: significant difference between 2 treatment groups, **more pts in control experience greater incidence of CIN (RR = 0.20; 95% CI 0.07-0.57)** • In **low-risk**: **no significant difference** between the 2 groups (RR = 0.46; 95% CI 0.21-1.02) although the incidence of CIN was lower in NAC group • No significant heterogeneity among these trials (I^2=0%) • **NNT 8.73 (Treat 8 with NAC to prevent 1 CIN)** <u>Requirement for dialysis</u> (3 studies reported, Hsu, Burns, Poletti) - Hsu et al incidence of temporary renal replacement therapy was **0% in NAC group and 1.0% in the control group** <u>Changes in Creatinine</u> - 3 studies (Poletti, Tepel, Kitzler) – protective effect of NAC - Creatinine serum was measured from admission to 48 hrs, 72 hrs or 96 hrs after administration of the contrast agent and changes in each study were calculated accordingly - Significant difference in 2 groups with greater improvement of changes in creatinine level in NAC group (WMD = -0.22; CI -0.41 to -0.03) - Significant heterogeneity between trials for changes in creatinine level (I^2 = 87%; X^2 = 23.95; P < 0.0001) <u>Changes in Cystatin C</u> - Cystatin C was more sensitive than creatinine to detect mild decrease in GFR – earlier indicator of acute renal failure - 1 study (Poletti) investigated changes in serum cystatin C – measured at admission and on days 2 and 4 after CT - 25% greater increase in serum cystatin C concentration was found in 9 (22%) of 40 pts in control group and 7 (17%) of 41 pts in NAC group (P = 0.59) - No significant difference in both groups on Days 2 and 4 CONCLUSION - NAC decreases the risk of CIN and improves the changes of serum creatinine	

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7. Sun Z, Fu Q, Cao L, Jin W, Cheng L, & Li Z. Intravenous N-Acetylcysteine for Prevention of Contrast-Induced Nephropathy: A Meta-Analysis of Randomized, Controlled Trials. PloS ONE. 2013; 8(1): e55124 doi:10.1371/ journal. pone.0055124	SR and Meta-Analysis Studies Criteria Studies were limited to prospective, randomized, controlled trials (PRCTs) investigating the efficacy of intravenous NAC in preventing CIN, in which at least one of the treatment groups received NAC, administered intravenously, immediately before, during, or immediately after contrast exposure at any dose, for any length of time. All studies were performed in patients undergoing cardiac catheterization or peripheral angiography, except for the study by Poletti et al., which was performed in patients undergoing computed tomography. Of the 10 trials, one trial evaluated the efficacy of N-acetylcysteine in patients with normal kidney function, five trials evaluated patients with chronic kidney disease (CKD), and the other four trials evaluated patients with both normal renal function and CKD. Patients with diabetes mellitus were included in all studies, with the prevalence varying between 12.5% and 46.9%.	1	10 RCTs Total pts 1,914 (pts with DM) - NAC n = 962 - Control n = 954 Patients undergoing cardiac catheterization Peripheral angiography Patients undergoing CT • Baker et al (2003) - CKD • Carbonell et al (2007) – in normal kidney function • Carbonell N et al (2010) - CKD • Jaffery Z et al (2012) – CKD n normal • Kefer JM et al (2003) – CKD n normal • Koc F et al (2012) - CKD • Poletti PA et al (2007) - CKD • Rashid ST et al (2004) – CKD n normal • Thiele H et al (2010) – CKD n normal • Webb JG et al (2004) - CKD 9 studies – to prevent CIN in procedure cardiac catheterization or peripheral angiography 1 study by Poletti - to prevent CIN in CT Contrast Media – low or iso-osmolar non-ionic contrast media	Intravenous NAC (varies) but not less than 50 0mg Bolus NAC	Placebo No control	48 hrs – 96 hrs	<u>Contrast-induced Nephropathy Incidence</u> - Control groups: 5.9% to 23.8% (average **14.3%**) - Treatment groups: 2.5% to 16.0% (average **7.9%**) - 3 studies risk reduction of CIN with NAC (Baker, Carbonell and Koc) - 7 studies : no benefit (Kefer, Rashid, Webb, Carbonell, Poletti, Thiele, Jaffery) - **Overall pooled risk ratio (RR)** of CIN using random effects model; **RR = 0.68 (95% CI, 0.45-1.02, p = 0.06)** → indicated **non-significant trend towards benefit in pts who received NAC** - Significant heterogeneity in the analysis comparing occurrence of CIN across studies (Q = 17.42, P = 0.04, I^2 = 48% <u>Sensitivity Analyses</u> i) All studies except Poletti (CT) - Summary risk ratio for CIN associated with NAC used was essentially unchanged at 0.72 (95% CI, 0.47-1.09, p = 0.12) and remained heterogeneity (P = 0.03) ii) All studies except Webb (low dose NAC) - Summary risk ratio became statistically significant (RR = 0.59; 95% CI 0.36-0.97, p = 0.04) and heterogeneity P = 0.03 iii) Restrict the analysis to studies with quantified Jadad Score of 3 or more → no benefit for NAC with summary risk ratio of 0.77 (95% CI, 0.50-1.15, p = 0.20) and no heterogeneity observed P = 0.23) <u>Meta-Regression</u> - Random effects meta-regression examining 1 covariate at a time - Refer Table 1 of full text article <u>Publication Bias</u> - There was publication bias among the studies (Egger's Test, p = 0.013) - Funnel plot was asymmetry <u>Secondary Outcomes</u> - *Renal failure requiring dialysis* Extremely low – 7 out of 1,914 pts (4 in NAC, 3 in placebo) Pooled risk ratio of RF requiring dialysis: 0.72 (95% CI, 0.34 to 4.75, P = 0.72) Heterogeneity not significant: P = 0.32 - *Mortality* Pooled relative risk of in-hospital mortality with IV NAC in 4 trials (Carbonell, Webb, Carbonell, Jaffery): 0.67 (95% CI, 0.32-1.40, P = 0.29) Heterogeneity not significant: P = 0.99 1 year mortality in 1 study (Carbonell 2010): not significantly lower in NAC pts (15.4% (NAC) vs 21.4% (Control): P = 0.67) - *Length of hospitalization* 3 trials reported about it (Carbonell, Carbonell, Jaffery) None found significant reduction in length of stay among NAC recipients No sufficient data for pooling - *Adverse events* Specific ADRs reported in 1 study (Baker) High rate (14.6%) of transient itching, flushing and rash in patients received loading dose of 150mg/kg over 30 minutes Safely treated with hydrocortisone and stopped therapy CONCLUSION - Use of iv NAC was associated with a reduction in incidence of CIN : **borderline statistical significance P = 0.06** - Significant heterogeneity between trials - Insufficient data to show the efficacy of NAC on clinically meaningful endpoint; dialysis, length of hospital stay or mortality - Role of iv NAC to prevent CIN was inconclusive	

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8. Busch SV, Jensen SE, Rosenberg J, & Gogenur I. Prevention of Contrast-Induced Nephropathy in STEMI Patients Undergoing Primary Percutaneous Coronary Intervention: Systematic Review. J Interven Cardiol. 2013; 26(1): 97-105	Systematic Review Studies Criteria Studies were limited to randomized clinical trials evaluating a preventive strategy against CIN. The population was limited to patients with STEMI treated by primary PCI. No restrictions were made regarding the preventive strategy. The primary outcome measure was CIN and no restrictions were made regarding the definition of CIN. Secondary outcome measures were mortality, adverse clinical events and additional markers of kidney damage and/or function, for example, serum creatinine concentration (sCr) and estimated glomerular filtration rate (eGFR)	1	9 studies included Patients with STEMI treated by primary PCI 6 studies on NAC • Aslanger E et al 2012 • Droppa M et al 2011 • Jaffery Z et al 2012 • Marenzi G et al 2006 • Tanaka A et al 2011 • Thiele H et al 2010 1 study on recombinant human B-type natri-uretic peptide 1 study on hydration 1 study on iso-osmolar contrast medium	High dose NAC Oral NAC 1200 mg NAC twice daily	Low dose NAC Placebo Hydration no hydration / NaCl	72 hours after procedure	**N-Acetylcysteine:** - Administration form and doses varied among studies • High dose of NAC equivalent to IV bolus of 1,200mg before primary PCI and 1,200mg NAC iv BD for 48hrs after procedure (Droppa, Thiele) or 200mg/hr for 24 hrs (Jaffery) • Compared low dose with high dose of NAC equivalent to iv bolus of 600mg vs 1,200mg before primary PCI and 600mg vs 1,200mg orally BD for 48 hrs after procedure (Marenzi) • Compared the effect of a high dose of NAC equivalent to iv bolus of 1,200mgwith intra-renal bolus of NAC equivalent to 600mg onto both renal arteries before primary PCI. After procedure both groups received additional 1,200mg of NAC orally BD for 48 hours (Aslanger) • Low dose equivalent to 705mg NAC orally before procedure and 12, 24 and 36hrs after procedure (Tanaka) • All studies used additional hydration protocol Findings • 5 studies (Tanaka, Droppa, Thiele, Aslanger, Jaffery) - Did not show any effect of NAC on the incident of CIN, serum creatinine level, serum cystatin C level, creatinine clearance, clinical outcomes or mortality • 1 study (Meranzi) found that - Incidence of CIN in high dose or low dose NAC groups was reduced compared with placebo group - Incidence of CIN was significantly lower in high dose NAC compared with low dose NAC group - Dose depended protective effect - Greater increase in SrCr in placebo group than in NAC groups - High dose NAC significantly decrease in-hospital mortality, and the combined end-point of death, acute renal failure requiring temporal renal replacement therapy and the need for mechanical ventilation during acute phase of MI - Additional subgroup analysis showed that NAC prevented CIN in pts with normal renal function, in pts with reduced renal function and in those with mildly or severely reduced left ventricular function **Recombinant Human B-type Natriuretic Peptide (rhNBP)** - iv bolus 1.5µg/kg administered after admission followed by adjusted-dose infusion of 0.0075-0.030µg/kg/min for 24hrs after procedure - additional hydration protocol was followed - Incidence of CIN was significantly reduced in rhBNP group compared with control group - Incidence of main adverse cardiac events was significantly lower at 30 day follow up in rhBNP group compared with control group **Hydration** - Preventive effect of early vs late vs no hydration against renal dysfunction - Early hydration group received bolus of 3mL/kg of NaHCO3 solution in 1 hr (pre-procedure) followed by infusion of 1mL/kg/hr for 12 hrs after PCI (post-procedure) - Late hydration group received an infusion of isotonic NaCl of 1mL/kg/hr for 12hrs after primary PCI (post-procedure) Findings - Early and late hydration reduced the occurrence of CIN significantly and SrCr concentration was significantly lower compared with no hydration group - Incidence of decrease in eGFR by >25% at 72 hrs after PCI was significantly lower in the early hydration group - Incidence of major adverse cardiac events did not differ between 3 hydration groups - Subgroup analysis found that significant reduction in rate of CIN in early hydrated patients with ejection fraction <40% **Contrast Media (CM)** - No difference in volume of CM administered to 2 groups or in number of patients who received contrast dose >300mL - All patients underwent post-procedure hydration - Incidence of CIN n SrCr concentration did not differ between the 2 CM groups - Short-term mortality and major adverse cardiac events did not differ between the groups - Subgroup analysis of the pts with and without pre-existing renal impairment did not reveal any difference in incidence of CIN between the study group Discussion - Pt with heart failure : rhBNP significantly reduced CIN incidence and major adverse cardiac events - Early hydration with $NaHCO_3$ and late hydration with saline reduced CIN incidence compared with no hydration, the major adverse events did not differ between the groups - 1 out of 6 studies showed dose-dependent highly significant positive effect of NAC and subgroup analyses showed that NAC prevent CIN in pts with heart failure or kidney function	

EVIDENCE TABLE
(RCT : EFFICACY OF NAC TO PREVENT CIAKI)

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9. Habib M, Hillis A & Hammad A. N-Acetylcysteine and/or Ascorbic Acid versus Placebo to Prevent Contras-Induced Nephropathy in Patients Undergoing Elective Cardiac Catheterization: the NAPCIN Trial; A Single-Center, Prospective, Randomized Trial. Saudi J Kidney Dis Transp. 2016; 27(1):55-61	RCT Pts were randomized into 3 groups: 1. Group A 30 pts received NAC 1200mg orally every 12hrs for 2 days, 1 dose before coronary angiography and 3 doses after coronary angiography (Total NAC dose 4800mg including intervention dose) 2. Group B 30 pts received low-dose NAC 600mg orally every 12hrs for 2 days, 1 dose before procedure and 3 doses after procedure (Total doses of NAC 2400mg including the intervention dose Additional ascorbic acid 3000mg was given orally before procedure and 2000mg orally on night and morning after procedures (total dose of ascorbic acid = 7000mg) 3. Group C 45 pts received placebo Each pts with overt heart failure will received hydration with 0.9% saline just before and after procedure in each groups Serum urea and creatinine levels were measured before and 48 hrs after procedure		150 Consecutive pts with ischemic heart disease or peripheral vascular disease • Mean Age = 62.3±8.9 yrs (22% > 70yrs) • 80% diabetics, 4.8% with heart failure • Overall mean baseline creatinine clearance = 76.63 ± 19.6mL/min (8.7% had > 1.5mg/dL) • Overall mean serum creatinine level = 0.97 ± 0.36mg/dL • Overall mean plasma urea level = 37.58 ± 17.27mg/dL At least had 1 risk factors for CIN • Age > 70 yrs • Baseline creatinine level > 1.5mg/dL • Heart failure • Diabetes mellitus • Contrast media volume >300mL Study setting: coronary angiography at European Gaza Hospital Contrast type: Low-osmolal, non-ionic contrast agent ultravist iopromide	Oral NAC Oral NAC + Ascorbic Acid Additional of hydration with 0.9% saline in overt heart failure	Placebo	Pts observed for only 48 hours	*Primary End-Points* CIN = increase in serum creatinine concentration of 0.5mg/dL or ≥25% of the baseline value within 48 hrs after procedure *Secondary End-points* Comparison of the creatinine level , urea and creatinine clearance between those groups P < 0.05 = significant **RESULTS** *Primary End-points* Developed Contrast Media-Induced Nephropathy ✓ Group A = 2 patients (6.66%) ✓ Group B = 5 patients (16.66%) ✓ Group C = 8 patients (17.77%) ✓ Difference between Group A & B and Group A & C was highly statistically significant; **P = 0.001** ✓ Difference between Group B & C was not statistically significant, P = 0.37 *Second End-Points* Group A (Oral NAC) ✓ Creatinine clearance decreased to 70.83 ± 25.92mL/min (before 72.35 ± 22.97mL/min) ✓ Serum creatinine level decreased to 1.07 ± 0.45mg/dL (before 1.09 ± 0.45mg/dL) ✓ Plasma urea level increased slightly to 45.03 ± 22.29mmol/L (before 44.03 ± 19.33mg/dL) ✓ **Changes was not statistically significant** Group B (Oral NAC + Ascorbic Acid) ✓ Creatinine clearance decreased to 68.50 ± 27.76mL/min (reduced by 10.08%; **P = 0.037)** ✓ Serum creatinine level increased to 1.09 ± 0.52mg/dL (increased by 18.34%; **P = 0.005**) ✓ Plasma urea level increased to 42.74 ± 22.64mg/dL (increased by 31.58%; **P = 0.006**) ✓ Changes was statistically significant Group C (Placebo) ✓ Creatinine clearance decreased to 70.97 ± 25.27mL/min → reduced by 11.04%; **P = 0.006** (79.78 ± 18.53mL/min) ✓ Serum creatinine level increased to 1.05 ± 0.36mg/dL → increased by 0.02 (14.13%) unit; **P = 0.009** (0.92 ± 0.27mg/dL) ✓ Plasma urea level increased slightly to 39.82 ± 16.80mg/dL (31.02 ± 11.2mg/dL) → increased by 28.36%; **P = 0.002** ✓ Changes was statistically significant Comparison Group A & Group B ✓ Difference between A & B was statistically significant with respect to plasma urea level; **P = 0.029** ✓ Very close to be significant with respect to serum creatinine; P = 0.054 Comparison Group A & Group C ✓ Difference between A & C was statistically significant with respect to creatinine clearance; **P = 0.045** ✓ Not significant with respect to serum creatinine; P = 0.37 and plasma urea level; P = 0.11 Comparison Group B & Group C ✓ Difference was not statistically significant with respect to creatinine clearance or serum creatinine before and after interventions CONCLUSION High doses of NAC + hydration provide better protection against CIN than combination therapy of CIN and ascorbic acid + hydration or hydration alone	

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10. Poletti PA, Platon A, Seigneux SD, Dupuis Lozeron W, Sarasin F, Becker CD, Perneger T, Saudan P & Martin PY. N-Acetylcysteine Does not Prevent Contrast Nephropathy Emergency CT: a Randomized Study. BMC Nephrology. 2013; 14:119	RCT Obj: To determine whether 6000mg (ultra high dose) iv NAC (to account for dose dependent effect) was efficient in preventing CIN after emergency contrast CT-scan in pts admitted to the ER with elevated creatinine levels METHODS ✓ 120 pts were randomized to placebo or high dose iv NAC ✓ Contrast used was iohexol (iso-osmolar contrast media) ✓ Randomization was computer generated ✓ Investigators, patients and patient's primary physician were blinded to treatment group ✓ Randomized patients were then assigned to hydration of 250 ml of 0.45% NaCl before CT-scan and blindly allocated to either high dose NAC vs placebo ✓ After CT-scan all patients received 1000ml NaCl 0.45% ✓ Creatinine and cystatin C serum levels were collected 1 hr before CT-scan and at day 2, 4, and 10 ✓ SrCr and sCys C were measured by Jaffe method and by nephelometric assay		120 pts in ER with estimated creatinine clearance < 60ml/min/1.73m2 and request for urgent contrast CT Outcomes Measures ✓ Primary end point • Occurrence of CIN at day 2, 4 or 10 – increase of at least 25% or 44 µmol/l in SrCr level or 25% increase in cystatin C • Proportion of patients with contrast nephropathy regarding the biomarkers used and according to acute kidney injury network (AKIN) criteria → stage 1 AKI = increase creatinine between 150% and 199% froom baseline or an absolute increase of at least 26.2µmol/l → stage 2 AKI = increase creatinine between 200% and 299% from baseline → stage 3 AKI = increase of at least 300% fro, baseline or creatinine concentration higher than 345µmol/l with an acute rise of at least 44µmol/l or initiation of RRT ✓ Secondary end point → mean increases in creatinine and cystatin C concentration on days 2, 4 and 10 along with maximum increase during the time periods from day 2 to day 10 (peak increase) Statistical Analysis To achieve a power of 90% and 2-tailed risk alpha the minimal sample size required was estimated about 106 patients	iv NAC 6000 mg diluted in 100ml 0.45% saline administered during 60 minutes before the CT scan hydration given in all patients	Placebo (0.45% saline)		**Results** Data Collection ✓ Out of 120, 6 pts were excluded because : did not undergo contrast CT (n = 4) and presented with renal obstruction (n = 2) ✓ Follow up did not allow qualification of contrast nephropathy in 4 pts (1 in placebo; 3 in NAC group) because they died at day 0 (n = 2) or lost to follow up immediately (n = 2) → excluded from main analysis but included in sensitivity analysis ✓ In remaining 110, 8 pts did not have creatinine and cystatin C measure at day 4 because of dead (n = 4) or interrupted followed-up (n = 2) and technical reason (n = 2). 7 pts did not have cystatin c reading at day 4 ✓ 11 pts did not have creatinine and cystatin c measurement at day 10 due to dead (n = 6), could not be reached (n = 4), or for technical reasons (n = 1). 7 pts did not have cystatin c reading at day 10 Baseline Pts Characteristics ✓ Demographic and clinical characteristics were similar in both groups ✓ eGFR mean estimated based on MDRD was 42ml/min/1.73m2 ✓ 69 /114 (61%)= eGFR < 45ml/min/1.73m2 ✓ 10/114 (9%) = eGFR <30ml/min/1.73m2 on admission ✓ Data for 110 pts were analysed ✓ 52 of 110 received NAC and 58 received placebo Primary Outcome ✓ Number of pts developed contrast nephropathy **ranged between 16% (18/110) and 24.5% (27/110)** depending on definition of CIN ✓ Irrespective definition of CIN = no difference in CIN incidence between both groups (refer table 2 in full text article) Secondary Outcome ✓ The evolution from baseline to day 10 in creatinine and cystatin c levels concentration was not different between the 2 groups ✓ At day 10, both cystatin c and creatinine were lower than baseline suggesting that acute renal insufficiency was participating in the renal impairment observed at day 0 ✓ None sensitivity analysis performed to explore the impact of loss to follow-up or death, led to quantitatively different results: **all p-value ranged between 0.30 and 0.99** ✓ Composite event of death or acute kidney injury occurred in 14 (24%) of 58 pts (after exclusion of pts lost to follow-up) in placebo group and 18 (33%) of 54 pts in NAC group (including 2 pts who died at day 0) ✓ Correlation coefficient was computed between creatinine levels and cystatin c level at day 2 (0.87) , day 4 (0.83) and day 10 (0.67) → demonstrating a good congruence of the 2 measures ✓ No side effects reported in both group CONCLUSION ✓ CIN incidence was high in pts with low estimated GFR undergoing an emergency CT-scan ✓ IV NAC at high dose was not more efficient in this population than hydration alone for CIN prevention	