Contrast Induced Nephropathy

Mehmet OKUMUS

Ankara Training & Education Hospital

Clinic of Emergency Medicine

What is Contrast Induced Nephropathy?

Definition

serum creatinine ≧ 0.5 mg/dl increase in absolute value

an increase from baseline ≧ 25%

SCr levels peak between 2 and 5 days

No other causes

return to normal in 14 days

- With the increasing use of contrast agents, contrast-induced nephropathy (CIN) has become the third cause of acute renal failure in a hospital,
- The total incidence of CIN is about 3% to 14%, and the incidence rate of CIN is higher in high-risk patients with renal failure and diabetes mellitus.
- When comparing with elective PCI, the incidence of CIN in emergency PCI was higher.

McCullough PA, Wolyn R, Rocher LL, et al.
Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality.
Am J Med. 1997 Nov. 103(5):368-75

- In patients without risk factors,
  - The incidence of CIN 2%.
- With the introduction of risk factors,
  - Diabetes 9%,
  - Diabetes + CKD 90%.

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Risk factors

- Patient-related
  - Age
  - CKD
  - Diabetes mellitus
  - Hypertension
  - Metabolic syndrome
  - Anemia
  - Multiple myeloma
  - Hypoalbuminemia
  - Renal transplant
  - Hypovolemia and decreased effective circulating volumes

Risk factors

- Procedure-related risk factors:
  - Urgent versus elective
  - Arterial versus venous
  - Diagnostic versus therapeutic

Risk factors

- Contrast-related risk factors :
  - Volume of contrast
  - Contrast characteristics,
    - osmolarity,
    - ionicity,
    - molecular structure,
    - viscosity

Table 3 Comparison of CM agents by osmolality and viscosity

	Blood plasma	Iso-osmolar eg, Visipaque	Low-osmolar eg, Omnipaque	High-osmolar eg, Hypaque
Osmolality	290 mosmol/L	290 mosmol/L	890 mosmol/L	2100 mosmol/L
Viscosity	3–4 mPa s	8.8 mPa s	6.8 m mPa s	4.1 mPa s
CIN risk	N/A	Low	Low	High

CIN, contrast-induced nephropathy; CM, contrast media.

Rear R[1], Bell RM[1], Hausenloy DJ[2].
Contrast-induced nephropathy following angiography and cardiac interventions.
Heart. 2016 Apr;102(8):638-48. doi: 10.1136/heartjnl-2014-306962. Epub 2016 Feb 8.

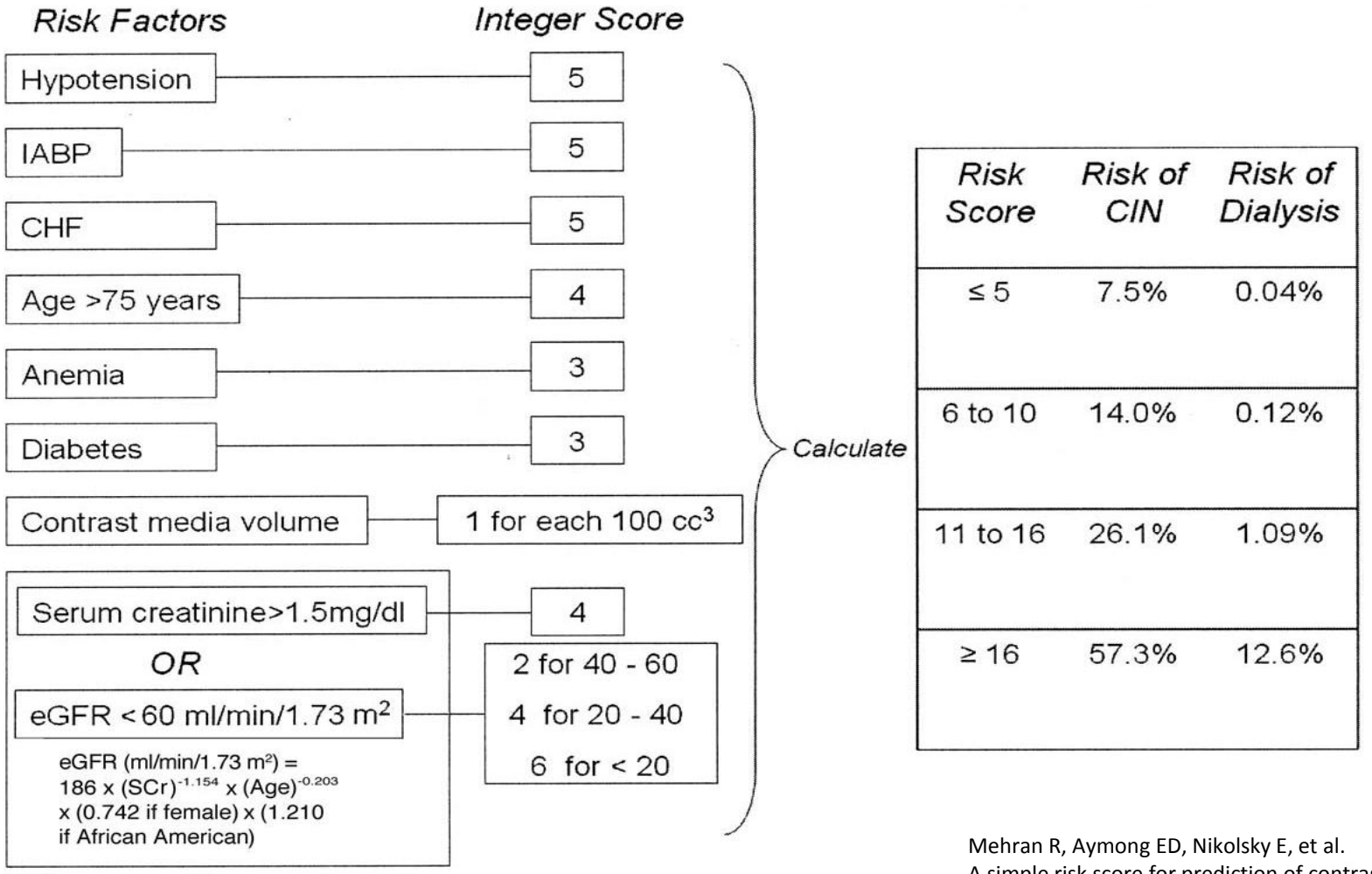
Dialysis

- CIN is normally a transient process
  - Renal function reverting to normal within 7-14 days
- Dialysis is required in less than 1% of patients
- Primary PCI for myocardial infarction (MI) 3%
- Underlying renal impairment 3.1%
- Diabetes with CKD 12%

Mortality

- Patients who require dialysis have a considerably worse mortality rate, with reported rates of 35.7% inhospital mortality (compared with 7.1% in the nondialysis group) and a 2-year survival rate of only 19%.
- Following invasive cardiology procedures, have reduced survival

Mehran Risk Score



Risk Score	Risk of CIN	Risk of Dialysis
≤ 5	7.5%	0.04%
6 to 10	14.0%	0.12%
11 to 16	26.1%	1.09%
≥ 16	57.3%	12.6%

For patients undergoing percutaneous coronary intervention

Mehran R, Aymong ED, Nikolsky E, et al.
A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol*. 2004 Oct 6. 44(7):1393-9.

The main mechanism

1. They cause a direct cytotoxic effect on the renal proximal tubular cells, enhance cellular damage by reactive oxygen species, and increase resistance to renal blood flow.
2. They also exacerbate renal vasoconstriction, particularly in the deeper portions of the outer medulla.

Risk reduction strategies

- Contrast
- IVF
- $NaHCO_3$
- N-Acetylcysteine
- Ascorbic acid
- Statin
- ACEi
- Theophyllin/aminophylline
- Diuresis
- Dopamine/Fenoldopam
- Prostaglandin/prostacyclin
- ANP
- Mechanical (HD, hemofiltration, RenalGuard)

IV Fluids

- The cornerstone of CIN prevention.
- Renal perfusion is decreased for up to 20 hours following contrast administration.
- Intravascular volume expansion maintains
  - renal blood flow
  - preserves nitric oxide production
  - prevents medullary hypoxemia
  - enhances contrast elimination

N-acetylcysteine

Excellent antioxidant against free oxygen radicals

Enhances the vasodilatory properties of nitric oxide.

Statins

- Used for their pleiotropic effects
  - favorable effects on endothelin
  - plaque stabilization
  - anti-inflammatory properties

Because of the vascular nature of CIN they might have similar renoprotective effects.

Meta-Analysis

- The Agency for Healthcare Research and Quality
- Johns Hopkins University Evidence-based Practice Center

Contrast-Induced Nephropathy: Comparative Effectiveness of Preventive Measures .
Subramaniam RM, Wilson RF, Turban S, Suarez-Cuervo C, Zhang A, Sherrod C, Aboagye J, Eng J, Choi MJ, Hutfless S, Bass EB.
Rockville (MD): Agency for Healthcare Research and Quality (US); 2016 Jan. Report No.: 15(16)-EHC023-EF.
AHRQ Comparative Effectiveness Reviews.

Data sources

- MEDLINE®,
  - Embase®,
    - Cochrane Library
      - ClinicalTrials.gov
        - Scopus

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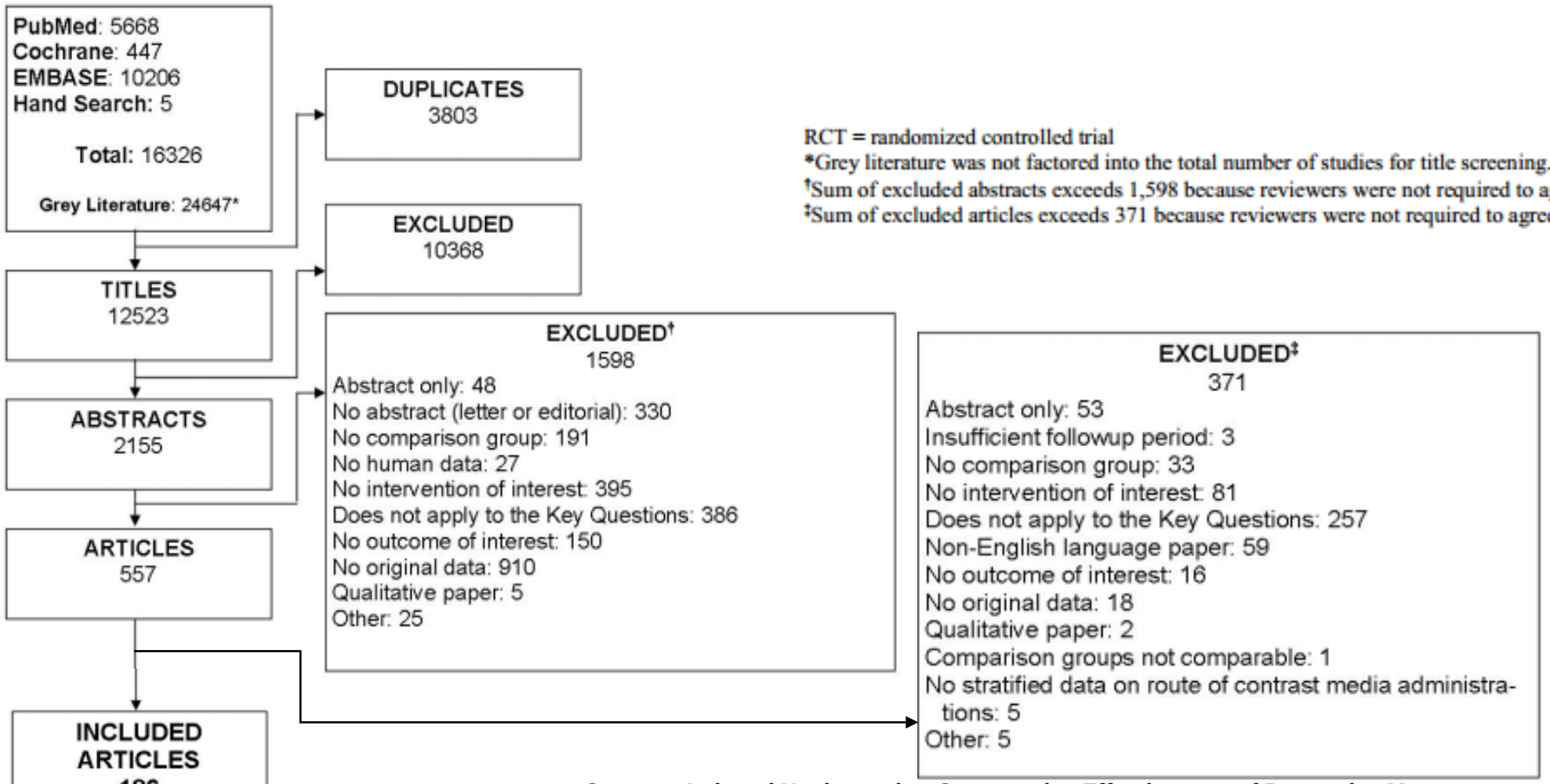
Figure 2. Results of the literature search



RCT = randomized controlled trial
*Grey literature was not factored into the total number of studies for title screening.
†Sum of excluded abstracts exceeds 1,598 because reviewers were not required to agree on reasons for exclusion.
‡Sum of excluded articles exceeds 371 because reviewers were not required to agree on reasons for exclusion.

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Studies published between 1998-2015 (186)

Randomized controlled trials (RCTs) 163
Prospective studies 23

- RCTs comparing N-acetylcysteine with IV saline versus IV saline with or without a placebo 67
- RCTs comparing IV sodium bicarbonate versus IV saline 28
- RCTs comparing IV sodium bicarbonate versus N-acetylcysteine plus IV saline 7
- RCTs comparing a statin versus IV saline 8
- RCTs comparing a statin plus N-acetylcysteine versus N-acetylcysteine 5
- RCTs comparing statin versus statin, statin by dose, or statins plus other agents 6
- RCTs comparing an adenosine antagonist versus IV saline 5
- RCTs investigating hemodialysis or hemofiltration versus IV saline 6
- RCTs comparing ascorbic acid versus IV saline 6
- RCTs comparing ascorbic acid to N-acetylcysteine 3

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Methods

- Two reviewers independently reviewed each published article for eligibility.
- One reviewer extracted the data and a second reviewer verified the accuracy.
- Graded the strength of evidence (SOE)

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Results

- The SOE was low

High-dose [>1,200 mg/day] N-acetylcysteine versus IV saline
(RR, 0.78; 95% CI, 0.59 to 1.03)
small clinically unimportant effect

Low-dose [≤1,200mg/day] N-acetylcysteine versus IV saline
(RR, 0.75; 95% CI, 0.63 to 0.89)
Borderline important effect

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Results

- The SOE was moderate

N-acetylcysteine was given for LOCM versus IV

(RR,0.69; 95% CI, 0.58 to 0.84),

clinically important effect

!!!Not in IOCM!!!

(low SOE; RR, 1.12; 95% CI,0.74 to 1.69)

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Results

- The SOE was low

Intra-veneous versus Intra-arterial routes

did not differ

Statin + N-acetylcysteine versus N-acetylcysteine (intra arterial)

(RR, 0.52; 95% CI, 0.29 to 0.93)

Statin + N-acetylcysteine more effective

statin + IV saline versus IV saline alone

(RR, 0.68; 95% CI, 0.39 to 1.20)

did not differ

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Results

- The SOE was low

IV sodium bicarbonate versus IV saline

(RR, 0.93; 95% CI, 0.68 to 1.27)

did not differ

IV sodium bicarbonate versus IV saline using LOCM

(RR, 0.65; 95% CI, 0.33 to 1.25)

did not differ

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Results

- The SOE was low that

Ascorbic acid versus IV saline

(RR, 0.72; 95% CI, 0.48 to 1.01)

did not differ

Hemodialysis versus IV saline

(RR, 1.50; 95%CI, 0.56 to 4.04)

did not differ (harmful?)

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Conclusions

Benefit in studies of three comparisons

Low-dose N-acetylcysteine + IV saline versus IV saline

N-acetylcysteine + IV saline versus IV saline (LOCM)

Statins + N-acetylcysteine versus N-acetylcysteine (IA)

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Table 6 European Society of Cardiology CIN prevention guidelines, 2014

Recommendation	Detail	Class	Level
Intravenous hydration with isotonic saline is recommended		I	A
Use of either LOCM or IOCM is recommended	<350 mL or <4 mL/kg or V/CrCl <3.7:1	I	A
IOCM use should be considered over LOCM		IIa	A
Short term, high-dose statin therapy should be considered	Rosuvastatin 20/40 mg or atorvastatin 80 mg or simvastatin 80 mg	IIa	A
Volume of CM should be minimised		IIa	B
A CIN risk assessment should be performed		IIa	C
In patients at very high CIN risk or when prophylactic hydration is impossible, furosemide with matched hydration may be considered over standard hydration	250 mL 0.9% saline intravenously over 30 min (or ≤150 mL in LV dysfunction) with 0.25–0.5 mg/kg of furosemide intravenous bolus. Adjust intravenous fluid rate to match urine output until >300 mL/h then perform CM procedure. Continue matched fluid replacement for 4 h post procedure	IIb	A
In severe CKD, prophylactic haemofiltration prior to complex PCI may be considered	Fluid replacement rate 1 L/h without negative loss, 0.9% sodium chloride intravenous hydration for 24 h post procedure	IIb	B
N-acetyl-cysteine instead of intravenous hydration is not recommended		III	A
Infusion of 8.4% sodium bicarbonate instead of 0.9% sodium chloride is not recommended		III	A
In severe CKD prophylactic renal replacement therapy is not routinely recommended		III	B

CIN, contrast-induced nephropathy; CKD, chronic kidney disease; CM, contrast medium; IOCM, iso-osmolar contrast medium; LOCM, low-osmolar contrast medium; LV, left ventricular; PCI, percutaneous coronary intervention; V/CrCl, volume of contrast media to creatinine clearance.
Adapted from Windecker *et al*.[59]

Rear R[1], Bell RM[1], Hausenloy DJ[2].
Contrast-induced nephropathy following angiography and cardiac interventions.
Heart. 2016 Apr;102(8):638-48. doi: 10.1136/heartjnl-2014-306962. Epub 2016 Feb 8.

Table 7 Nephrotoxic medications requiring withdrawal 24 h pre-procedure

Drug class	Examples
Non-steroidal anti-inflammatory	Naproxen, Ibuprofen, Diclofenac, Celecoxib[90]
Antibiotics	Aminoglycosides: (Gentamycin, Tobramycin, Amikacin)[91]
Antifungals	Amphotericin B[92]
Antivirals	Acyclovir, Tenofovir, Foscarnet[93]
Immunomodulatory	Ciclosporin A[94]
Antineoplastic	Cisplatin, Ifosfamide, Mitomycin[95]

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Summary

- Select the appropriate patient
- Remind alternative diagnostic tools (Echo, MRI, Doppler USG)
- Rehydrate the patient
- Give LOCM/IOCM
- Give low volume of CM
- Quit the nephrotoxic drugs