Contrast-induced Acute Kidney Injury (CI-AKI)

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Introduction

1. Definition of CI-AKI
2. Pathophysiology
3. Patients at risk

Definition of CI-AKI

- A lack of consensus on how to define CI-AKI, which hampers comparisons across studies.

Table 1. Definitions of contrast-induced nephropathy

Definition	Author
Increase of ≥ 0.5 mg/dL (44 μmol/L) or ≥ 25% in serum creatinine at 48 h	Mehran et al.[12]
Increase of > 0.5 mg/dL (44 μmol/L) or > 25% in serum creatinine within 72 h	European Society of Urogenital Radiology[13]
Increase of ≥ 0.3 mg/dL (27 μmol/L) or ≥ 50% in serum creatinine with oliguria (< 0.5 mL/kg/h for > 6 h)	Acute Kidney Injury Network[14]
Increase of > 50% in serum creatinine or decrease of > 25% in glomerular filtration rate with oliguria (< 0.5 mL/kg/h for > 6 h)	RIFLE (**R**isk, **I**njury, **F**ailure, **L**oss of Kidney Function and **E**nd-Stage Kidney Disease) Classification[15]
Increase of > 100% in serum creatinine with oliguria (< 0.5 mL/kg/h for > 12 h)	Kidney Disease Improving Global Outcomes[16]
Increase of > 0.5 mg/dL (44 μmol/L) or > 25% in serum creatinine at 72 h	Canadian Association of Radiologists[17]

Can J Cardiol, 2016. **32**(2): p. 247-55.

Definition of CI-AKI

- Based upon the clinical presentation with 3 necessary components

Serum Cr
≥ 0.5 mg/dl or
≥ 25% of baseline

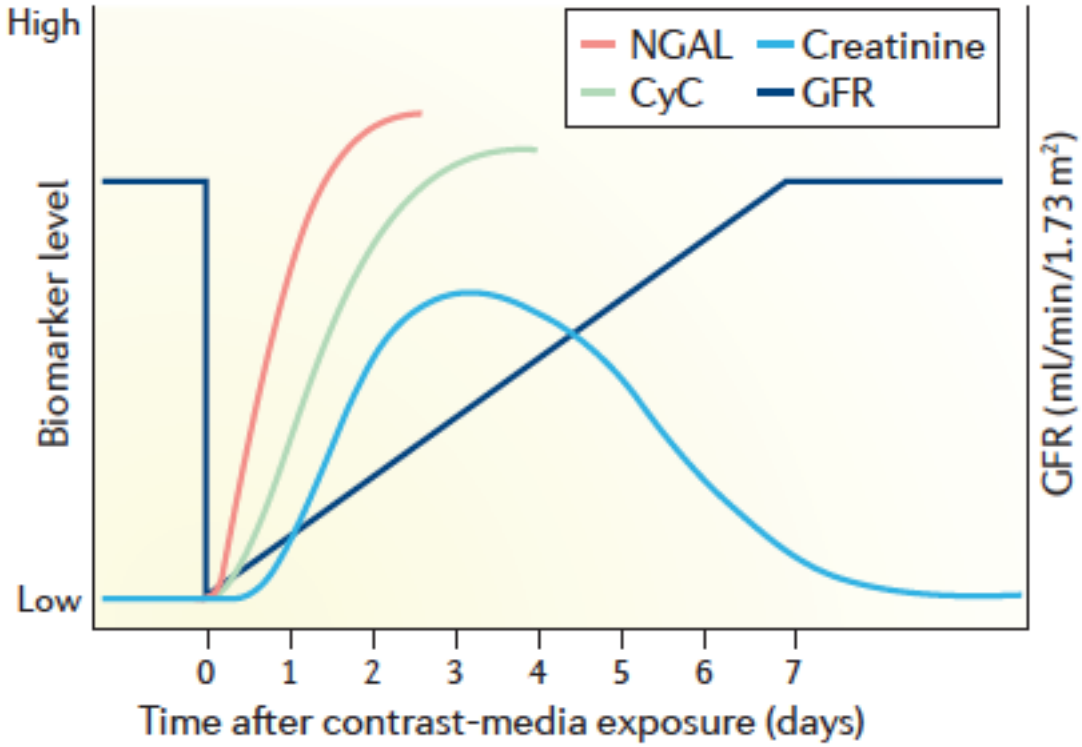
CI-AKI (AKIN)
Serum Cr ≥ 0.3 mg/dl or
≥ 50% of baseline

Within 48-72 hrs following the exposure

Exclusion of other causes

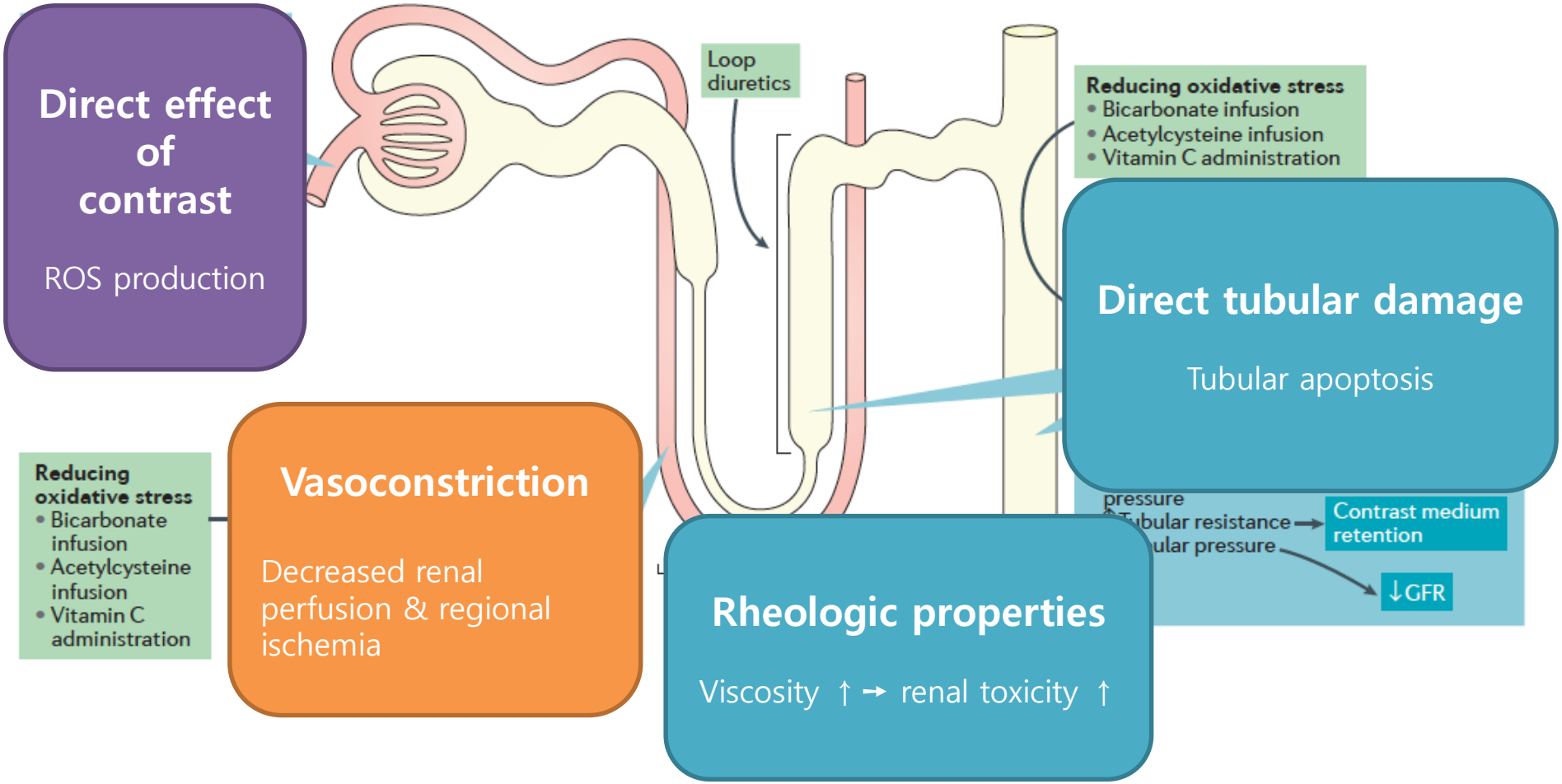
Definition of CI-AKI

- Reversible



Nat Rev Nephrol, 2017. **13**(3): p. 169-180.

Pathophysiology



Nat Rev Nephrol, 2017. **13**(3): p. 169-180.

Patients at risk

Box 2 | Common risk factors for contrast-induced acute kidney injury

- Associated with the patient
  - Concomitant acute kidney injury of other origins
  - Reduced glomerular filtration rate (<45 ml/min/1.73 m^2 or <60 ml/min/1.73 m^2 for intravenous or intra-arterial administration, respectively)
  - Previous acute kidney injury or chronic kidney disease
  - Diabetic nephropathy
  - Dehydration
  - Anaemia
  - Poor haemodynamic status
  - Age >70 years
  - Concurrent nephrotoxic drug treatment
- Associated with the procedure
  - Large doses of contrast medium
  - Multiple administrations of contrast medium
  - Use of contrast medium with excessive osmolality or viscosity
  - Intra-arterial administration (debated)

Nat Rev Nephrol, 2017. **13**(3): p. 169-180.

Patients at risk (Mehran Score)

Risk Factors	*Integer Score*
Hypotension	5
IABP	5
CHF	5
Age >75 years	4
Anemia	3
Diabetes	3
Contrast media volume	1 for each 100 cc^3
Serum creatinine>1.5mg/dl	4
OR	
eGFR < 60 ml/min/1.73 m^2	2 for 40 - 60 4 for 20 - 40 6 for < 20

eGFR (ml/min/1.73 m^2) = 186 x $(SCr)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.210 if African American)

Calculate

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%

J Am Coll Cardiol, 2004. **44**(7): p. 1393-1399.

Epidemiology

Major risk factors

1. Chronic kidney disease
2. DKD with reduced GFR
3. Elderly patients
4. Dose and type of contrast agent
5. Specific radiologic procedure
6. Others

Chronic Kidney Disease

- The threshold GFR at which a clinically significant risk is incurred is not well defined.

eGFR < 30 ml/min/1.73m²	30 ≤ eGFR > 60 ml/min/1.73m²	eGFR ≥ 60 ml/min/1.73m²
31% ~ 55%	4.2 % ~ 15%	0 ~ 2%

Proteinuria ≥ 1g/day (62%)
vs.
Proteinuria < 1g/day (21%)

J Sug Res 1992;53:317-320, Catheter Cardiovasc Interv 2001;52:409-416, Circulation 2002;105(19):2259, Ren Fail 2013;35(1):62

Diabetes with reduced eGFR

- Diabetes + normal renal function = non DM
- Diabetes with reduced renal function

Table 2. Incidence of contrast-induced renal failure in diabetic patients[a]

Creatinine <2.0 mg/dl	11/306	3.6%
Creatinine 2.0–4.0 mg/dl	22/81	27.0%
Creatinine >4.0 mg/dl	30/37	81.0%

[a] Data from Refs. 19–22, 27, 28, 31, 32, 34, 35, 41.

Am J Med, 1997. **103**(5): p. 368-75, Kidney Int 1989;36:730-740

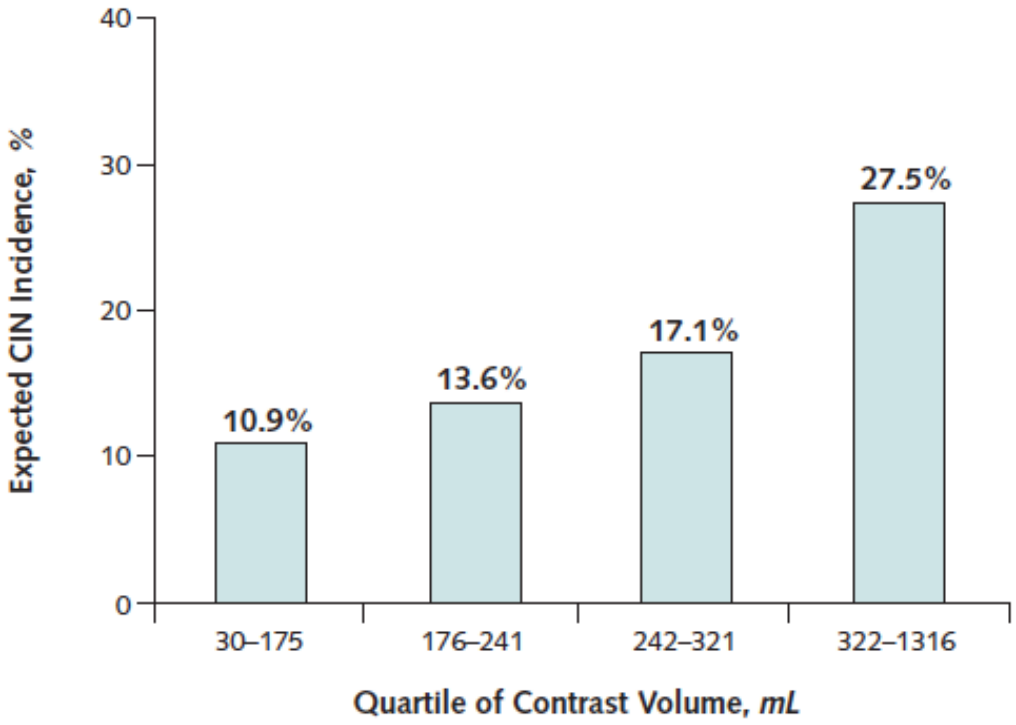
Elderly patients

- Multifactorial age-related changes
  - Diminished eGFR, tubular secretion, and concentration abilities
  - Other risk factors

Arch Intern Med, 1990. **150**(6): p. 1237-42.

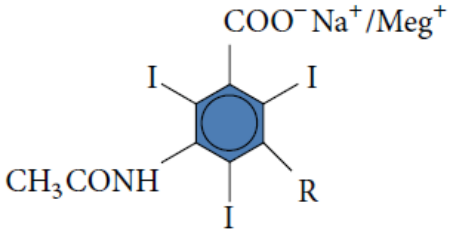
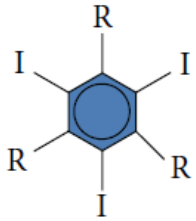
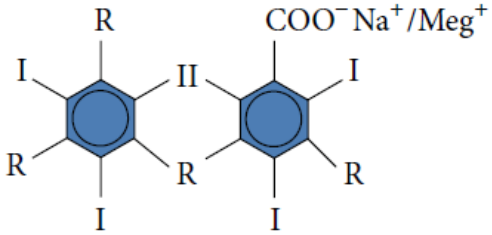
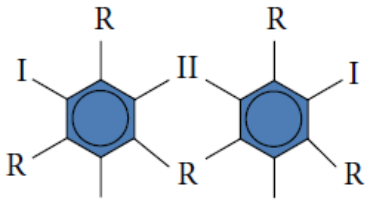
Dose and type of iodinated contrast agent

- Dose
  - Volume
- Types
  - Osmolality
  - Viscosity



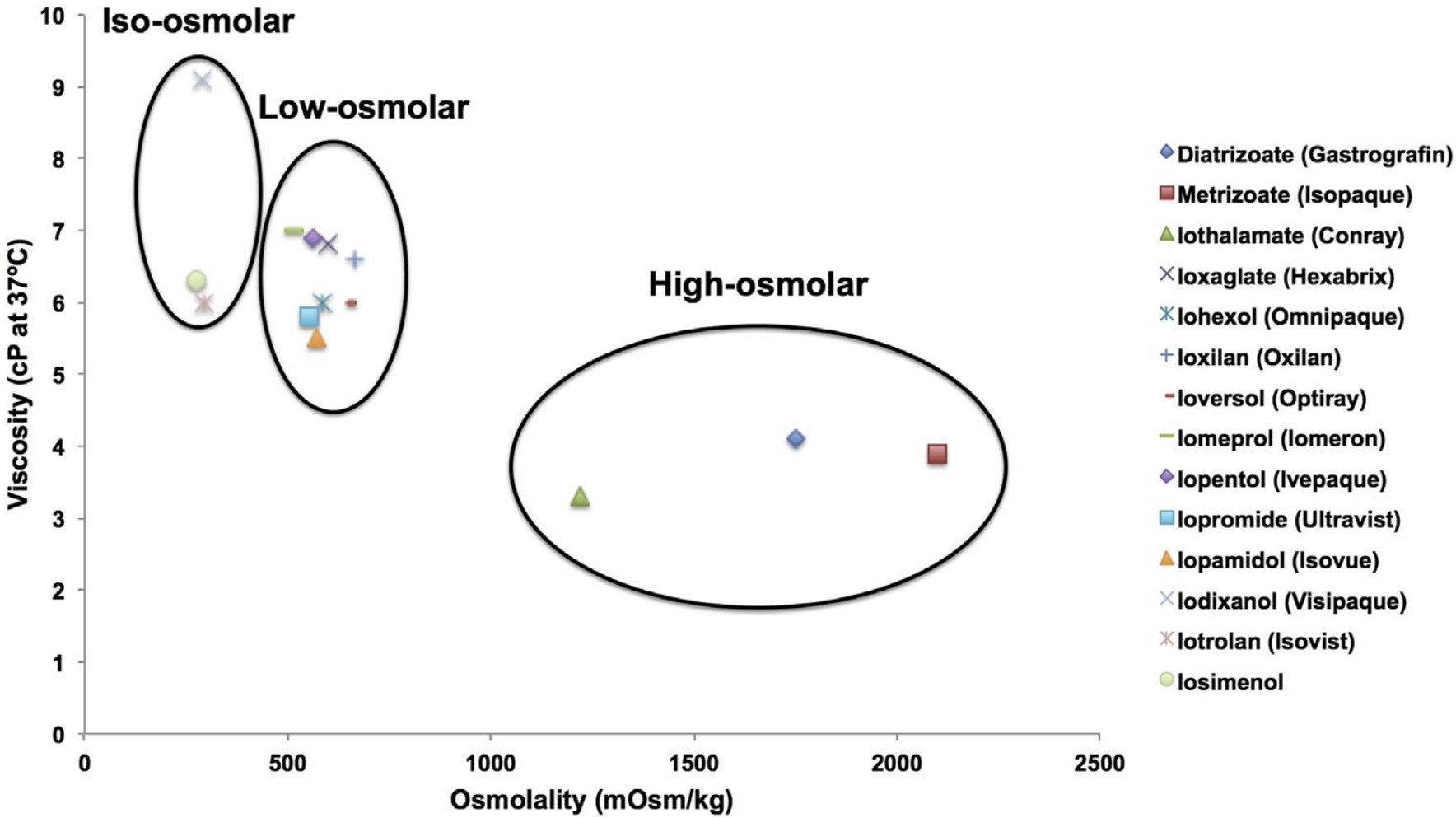
Ann Intern Med, 2009. **150**(3): p. 170-7.

Sub-classification of iodinated contrast media

Molecular structure	Era	Examples	Comment	Iodine/particles
	1950s	Ionic monomer Diatrizoate Iothalamate	High osmolality, 5–8*x* blood	3/2 = 1.5
	1980s	Nonionic monomer Iopamidol Iohexol Ioversol	Low osmolality, 2–3*x* blood, improved hydrophilicity	3/1 = 3
	1980s	Ionic dimer Ioxaglate	Low osmolality, ~2*x* blood	6/2 = 3
	1990s	Nonionic dimer Iodixanol (iotrolan)	Isoosmolality Osmolality = blood	6/1 = 6

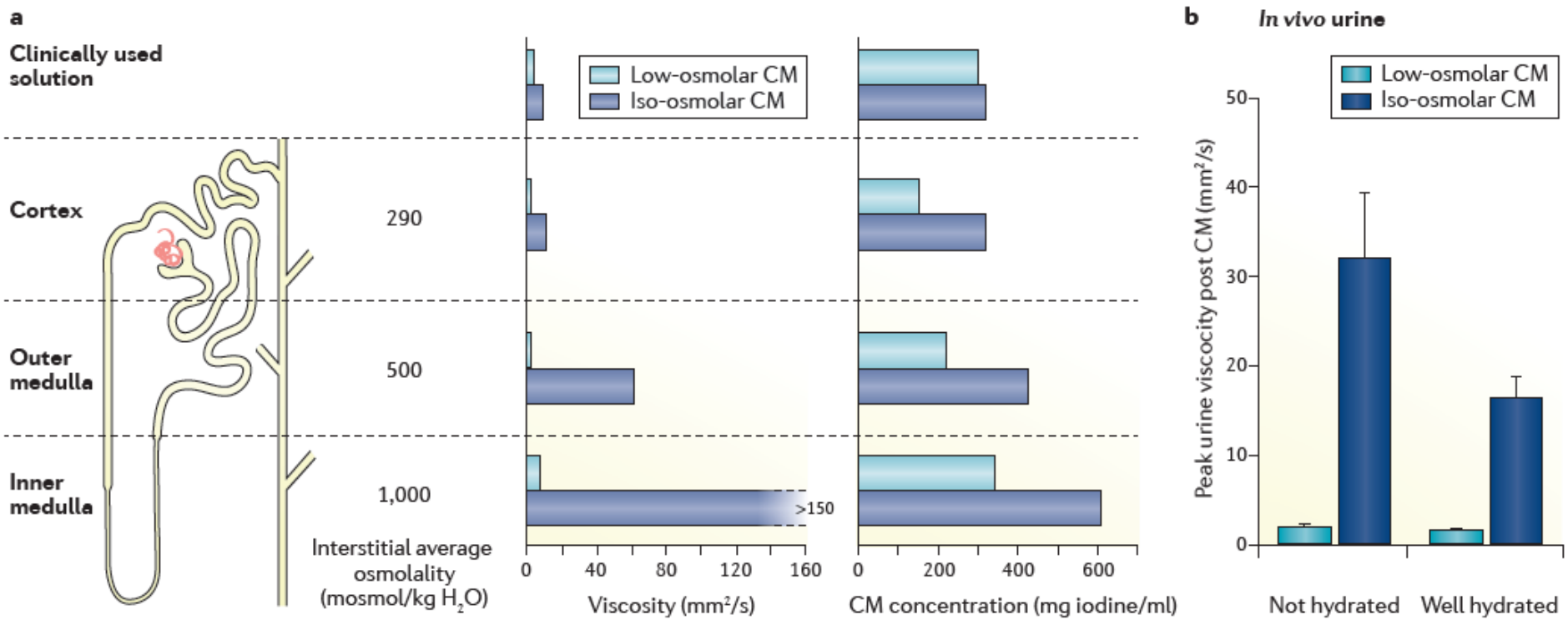
Biomed Res Int, 2014. 2014: p. 934947.

Dose and type of iodinated contrast agent



Can J Cardiol, 2016. **32**(2): p. 247-55.

Dose and type of iodinated contrast agent



Nat Rev Nephrol, 2017. **13**(3): p. 169-180.

Specific radiologic procedures

- Route of administration
  - Intra-arterial
  - Intravenous
- Level
  - Renal artery
  - Peripheral vessels
- Procedure
  - Diagnostic
  - Intervention

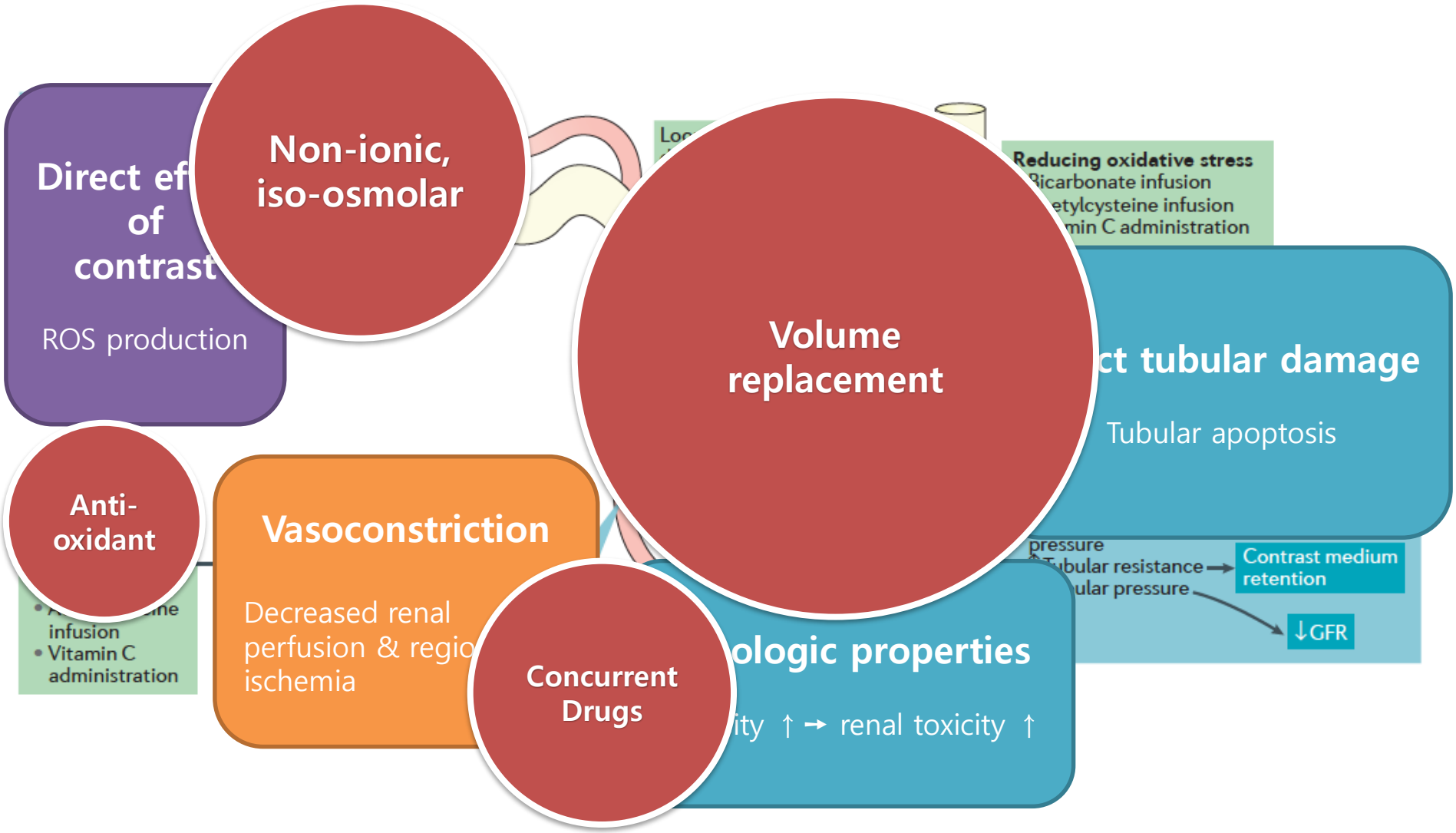
Eur Radiol, 2011. **21**(12): p. 2527-41.

Preventive strategies

Major modifiable factors

1. Selection of contrast agents
2. Volume supplementation
3. Pharmacological prophylaxis
4. Dialysis

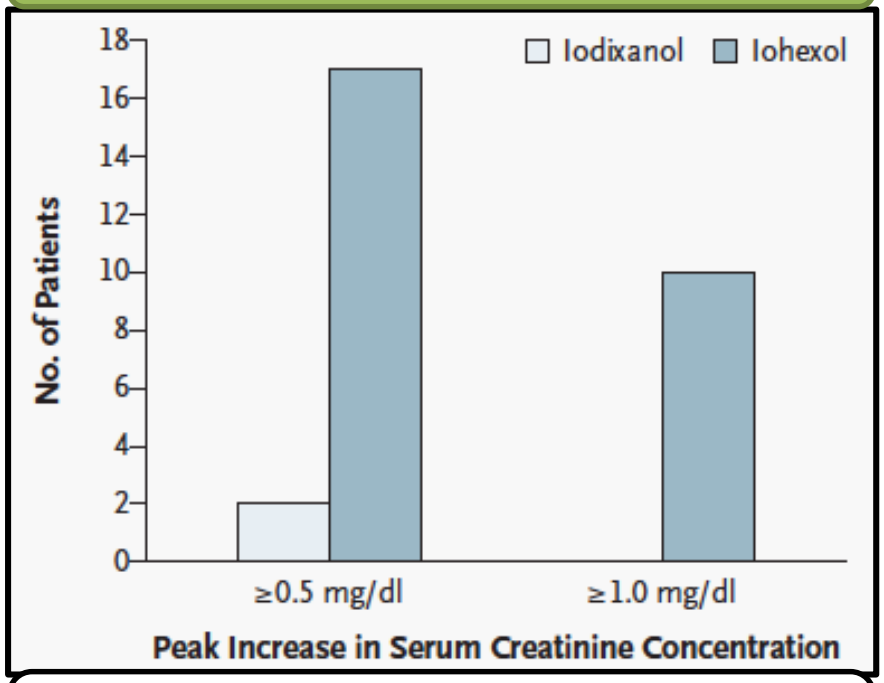
Preventive strategies



Nat Rev Nephrol, 2017. **13**(3): p. 169-180.

Selection of contrast agents

NEPHRIC trial



Superiority of IOCA

Iodixanol (Visipaque®) vs. Iohexol (Omnipaque®)

CARE trial

Similar CIN incidence

Peak increase in sCr ≥ 0.5 mg/dl

Iodixanol+NAC (3/100 pt)

2.7% vs. 3.5%

Iobitridol+NAC (4/115)

Similar

Iodixanol (Visipaque®) vs. Iobitridol (Xenetrix®)

N Engl J Med, 2003. **348**(6): p. 491-9.

Kidney Int, 2005. **68**(5): p. 2250-5.

Volume supplementation (cornerstone)

- **Volume supplementation seems to be effective**

Table 1 | Summary of randomized controlled trials assessing the prevention of contrast-induced nephropathy (CIN) with volume supplementation

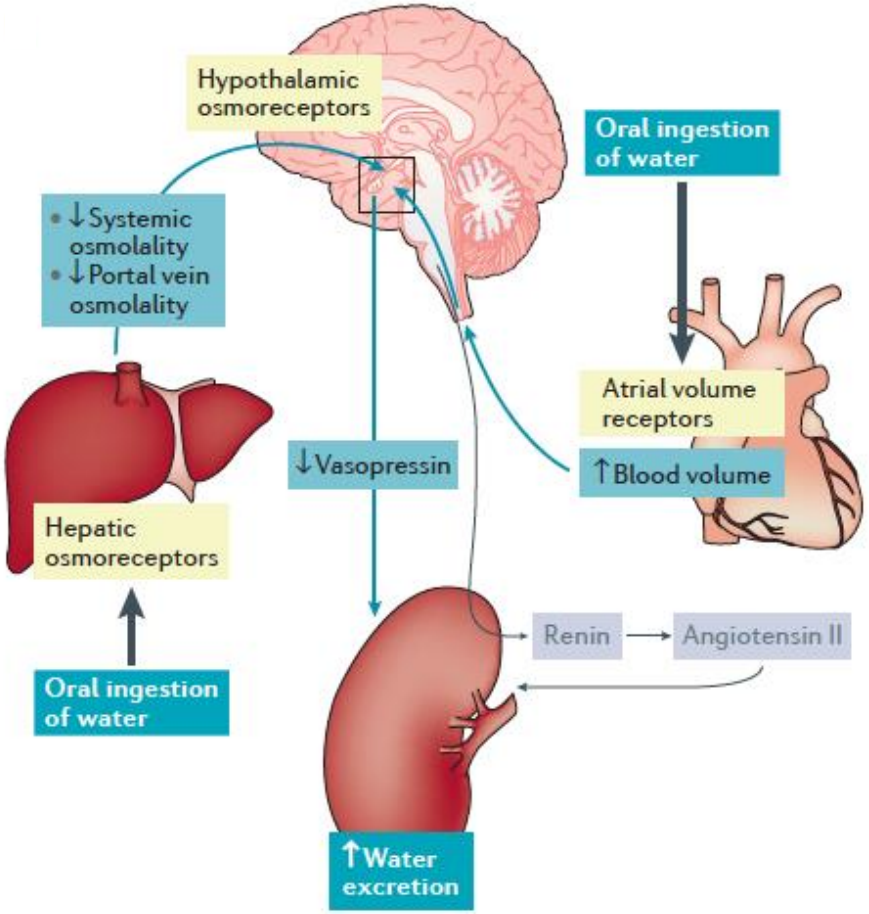
Study	Number of patients	Baseline serum creatinine	Duration of infusion before contrast	Duration of infusion after contrast	Infusion rate	Infusate	CIN rate
Solomon *et al.*[1]	78	2.1 mg/dl	12 h	12 h	1 ml/kg per h	0.45 Saline versus 0.45 saline+mannitol versus 0.45 saline+furosemide	11 versus 28 versus 40%
Taylor *et al.*[2]	36	1.74 mg/dl	12 h versus $\frac{1}{2}$–1 h	12 h versus 6 h	75 versus 300 ml/h	0.45 Saline	11.1 versus 5.6%
Mueller *et al.*[4]	1383	0.93 mg/dl	Started at 0800 hours	12 h	1 ml/kg per h	0.9 Saline versus 0.45 saline	0.7 versus 2.0%
Trivedi *et al.*[5]	53	106 μmol/l	12 h versus none	12 h versus none	1 ml/kg per h	0.9 Saline	3.7 versus 34.6%
Bader *et al.*[6]	39	0.9 mg/dl	12 h versus bolus only	12 h versus none	2000 ml/24 h	0.9 Saline	5.3 versus 15%
Krasuski *et al.*[15]	63	2.1 mg/dl	12 h versus 20 min	12 h	1 ml/kg per h versus 250 ml/20 min	0.45 Saline	0 versus 10.8%
Merten *et al.*[16]	119	1.80 mg/dl	1 h	6 h	3 ml/kg per h before 1 ml/kg per h after	Sodium bicarbonate versus saline	1.7 versus 13.6%

CIN is defined as an increase in serum creatinine of at least 0.5 mg/dl within 48 h,[1,2,4,5] an increase in serum creatinine of 25% or more within 48 h,[16] or a decrease in glomerular filtration rate of more than 50% within 48 h.[6]

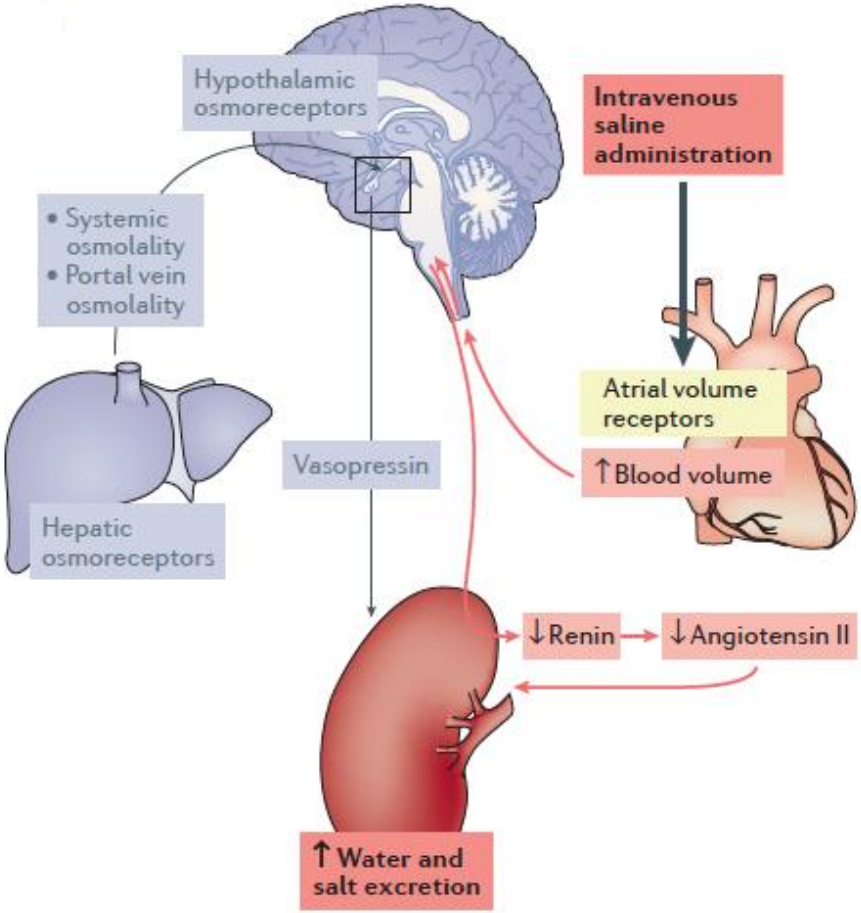
Kidney Int Suppl, 2006(100): p. S16-9.

Volume supplementation

Oral hydration



IV hydration



Nat Rev Nephrol, 2017. **13**(3): p. 169-180.

Volume supplementation

PREPARED: Preparation for Angiography in Renal Dysfunction (RCT)

- **Inpatient hydration protocol**
  - 0.45% NS IV at a rate of 75 mL/h for 12 h before and 12 h after cardiac catheterization.

- **Outpatient hydration protocol**
  - began with 1,000 mL of water taken orally over the 10 h before the scheduled cardiac catheterization.
  - Following this , IV 0.45% NS at a rate of 300 mL/h was started "on call" to the cardiac catheterization laboratory (30 to 60 min before exposure to radiocontrast material) and continued for a total of 6 h.

Chest, 1998. **114**(6): p. 1570-4.

Volume supplementation

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

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Oral Salt and Water to Prevent Contrast Nephropathy

This study has been withdrawn prior to enrollment.

(The recruitment rate was very slow, and it was concluded that it was not feasible to do this trial.)

Sponsor:
Ottawa Hospital Research Institute

Information provided by (Responsible Party):
Ottawa Hospital Research Institute

ClinicalTrials.gov Identifier:
NCT02084771

First received: November 5, 2013
Last updated: March 29, 2016
Last verified: March 2016
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Withdrawn

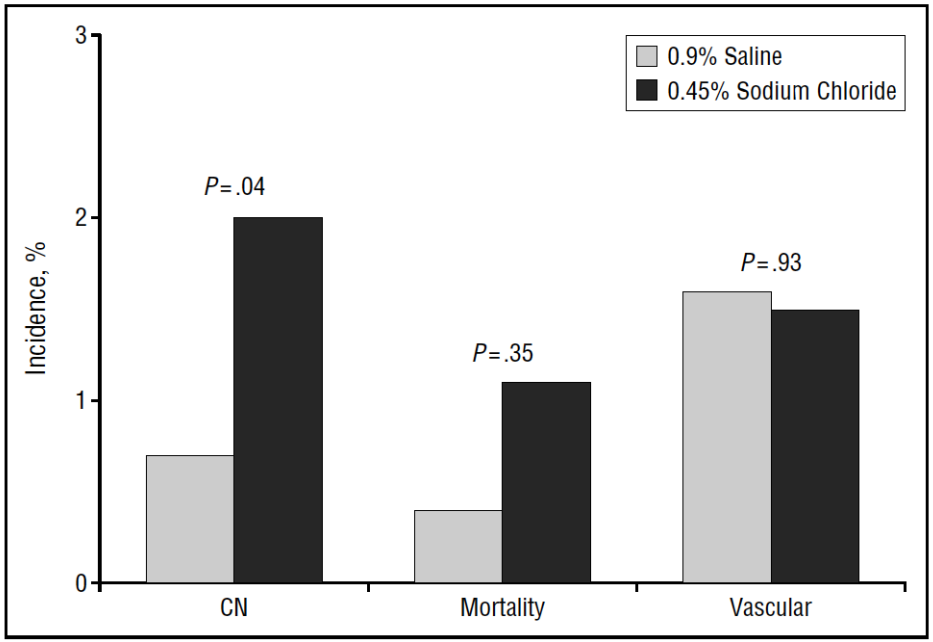
Purpose

The purpose of this pilot trial is to determine the safety and feasibility of using oral salt and water loading compared to intravenous saline for the prevention of contrast-induced acute kidney injury in patients with chronic kidney disease receiving a contrast-enhanced CT scan.

US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT02084771 (2016).

Volume supplementation

- **Saline is better than half saline**
  - N=1620, CAG, RCT
  - 0.7% vs. 2.0% (P=0.04)



Arch Intern Med, 2002. **162**(3): p. 329-36.

Volume supplementation

- **NaHCO3 would be alternative**
  - N=137, RCT
    - NS (154 mEq/L) vs. NaHCO3 (154 mEq/L)
    - as a bolus of 3 mL/kg/hr for 1 hour before procedure
    - Followed by an infusion of 1 mL/kg/hr for 6 hours aft

$$Fe^{3+} + O_2^- \rightarrow Fe^{2+} + O_2$$
$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {}^{\cdot}OH + OH^-$$

Alkalization may reduced the level of pH-dependent oxygen free radical

	Mean (SD)			
	Sodium Chloride (n = 59)	Sodium Bicarbonate (n = 60)	Mean Difference (95% CI)	*P* Value
Change in mean arterial pressure after initial bolus, mm Hg	11 (14)	14 (13)	–3.0 (–7.9 to 1.9)	.35
Urine pH after initial bolus	5.6 (0.6)	6.5 (0.8)	–0.9 (–1.4 to –0.4)	.002
Contrast volume, mL	134 (63)	130 (72)	4.0 (–25.3 to 33.3)	.75
Cardiac catheterizations	133 (62)	135 (76)	–2.0 (–30.0 to 26.0)	.89
Computed tomography	110 (20)	122 (27)	–12.0 (–51.0 to 27.0)	.49
Other procedures†	141 (50)	110 (76)	31.0 (–46.0 to 108.0)	.40
Change in serum bicarbonate, mEq/L‡	–0.7 (2.8)	2.1 (2.6)	–2.8 (–4.0 to –1.6)	<.001
Change in serum potassium, mEq/L‡	–0.17 (0.59)	–0.26 (0.48)	0.09 (–0.10 to 0.30)	.36
Change in serum creatinine, mg/dL	0.04 (0.28)	–0.07 (0.41)	0.11 (–1.10 to 0.30)	.09
Change in estimated glomerular filtration rate, %§	–0.1 (17.0)	8.5 (21.7)	–8.6 (–17.0 to –0.2)	.02
Incidence of contrast-induced nephropathy, % (No. of patients)	13.6 (8)	1.7 (1)	11.9 (2.6 to 21.2)	.02

JAMA, 2004. **291**(19): p. 2328-34

Volume supplementation

- **POSEIDON trial**
  - N=396, RCT.

LVEDP-guided group	Control group
LVEDP<13: 5 ml/kg/hr 13 ≤LVEDP<18: 3 ml/kg/hr LVEDP ≥18: 1.5 ml/kg/hr	1.5 ml/kg/hr

	LVEDP hydration-guided group	Control group	Relative risk (95% CI)	Risk difference (95% CI)	p value
Primary endpoint					
>25% or 0·5 mg/dL increase in serum creatinine	12/178 (6·7%)	28/172 (16·3%)	0·41 (0·22–0·79)	–9·5 (-2·9 to –16·2)	0·005
Secondary endpoints					
>25% increase in serum creatinine	12/178 (6·7%)	27/172 (15·7%)	0·43 (0·22–0·82)	–9·0 (–2·5 to –15·5)	0·008
>0·5 mg/dL increase in serum creatinine	5/178 (2·8%)	11/172 (6·4%)	0·44 (0·16–1·24)	–3·6 (–8·0 to 0·8)	0·11
Sensitivity analyses					
≥0·3 mg/dL increase in serum creatinine	24/178 (13·5%)	43/172 (25·0%)	0·54 (0·34–0·85)	–11·5 (–3·3 to –19·7)	0·006
>25% or 0·5 mg/dL increase in serum creatinine in participants with ≥1 serum creatinine value available	12/190 (6·3%)	28/196 (14·3%)	0·44 (0·23–0·84)	–8·0 (–2·0 to –14·0)	0·01

Data are n/N (%). LVEDP=left ventricular end-diastolic pressure.

Table 2: Occurrence of contrast-induced acute kidney injury

Lancet, 2014. **383**(9931): p. 1814-23.

Volume supplementation (summary)

1. Normal saline at a rate of 1 ml/kg/hr ~ 5 ml/kg/hr (LVEDP)
   - 12 hrs before till 12 hrs after exposure

2. NaHCO3 at a rate of 3 mg/kg/hr
   - 1 hr before till 6 hrs after exposure

3. Oral hydration 1000 ml + On call IV hydration with NS 300 ml/hr
   - PO 12 hrs before + IV hydration 6 hrs after exposure

Pharmacologic prophylaxis

1. Anti-oxidant
   - N-acetylcysteine (NAC)
   - Ascorbic acid

2. Inhibition of renal vasoconstriction
   - Calcium channel blockers
   - Adenosine antagonists (theophylline)
   - Dopamine and fenoldopam

3. Reduced viscosity
   - Diuretics (mannitol and furosemide)

Antioxidant: N-acetylcysteine

- Classically known as mucolytic agent
- Plausible mechanism
  - Scavenge oxygen free radicals
  - Improving renal hemodynamics
  - Prevent direct toxic tissue damage
- Little adverse effects (e.g. nausea)

Antioxidant: N-acetylcysteine

- Hydration + NAC **(600 mg bid)** vs. Hydration alone, RCT

Table 1 | Clinical studies on the prophylactic use of NAC to prevent CIN

Author	Number of pateints	Design	Baseline sCr (mg/dl)	NAC dose and route of administration	CIN in the NAC group (%)	CIN in the control group (%)	Effect of NAC	Volume of Contrast dye (ml)
Tepel[5]	83	RPCT	2.5±1.3	600 mg b.i.d. OS, day before and after	2	21	+	75
Diaz-Sandoval[6]	54	BRPCT	1.6±0.4	600 mg b.i.d. OS 1 dose before and 3 after	8	45	+	184±10
Shyu[7]	121	RPCT	2.8±0.8	400 mg b.i.d. OS, day before and after	3.3	24.6	+	117±25
Kay[8]	200	BRPCT	1.25[a] (0.70–3.30)	600 mg b.i.d. OS, day before and after	4	12	+	125 (70–320)[a]
Briguori[9]	183	RCT	1.5±0.4	600 mg b.i.d. OS, day before and after	6.5	11	Null	197±135
Allaqaband[10]	123	RCT	2.1±0.8	600 mg b.i.d. OS, day before and after	17.7	15.3	Null	125±65
Durham[11]	79	RPCT	1.6±0.7	1200 mg b.i.d. OS, 1 h before and 3 h after	26.3	22	Null	81±39
Webb[12]	447	BRPCT	2.2±0.4	500 mg i.v., 1 h before	7.3	5.7	Null	120 (80–175)[a]
Boccalandro[13]	181	CT	1.8±0.5	600 mg b.i.d. OS day before and after	13	12	Null	191±130
Goldenberg[14]	80	BRPCT	2.0±0.4	600 mg b.i.d. OS day before and after	10	8	Null	116±45
Oldemeyer[15]	96	BRPCT	1.6±0.7	1500 mg b.i.d. OS, day before and after	8.2	6.4	Null	130±72
Baker[16]	80	RCT	1.8±0.5	150 mg/kg over 30 min immediately before and 50 mg/kg over 4 h	5	21	+	230±158
Miner[20]	180	BRPCT	1.4±0.6	2000 mg OS, one dose before and and two doses after	9.6	22.2	+	347±199

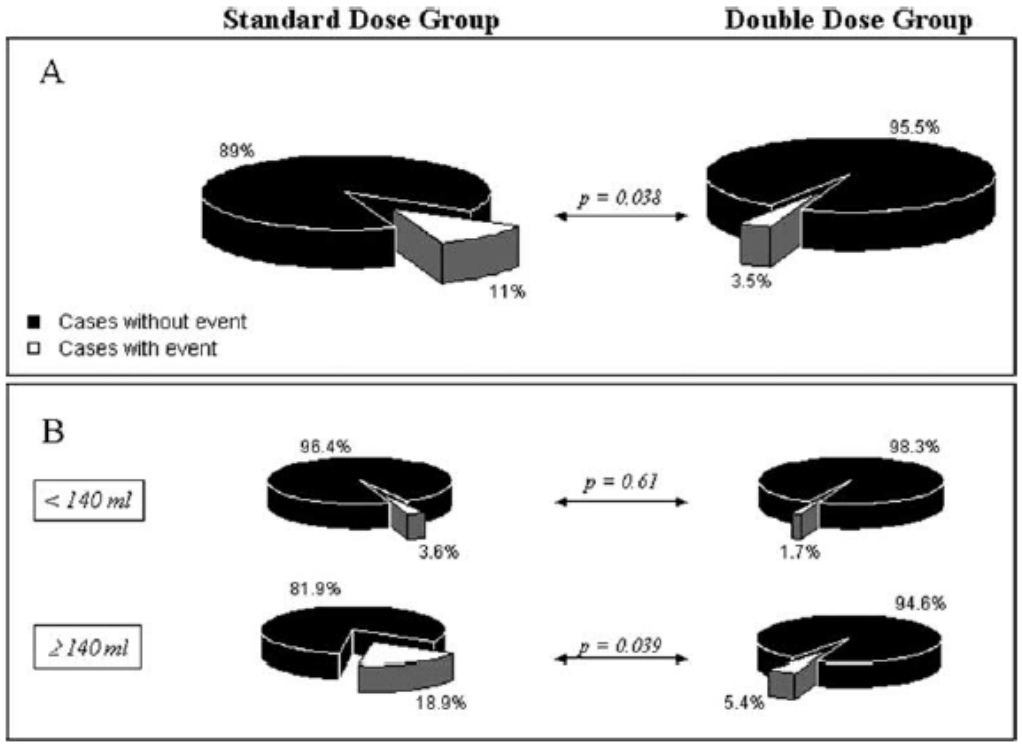
BRPCT=double-blinded, randomized, placebo-controlled trial; RPCT=randomized, placebo-controlled trial; RCT=randomized-controlled trial, placebo-controlled trial; CT=controlled trial; NAC=*N*-acetylcysteine; CIN=contrast-induced nephrotoxicity.
[a]median (interquatile range); sCr=serum creatinine concentration.

Kidney Int Suppl, 2006(100): p. S30-8.

Antioxidant: N-acetylcysteine

- RCT, 274 pts (Cr ≥ 1.5 mg/dl or Ccr ≤ 60 ml/min/1.73m2)

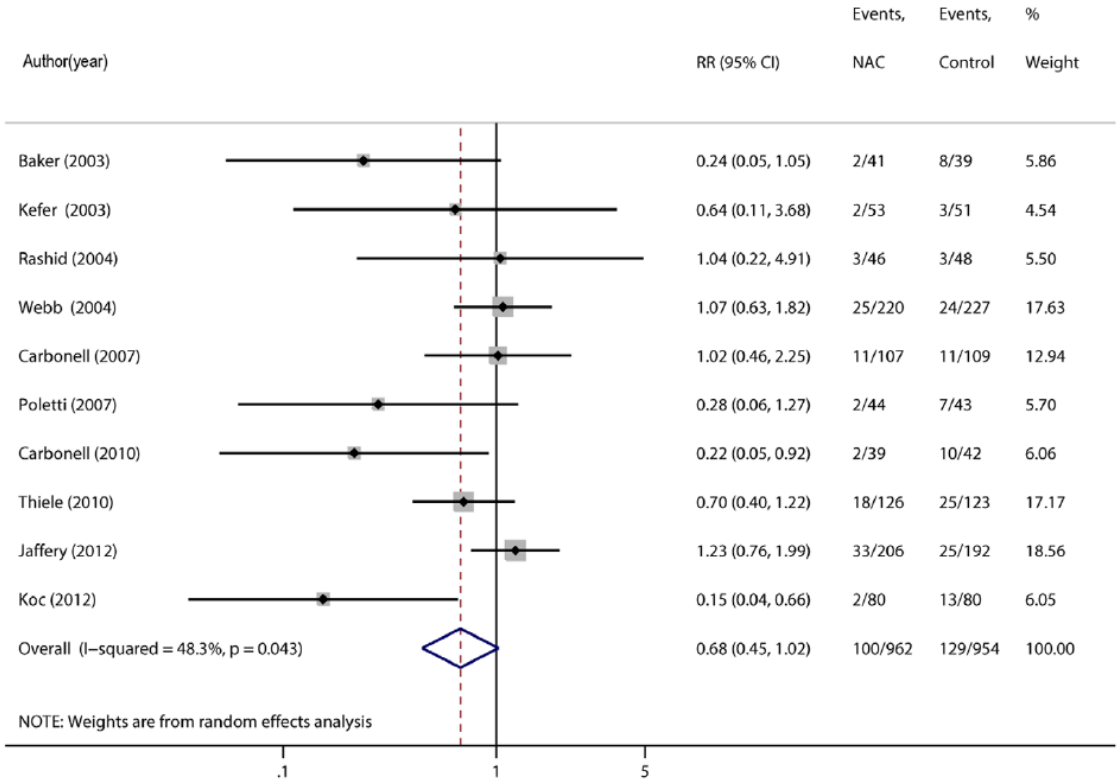
Standard dose (600mg bid)+0.45% Saline vs. **Double dose (1200 mg bid)**+0.45% Saline



Eur Heart J, 2004. **25**(3): p. 206-11.

Antioxidant: N-acetylcysteine (IV)

- Bioavailability of oral NAC is low, ranging from 4% to 10%, as a result of first-pass hepatic metabolism, suggests that only a small proportion of the administered dose is available for renal protection



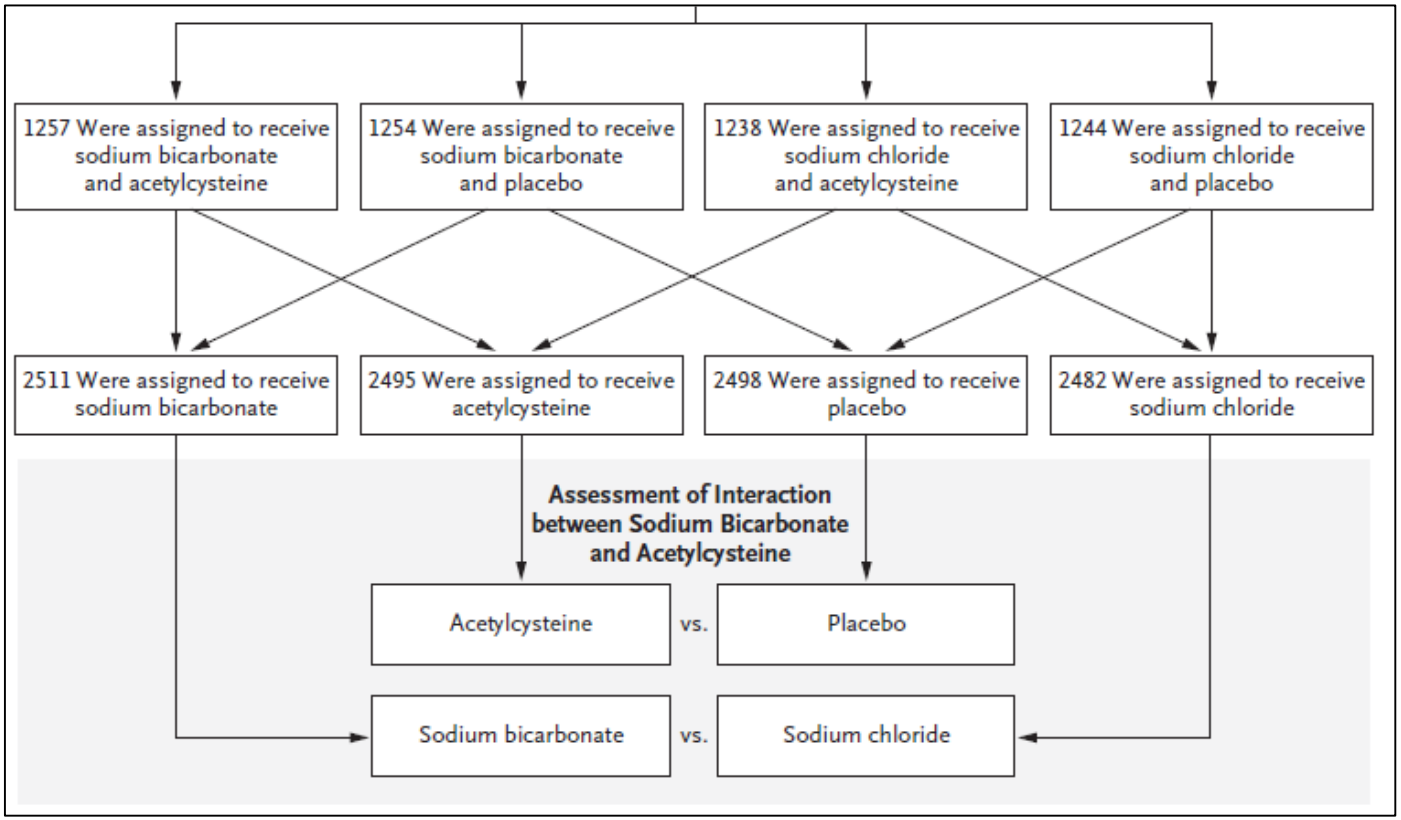
- IV N-acetylcysteine and the incidence of CIN is too inconsistent at present to warrant a conclusion on efficacy.

PLoS One, 2013. 8(1): p. e55124.

PRESERVE trial: No added benefit of bicarbonate or NAC over saline

- RCT, 5177 pts (decreased eGFR [15 – 45] or decreased eGFR [45-60] with DM)

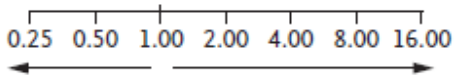
2 x 2 factorial design



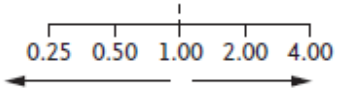
N Engl J Med, 2018. 378(7): p. 603-614.

PRESERVE trial: No added benefit of bicarbonate or NAC over saline

Subgroup	Total No.	Sodium Bicarbonate vs. Sodium Chloride: Odds Ratio (95% CI)	P Value	Acetylcysteine vs. Placebo: Odds Ratio (95% CI)	P Value
Contrast-Associated Acute Kidney Injury					
All patients	4993	1.16 (0.96–1.41)		1.06 (0.87–1.28)	
Estimated GFR			0.27		0.53
<45 ml/min/1.73 m^2	2615	1.28 (0.99–1.67)		1.00 (0.77–1.30)	
45–60 ml/min/1.73 m^2	2377	1.03 (0.77–1.37)		1.13 (0.85–1.51)	
Diabetes			0.99		0.79
Yes	4041	1.17 (0.94–1.44)		1.07 (0.87–1.32)	
No	949	1.16 (0.71–1.92)		1.00 (0.61–1.64)	
Urine ACR			0.40		0.53
<30	1723	1.39 (0.94–2.03)		0.92 (0.63–1.34)	
30–300	1637	0.98 (0.71–1.36)		1.20 (0.87–1.66)	
>300	1155	1.11 (0.77–1.60)		1.00 (0.70–1.44)	
Contrast volume			0.39		0.25
≤125 ml	3525	1.29 (1.01–1.65)		1.03 (0.81–1.32)	
>125 ml	1403	0.97 (0.70–1.34)		1.12 (0.81–1.54)	
Angiography			0.81		0.18
Coronary	4466	1.14 (0.93–1.40)		1.09 (0.89–1.34)	
Noncoronary	471	1.41 (0.75–2.65)		0.85 (0.45–1.58)	
Geographic region			0.51		0.95
United States	4267	1.19 (0.97–1.47)		1.06 (0.86–1.30)	
Australia/New Zealand/ Malaysia	726	0.98 (0.57–1.68)		1.07 (0.63–1.83)	



Sodium Bicarbonate Better | Sodium Chloride Better



Acetylcysteine Better | Placebo Better

N Engl J Med, 2018. 378(7): p. 603-614.

Fact or Myth?

- **AMACING trial**
  - N=603, single center, eGFR: 30~59 ml/min/1.73m^2
  - No benefit of IV saline (2.6%) vs. no saline (2.7%)

		Group size n	Contrast-induced nephropathy incidence n (%) H+ group	H- group	Absolute difference	95% CI
Diabetes	Yes	190	2/94 (2·1)	3/96 (3·1)	1·00	(–2·81 to 4·81)
	No*	413	6/202 (3·0)	5/211 (2·4)	–0·60	(–3·21 to 2·01)
eGFR<45	Yes	210	3/104 (2·9)	2/106 (1·9)	–1·00	(–4·46 to 2·47)
	No	393	5/192 (2·6)	6/201 (3·0)	0·38	(–2·35 to 3·12)
Contrast administration route	IA	289	6/144 (4·2)	6/145 (4·1)	–0·03	(–3·89 to 3·83)
	IV	314	2/152 (1·3)	2/162 (1·2)	–0·08	(–2·17 to 2·00)
Interventional procedure	Yes	92	3/49 (6·1)	1/43 (2·3)	–3·80	(–10·58 to 2·99)
	No	511	5/247 (2·0)	7/264 (2·7)	0·63	(–1·57 to 2·82)
Total population		**603**	**8/296 (2·7)**	**8/307 (2·6)**	**–0·10**	**(–2·25 to 2·06)**

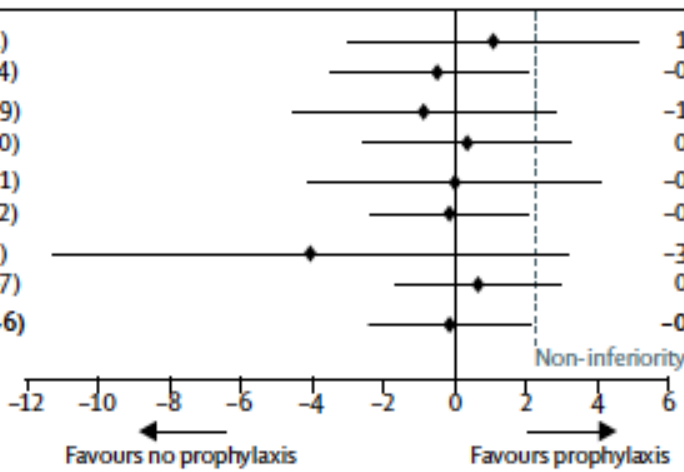


Figure 2: **Incidence of contrast-induced nephropathy in the total study population and by patient subgroup**

The Lancet, 2017. **389**(10076): p. 1312-1322.

BASIC trial: balanced plasma solution vs. saline

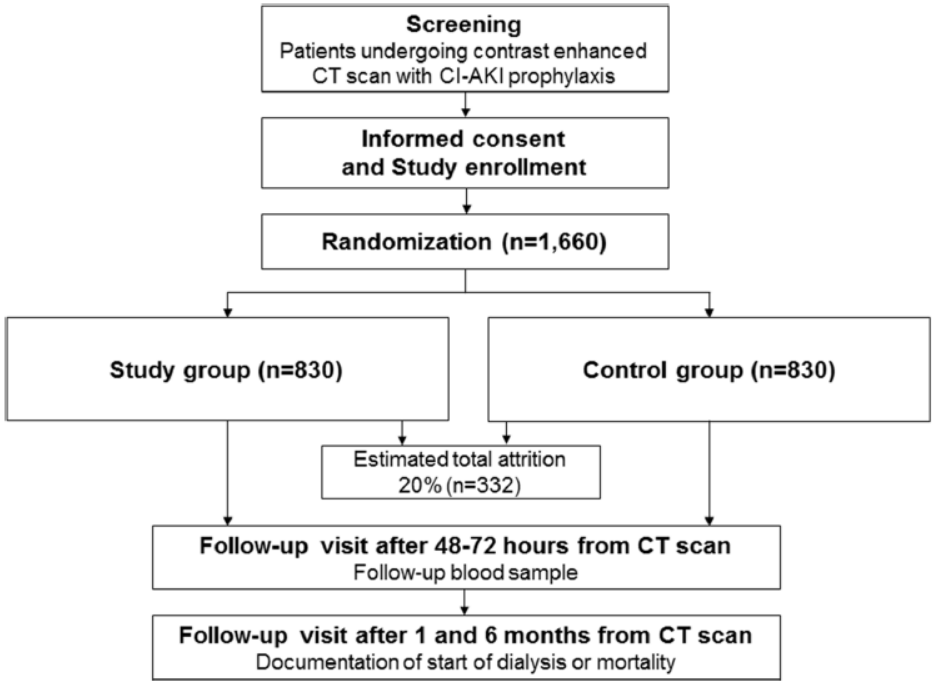


Table 1 Components of the two fluids used in the study

	0.9% saline	Plasma solution A
Na^+ (mEq/L)	154	140
K^+ (mEq/L)		5
Ca^{2+} (mEq/L)		
Mg^{2+} (mEq/L)		1.5
Cl^- (mEq/L)	154	98
Acetate (mEq/L)		27
Gluconate (mEq/L)		23
Osmolarity (mOsm/L)	308	295
pH	6.0	7.4

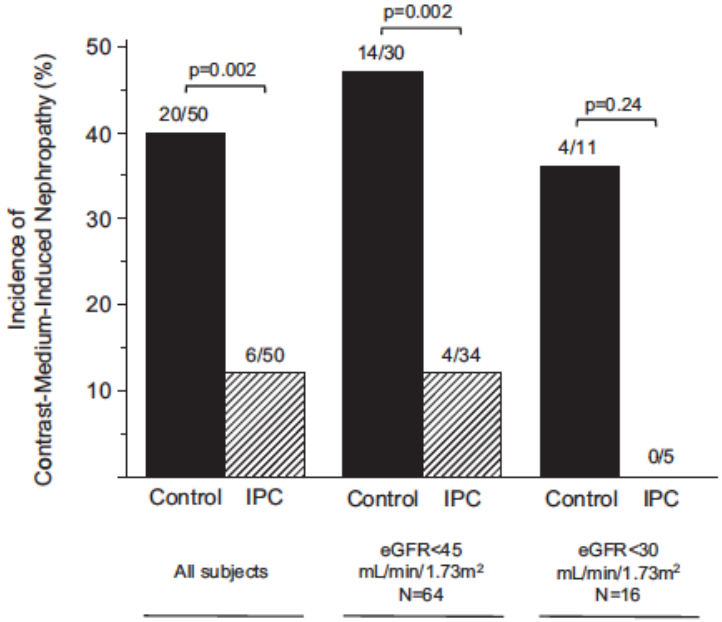
Trials, 2017. 18(1): p. 461.

Other unproven interventions

1. Remote ischemic preconditioning
2. Prophylactic hemofiltration and hemodialysis
3. Withholding ACEis and/or ARBs
4. Statins
5. Control the concomitant drugs

Remote ischemic preconditioning

- RCT, 100 pts (eGFR ≤ 60 ml/min/1.73m^2) , Single center, PILOT study
- RIPC
  - 4 cycles of alternating 5-minute inflation and 5-minute deflation of a standard upper-arm blood pressure cuff to the individual's systolic blood pressure plus 50 mmHg.



Circulation, 2012. **126**(3): p. 296-303.

Prophylactic hemofiltration and hemodialysis

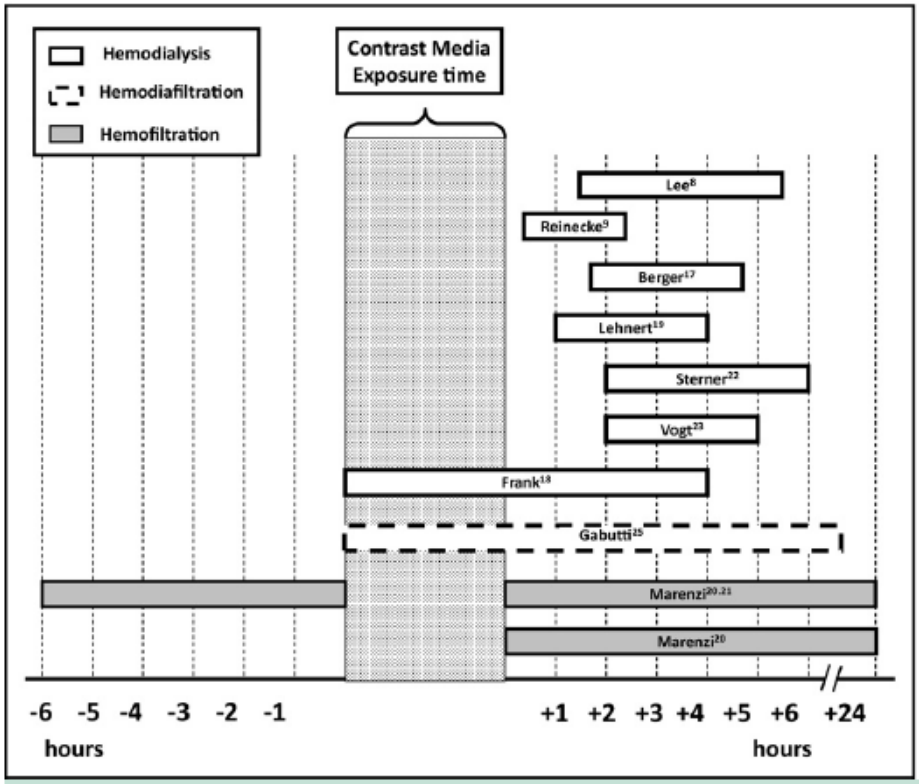
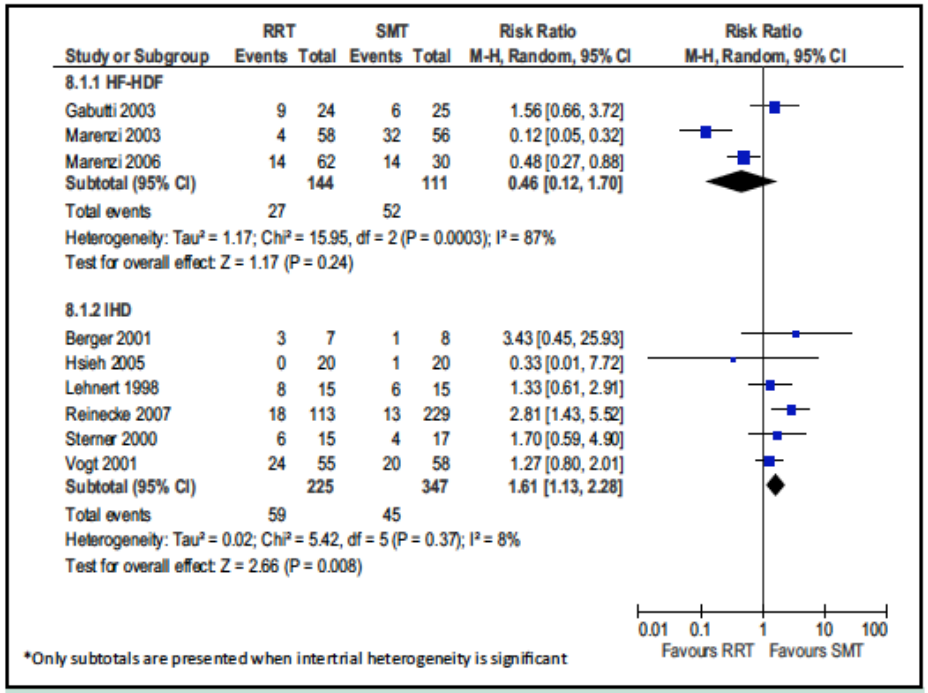


Figure 2 Timing and duration of renal replacement therapy.



Study or Subgroup	RRT Events	RRT Total	SMT Events	SMT Total	Risk Ratio M-H, Random, 95% CI
8.1.1 HF-HDF					
Gabutti 2003	9	24	6	25	1.56 [0.66, 3.72]
Marenzi 2003	4	58	32	56	0.12 [0.05, 0.32]
Marenzi 2006	14	62	14	30	0.48 [0.27, 0.88]
Subtotal (95% CI)		144		111	0.46 [0.12, 1.70]
Total events	27		52		
Heterogeneity: Tau² = 1.17; Chi² = 15.95, df = 2 (P = 0.0003); I² = 87%					
Test for overall effect: Z = 1.17 (P = 0.24)					
8.1.2 IHD					
Berger 2001	3	7	1	8	3.43 [0.45, 25.93]
Hsieh 2005	0	20	1	20	0.33 [0.01, 7.72]
Lehnert 1998	8	15	6	15	1.33 [0.61, 2.91]
Reinecke 2007	18	113	13	229	2.81 [1.43, 5.52]
Sterner 2000	6	15	4	17	1.70 [0.59, 4.90]
Vogt 2001	24	55	20	58	1.27 [0.80, 2.01]
Subtotal (95% CI)		225		347	1.61 [1.13, 2.28]
Total events	59		45		
Heterogeneity: Tau² = 0.02; Chi² = 5.42, df = 5 (P = 0.37); I² = 8%					
Test for overall effect: Z = 2.66 (P = 0.008)					

Figure 3 Risk for radiocontrast-induced nephropathy: renal replacement therapy (RRT) vs standard medical therapy, by RRT modality. CI = confidence interval; HD = hemodialysis; HDF = hemodiafiltration; HF = hemofiltration; SMT = standard medical therapy.

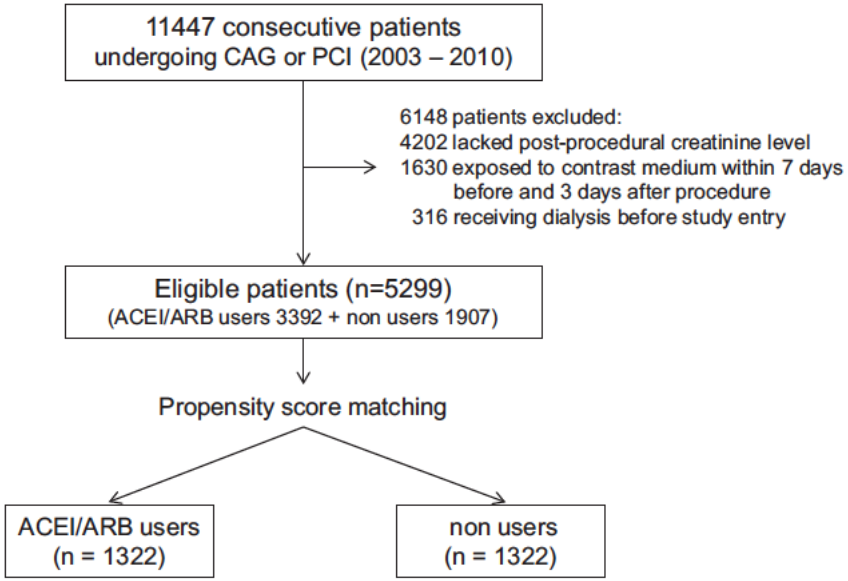
Am J Med, 2012. **125**(1): p. 66-78.e3.

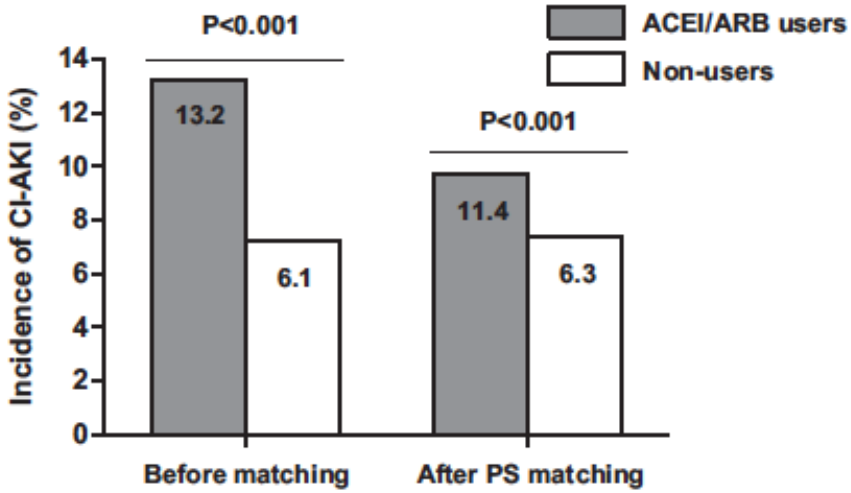
Withholding ACEis and/or ARBs

AJKD
Original Investigation

The Effect of Renin-Angiotensin-Aldosterone System Blockade on Contrast-Induced Acute Kidney Injury: A Propensity-Matched Study

Min Young Rim, MD,[1] Han Ro, MD, PhD,[1]* Woong Chol Kang, MD, PhD,[2]*
Ae Jin Kim, MD,[1] Hyeonsu Park, MD,[1] Jae Hyun Chang, MD,[1] Hyun Hee Lee, MD,[1]
Wookyung Chung, MD, PhD,[1] and Ji Yong Jung, MD, PhD[1]



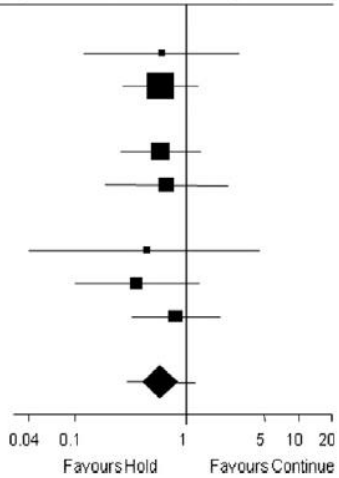


Am J Kidney Dis, 2012. **60**(4): p. 576-82.

Withholding ACEis and/or ARBs

- CAPTAIN trial
  - RCT
  - N=106 pts (Cr ≥ 1.5 mg/dL)

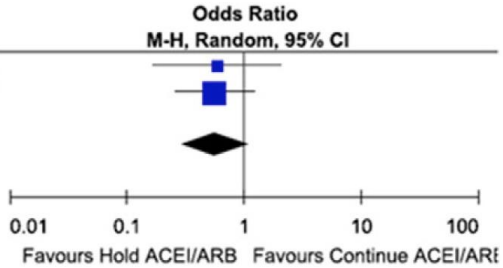
	Patient#	Event Rate (%) Continue	Event Rate (%) Hold	Risk Ratio (95% CI)
Age				
<65Yr	40	18.2	11.1	0.61[0.12,2.96]
>=65Yr	159	18.4	10.8	0.59[0.27,1.28]
Diabetes				
Yes	109	22.8	13.5	0.59[0.26,1.37]
No	90	12.2	8.2	0.67[0.19,2.33]
Mehran risk score				
0-5	40	10.6	4.8	0.45[0.04,4.60]
6-10	74	19.4	7.0	0.36[0.10,1.33]
>10	80	21.7	17.7	0.81[0.33,2.02]
Total	208	18.4	10.9	0.59[0.30,1.19]



Risk ratios for the primary end point in prespecified subgroups.

Study or Subgroup	Hold ACE/ARB Events	Hold ACE/ARB Total	Continue ACE/ARB Events	Continue ACE/ARB Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Rosenstock 2008	4	107	7	113	27.8%	0.59 [0.17, 2.07]	2008
Bainey 2013	12	106	19	102	72.2%	0.56 [0.26, 1.22]	2013
Total (95% CI)		**213**		**215**	**100.0%**	**0.57 [0.29, 1.10]**	
Total events	16		26				

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (*P* = 0.94); I² = 0%
Test for overall effect: Z = 1.68 (*P* = 0.09)



Meta-analysis of holding vs continuing ACEI/ARB prior to cardiac catheterization in patients with preexisting renal insufficiency.

Am Heart J, 2015. **170**(1): p. 110-6.

Statins

- PRATO-ACS trial
  - RCT, single center, N=543 pts (excluded patients with Cr ≥ 3 mg/dL)
  - Rosuvastatin (40 mg on admission, followed by 20 mg/day) vs. No Tx.

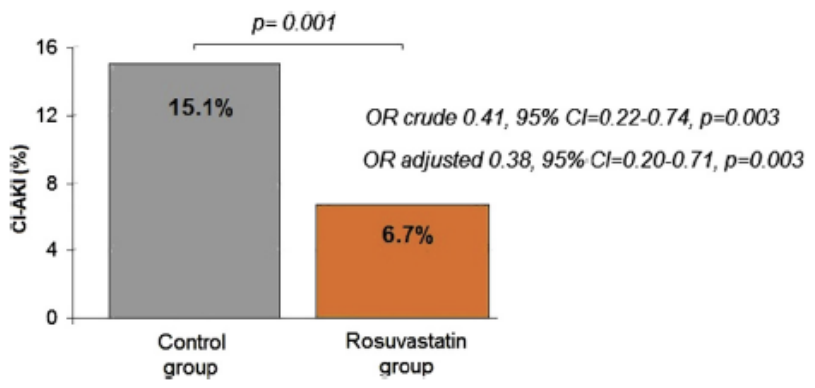


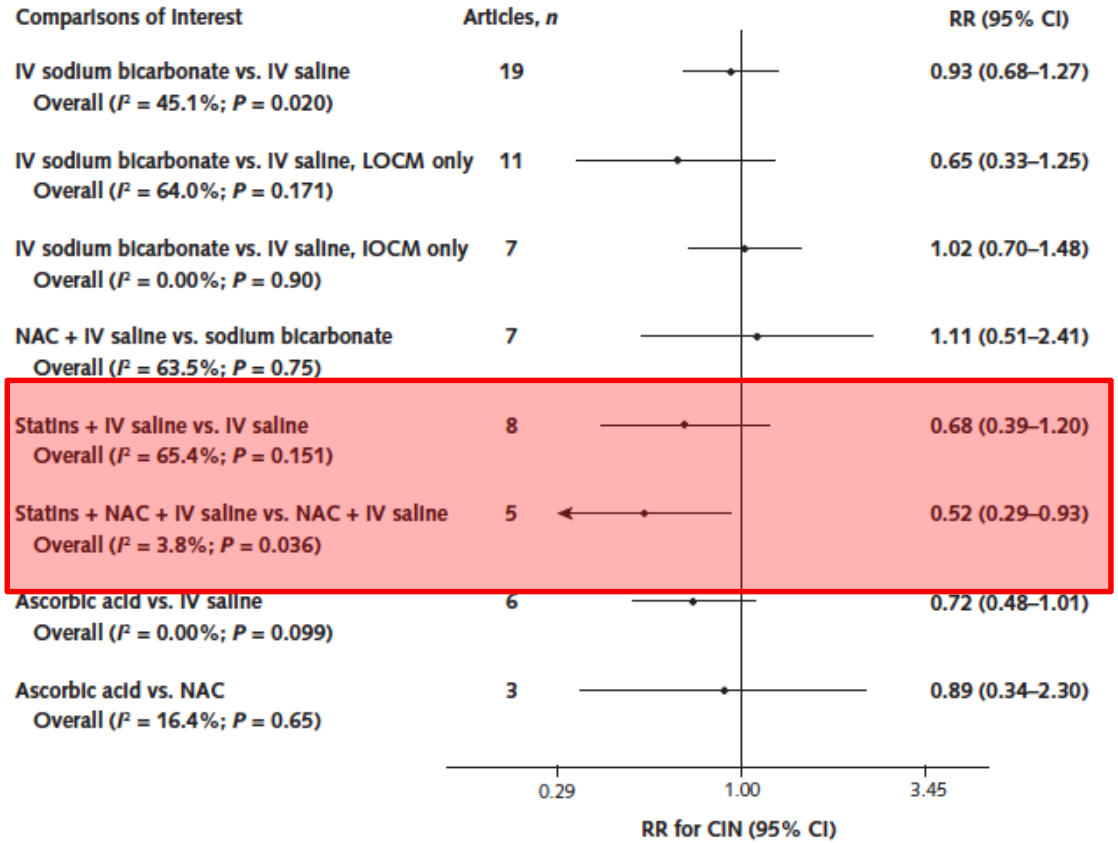
Figure 2 **Incidence of Contrast-Induced Acute Renal Injury**

Primary endpoint occurrence (increase in serum creatinine concentration of ≥0.5 mg/dl or ≥25% over baseline within 72 h) in the 2 study groups. CI = confidence interval; CI-AKI = contrast-induced acute renal injury; OR = odds ratio.

J Am Coll Cardiol, 2014. **63**(1): p. 71-9.

Statins

- Meta-analyses



Ann Intern Med, 2016. **164**(6): p. 406-16.

Control the use of concomitant drugs

- Vasoconstriction
  - Involving variable vasoactive substance
  - PGs, ANP, Adenosine, Endothelin, Vasopressin, Angiotensin
- Renal hemodynamics and tubular glomerular feedback
  - NSAIDs, COX-2 inhibitors
  - ACEi / ARB
  - Renal dose dopamine
- Direct tubular toxicity
  - Diuretics, mannitol, aminoglycosides, vancomycin, tacrolimus, CsA, Amphotericin B
- Drugs that might enhance their toxicity after exposure of contrast
  - Metformin, Statin

Am Heart J, 2015. **170**(1): p. 110-6.

Practical recommendations

Practical Recommendations

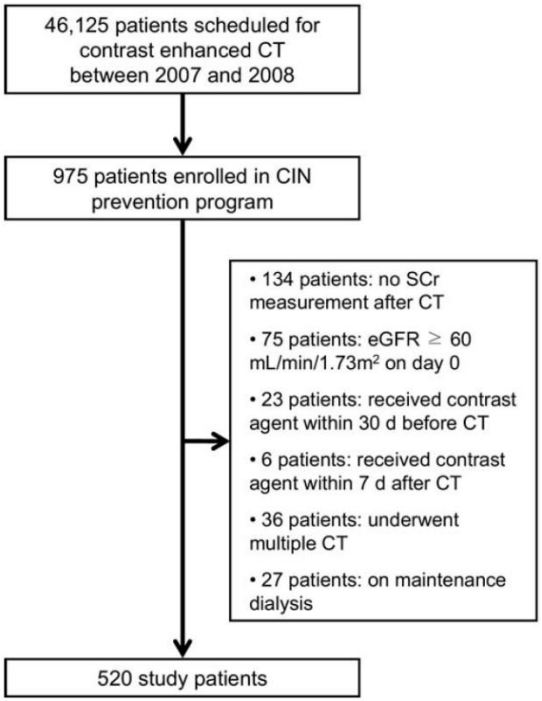
Contrast-Induced Acute Kidney Injury (CIAKI, CIARF, CIN) (*Mayo* 2009;84:170, *Kidney Int* 2006;69S100:11S, *Circ 2010;122:2451, NEJM 2006;354:379)*

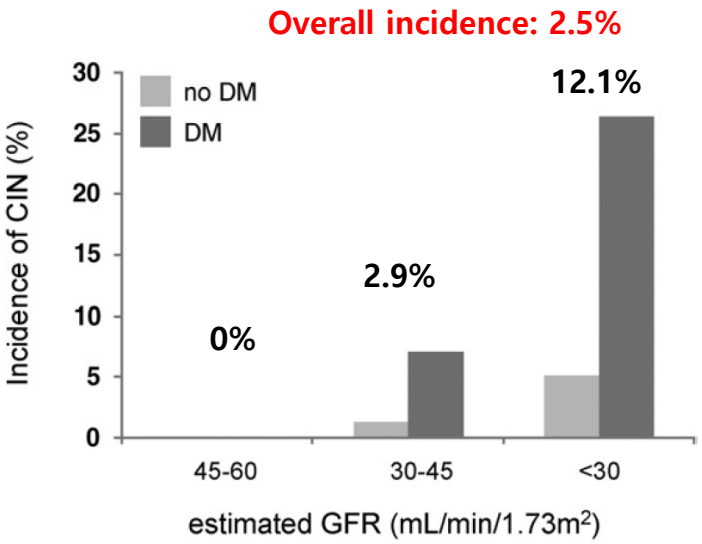
- **Definition**: ↑Cr ≥ 0.5 or 25% within 48-72h of contrast without other causes.
- **Clinical syndrome:** starts 24-48hr**, peaks 3-5d**, resolves 10d; FENa usually <1% but can be normal or high. Usually non-oliguric. **Pathophysiology**: 1) vasoconstriction → medullary hypoxia; 2) direct tubular osmolar toxicity 3) free radical-mediated damage.
- **Risk Stratification:** Renal perfusion key (diuresis and NSAIDs ↑risk)
  - Other risk factors include: CKD, CHF, female, and contrast dose
  - Risk of venous contrast in ICU patients may be very low (CCM 2013; 41)
- **Prevention:** Consider alternate imaging (ultrasound, MRA w/ time of flight, I-CT)
  - Minimize contrast volume and osmolarity
  - Avoid volume depletion or ↓EABV (hold NSAIDs, ACEI, ARB, diuretics in most cases) (*NDT* 2010;25:759; AJKD 2012;60;576)
- **Prophylaxis** (*NEJM* 2000;343:180; *Lancet* 2003;362:598)
  - Hydration: isotonic $NaHCO_3$ (D5W + 150mEq HCO3/L is either equivalent or slightly better than NS) (*JAMA 2008;300:1038*, *Annals* 2009;151:631)
    - **Isotonic $NaHCO_3$ 3 mL/kg/h x 1h before, 1 mL/kg/h during & 6h post (Merten Protocol,** *JAMA* 2004; 291:2328**) or 1ml/kg for 6-12 hrs pre and post procedure**
    - If EF <40%, decrease rate by half; hold IVF if in decompensated CHF. If in overt HF, diuresis may improve perfusion and optimize risk.
    - Should also encourage PO intake if no contraindications (*PLoS One* 2013;8(3):e60009)
  - N-acetylcysteine: most studies/meta-analyses suggest possible benefit and no harm (*NEJM 2006;354:2773*)
    - **Administer NAC 1200 mg PO bid x 4 (2 pre, 2 post contrast)** (*JACC* 2010;55:2201)
    - **ACT trial** showing no benefit of PO NAC was not in highest risk pt groups (<50% of pts with Cr > 1.5) (*Circ* 2011;124:1250)
    - Do not use IV NAC even if cannot give PO—risk of anaphylactoid reactions outweighs any benefit (*Am Heart J* 2004;148:422)
  - Statins: early evidence suggest statins protective against CIN, esp. in low risk pts with normal renal function and those with only mild renal impairment, but not yet standard of care. Pravastatin > Simvastatin (*J Cardio Pharm Ther* 2011;16(3-4):376; *J Pharm Sci* 2013; 16(4):588)
  - Prophylactic hemofiltration/hemodialysis: usually applies to very high risk patients, and is controversial.
    - An early study suggested benefit (*NEJM* 2003;349:1333). But most evidence suggests that hemofiltration is **not beneficial**, and that HD may be harmful. Recommend discussion with patient's nephrologist. (*Am J Med* 2012;125:66 and *AJKD* 2006;48:361)

CIN Risk Score		Points
Hypotension (SBP < 80 x 1h, req inotrope)		5
IABP (within 24h after procedure)		5
CHF (NYHA III and IV)		5
Age >75		4
Anemia: Hct male <39, female <36		3
Diabetes		3
Contrast volume		1/100cc
Serum Cr. >1.5		4
MDRD eGFR	<20 / 20-30 / 40-60	6 / 4 / 2
Risk Score	**Risk of CIN**	**HD risk**
0 to 5	7.5 %	0.04%
6-10	14.0 %	0.12%
11-16	26.1%	1.09%
>16	54.3%	12.6%

Incidence and Outcomes of Contrast-Induced Nephropathy After Computed Tomography in Patients With CKD: A Quality Improvement Report

Sun Moon Kim, MD,[1] Ran-hui Cha, MD,[1] Jung Pyo Lee, MD,[1] Dong Ki Kim, MD,[1] Kook-Hwan Oh, MD, PhD,[1] Kwon Wook Joo, MD, PhD,[1] Chun Soo Lim, MD, PhD,[1,2] Suhnggwon Kim, MD, PhD,[1,2] and Yon Su Kim, MD, PhD[1,2]





Am J Kidney Dis, 2010. **55**(6): p. 1018-25.

Summary

- Patients with near-normal renal function are at low risk for CI-AKI.
- Procedures involving intra-arterial contrast are higher risk than those involving intravenous contrast.
- Patients at risk

Preventive Strategies for CIN			
eGFR	**Stage of Kidney Function**	**Risk of CIN**	**Prophylaxis**
> 60 ml/min	1 and 2	Very low risk	None required
45 to 59 ml/min	3a	Low risk	In the absence of additional risk factors, no specific prophylaxis is required unless patients are receiving intra-arterial contrast
30 to 45 ml/min	3b	Moderate risk	Intravenous or oral hydration is recommended for patients receiving intra-arterial contrast
< 30 ml/min	4 and 5	High risk	Careful intravenous hydration with close monitoring for fluid overload is important

Summary

- Preventive strategies for all at-risk patients
  - IOCA or Non-ionic LOCA
  - Lower dose of contrast and avoid repetitive (< 48 hrs apart)
  - Avoid volume depletion and NSAIDs
  - **Volume supplementation** (isotonic saline rather than bicarbonate)
    - Outpatients: from 1hr before (3 ml/kg/hr) and during and for 4~6 hrs after (1~1.5 ml/kg/hr)
    - Inpatients: from 6~12hrs before and after (1 ml/kg/hr)
  - NAC
    - Not be given either PO or IV (inconsistent)

Summary

- Control the concurrent comorbidities and drugs
  - ACEi/ARB: withholding (CCB is alternative for BP control)
  - Diuretics: withholding in case of dehydration/hypotension
  - Mannitol: withholding several hours before and after / risk-benefit
  - Metformin/Statin: risk-benefit
  - Aminoglycoside: dose-reduction
  - Liposomal amphotericin B: risk-benefit

Take Home Messages

Automated Detect → Alert ! → Preventive strategies


Thank You
for your attention !