55th Annual Scientific Meeting of The Korean Society of Cardiology

11:50 – 12:10

Dec 03, 2011

Message from Nephrologists

Prevention of Contrast induced Nephropathy

Soo Wan Kim, MD, PhD

Department of Internal Medicine,
Chonnam National University Medical School

Contrast-induced AKI

1) **Definition**
2) Pathogenesis
3) Risk Factors
4) Prevention of Contrast-induced AKI
   - Radiocontrast agents
   - Hydration
   - Hemodialysis
   - N-Acetylcysteins
5) Recommendations

Definition

- Not yet well defined
- Commonly used definition:

  Increase in serum creatinine of ≥ 0.5 mg/dl or

  increase of ≥ 25% above baseline

  within 48-72 hr after exposure of contrast media

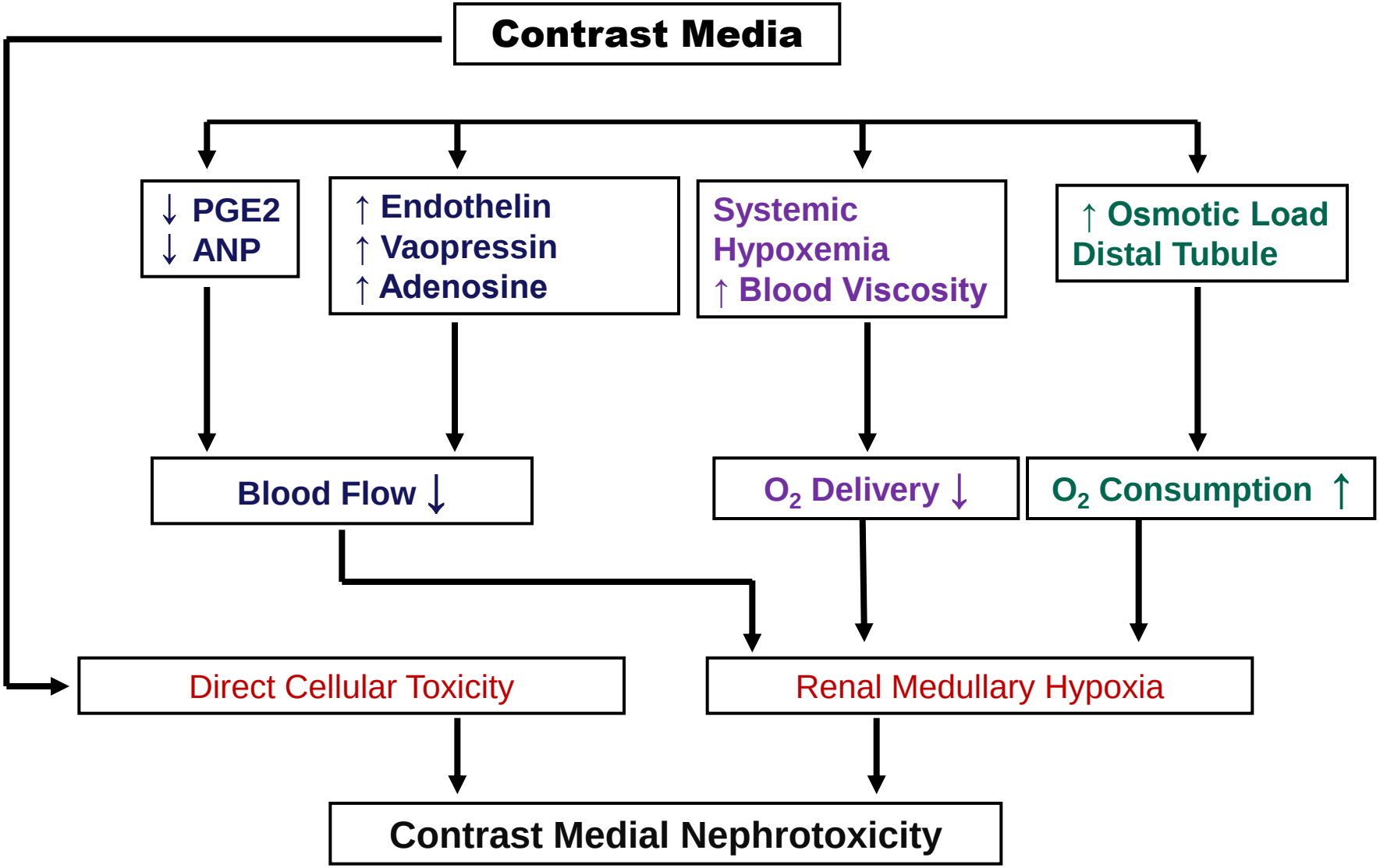
Clinical Courses

- In almost all cases, the decline in renal function is mild and transient and of little clinical importance.
- Increase in serum Cr within 24-48 hr
- Peak in serum Cr within 48-72 hr
- Recovery in serum Cr within 7-10 days

Pathogenesis for Contrast-induced AKI

The two major theories:

1. **Vasoconstriction-induced renal medullary ischemia**
2. **Direct toxic damage to renal tubular epithelial cells**



Heyman S et al. Exp Nephrol 1994;2:153

Incidence of Contrast-Induced Nephropathy Depending on Additional Risk Factors

Previously unimpaired renal function and no risk factor:	≤1%
Diabetes and serum creatinine > 1.7 mg/dl; LOCM/HOCM (Parfrey et al)	9%
Diabetes and creatinine ≥1.35mg/dl ; LOCM (Barrett et al)	13%
Serum creatinine ≥1.5 mg/dl; LOCM (Lautin et al)	18%
Serum creatinine ≥1.2 mg/dl, 75ml of LOCM (Tepel et al)	21%
Diabetes and mean serum creatinine of 2.6 mg/dl HOCM (Weisberg et al)	43%
Diabetes and mean serum creatinine of 5.9 mg/dl LOCM (Manske et al)	51%

Huber W et al, Invest Radiol 2002; 37:471-481

Risk Factors for Contrast-induced AKI

Patient related

- Chronic Kidney Disease
- Diabetes + CKD
- Multiple myeloma
- Volume depletion
- Hypotension
- Anemia
- Low cardiac output
- Class IV CHF
- Concomitant nephrotoxins

Procedure related

- Multiple contrast injections within 72 hrs
- Intra-arterial injection site
- Volume of contrast media
- Type of contrast media (Osmolality)
- Prophylactic strategies

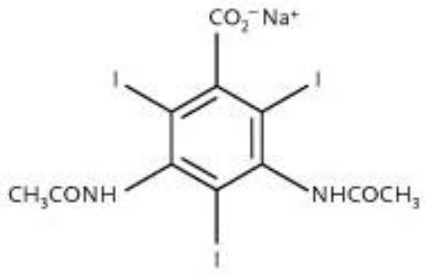
Murphy SW et al, JASN 2000;11:177-182

Contrast-induced AKI

1) Definition
2) Pathogenesis
3) Risk Factors
4) **Prevention of Contrast-induced AKI**
   - **Radiocontrast agents**
   - Hydration
   - Hemodialysis
   - N-Acetylcysteins
5) Recommendations

Radiocontrast Agents

1. **First-generation high-osmolar ionic contrast agents:**
   - **such as metrizamide, diatrizoate, iothalamate meglumine (Conray®)**
   - **1500 – 1800 mOsm / kg**



Radiocontrast Agents

2. **Second-generation low-osmolar agents:**

nonionic monomers:

- **such as**

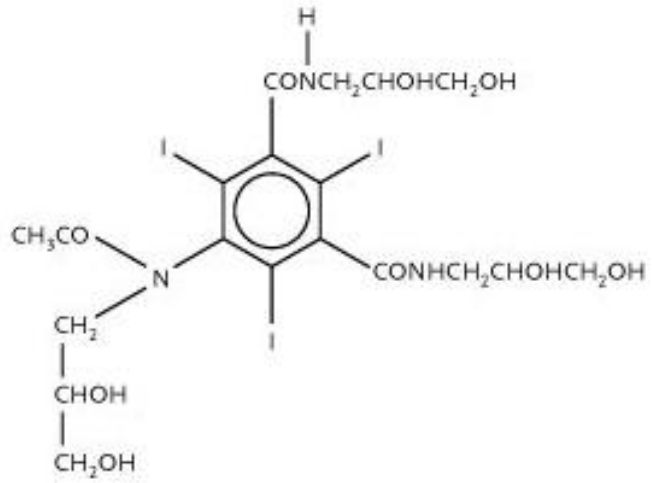
iohexol (Omnipaque®, Omnihexol®, Iobrix®),

iopamidol, iopromide (Ultravisit®),

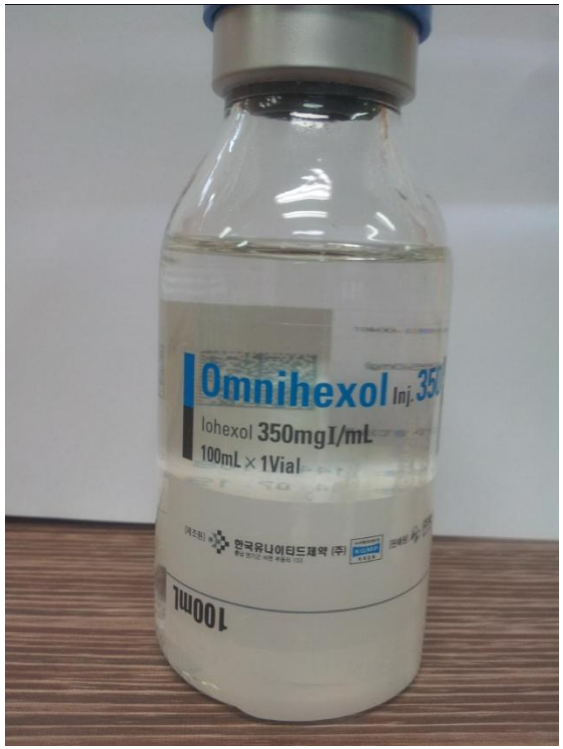
ioversol (Optiray®), gadodiamide, gadoteoridol

ionic dimer: - ioxaglate meglumine

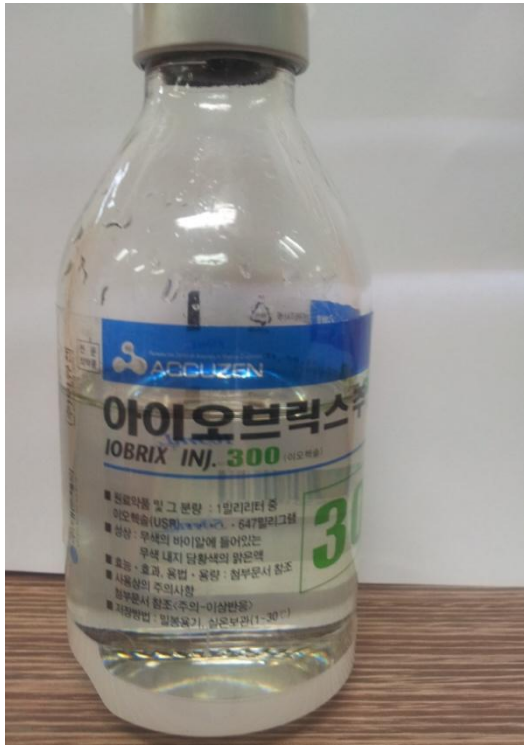
- **600 – 850 mOsm / kg**



2. Second-generation low-osmolar agents:



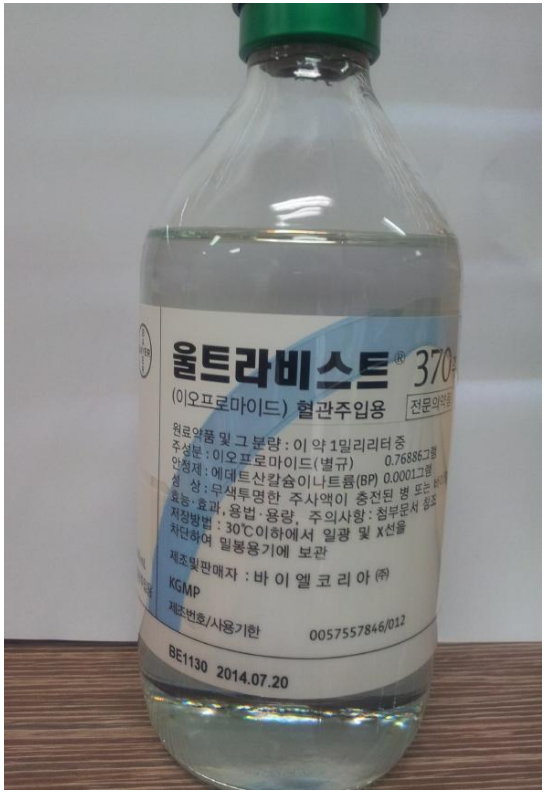
iohexol (Omnihexol®)



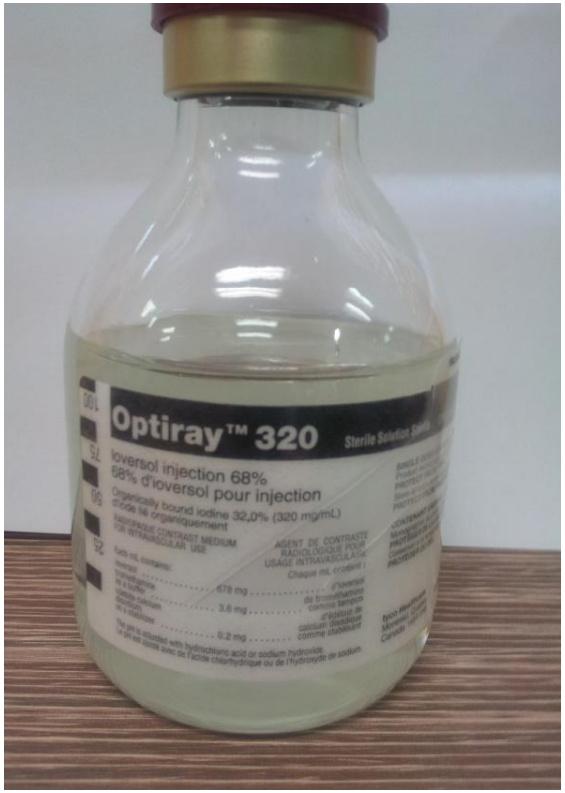
iohexol (Iobrix®)

iohexol (Omnipaque®)

2. Second-generation low-osmolar agents:



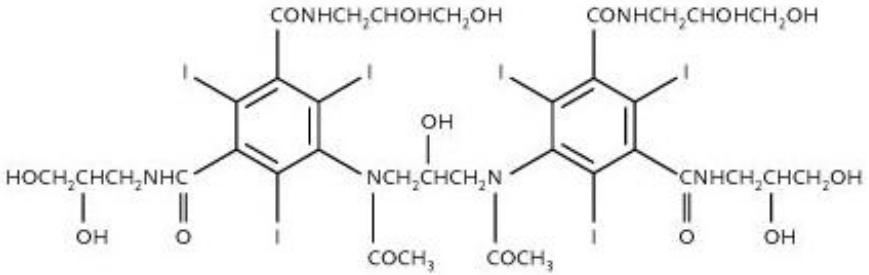
iopromide (Ultravisit®)

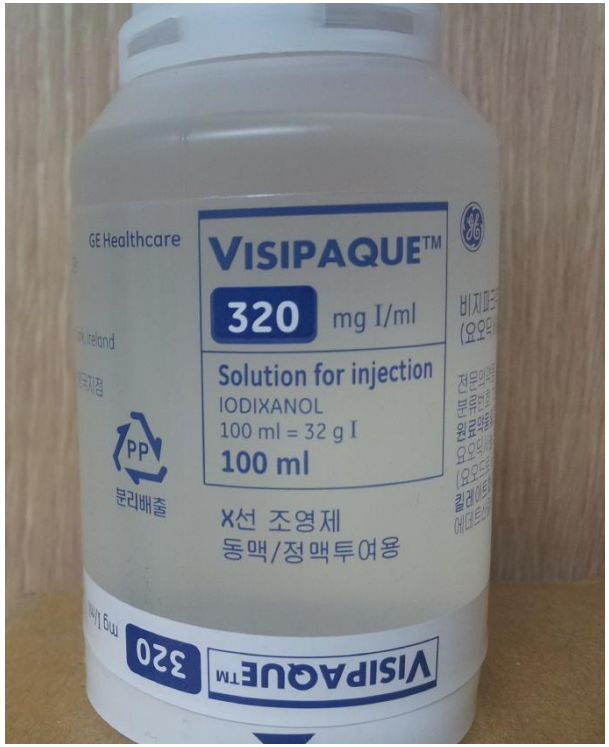


ioversol (Optiray®)

Radiocontrast Agents

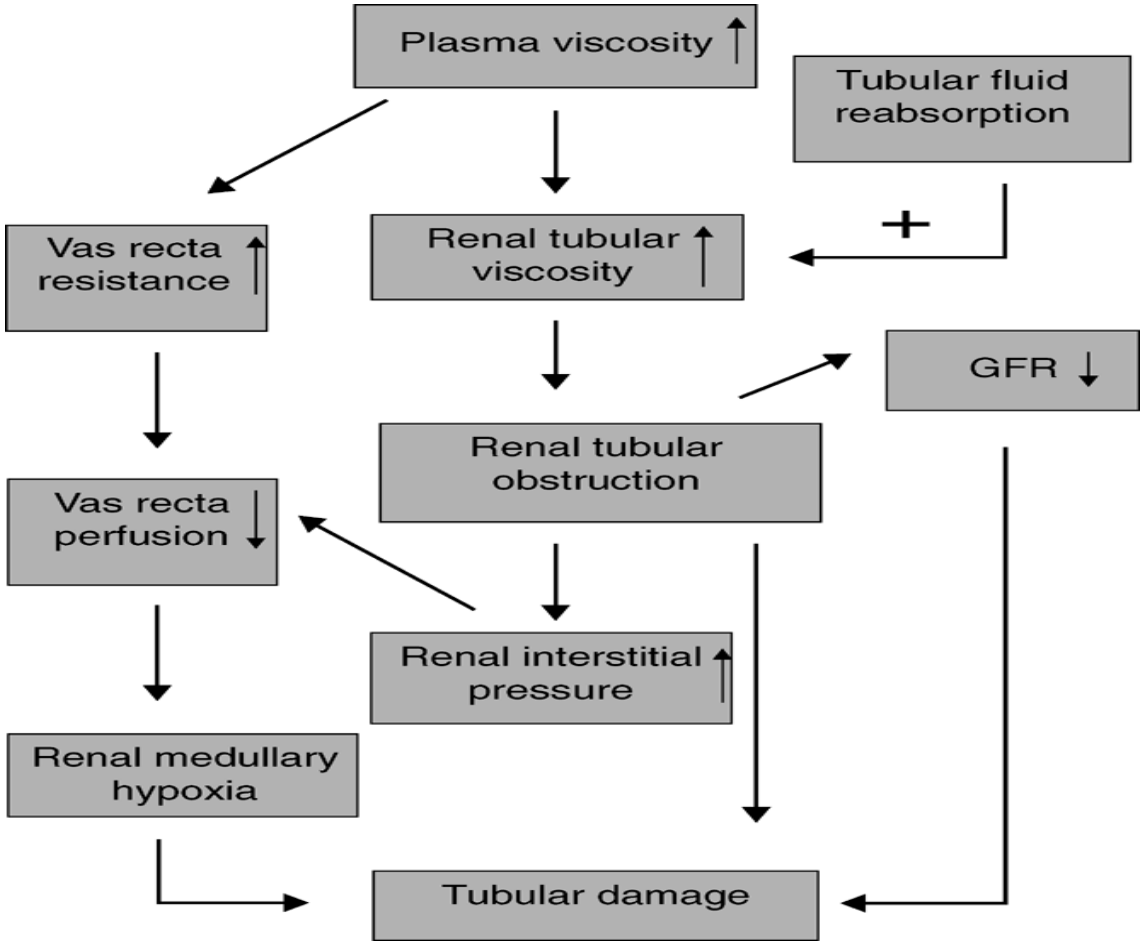
3. **Third-generation iso-osmolar nonionic dimer:**
   - **such as iodixanol (Visipaque®)**
   - **290 mOsm / kg**
   - **Lower osmolality than "low osmolal" second generation drugs**





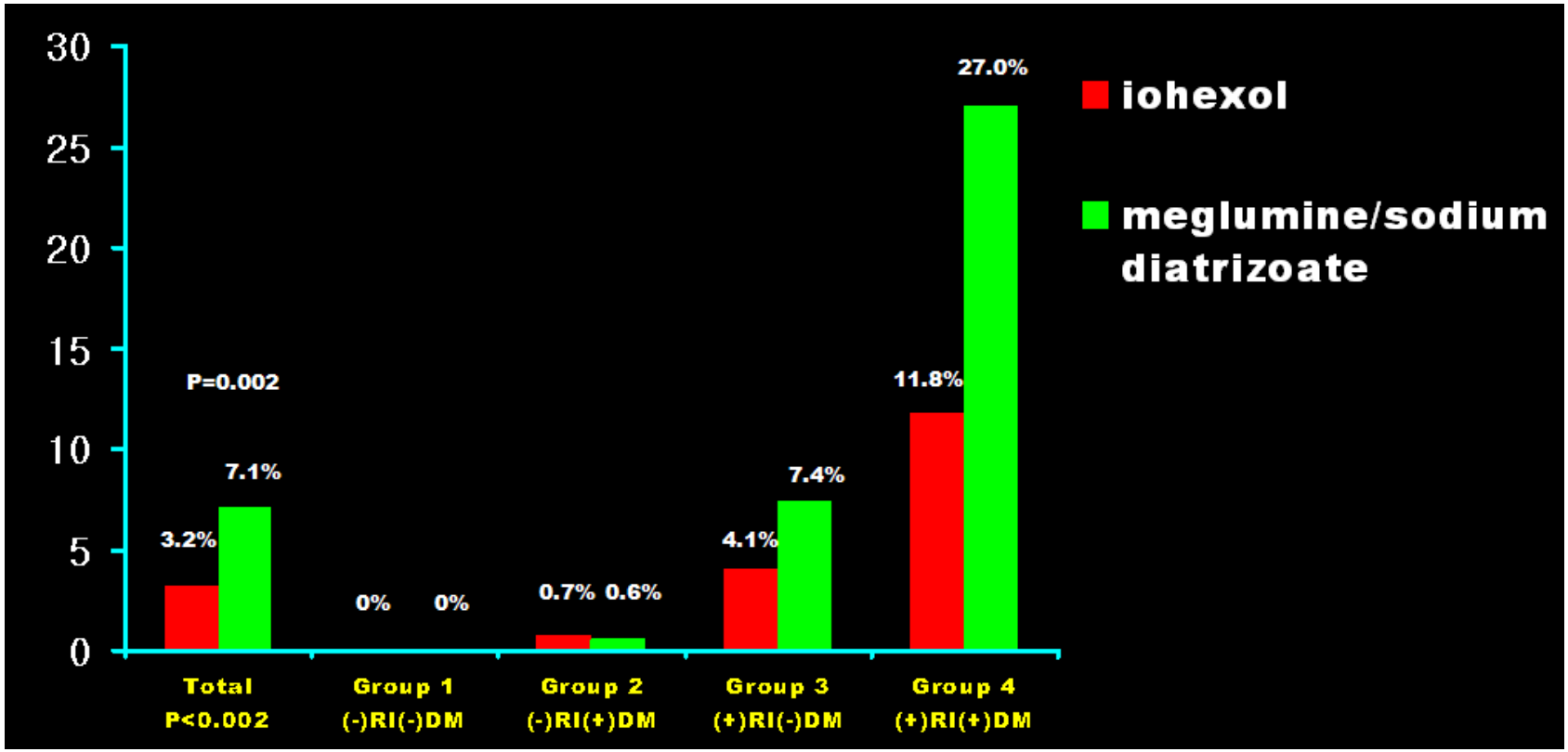
iodixanol (Visipaque®)

Mechanisms linking fluid osmolality to renal damage



Persson PB et al. Kidney Int 2005;68: 14-21

% of patients who developed nephrotoxicity following cardiac angiography



Nephrotoxicity is defined as increase in serum creatinine of ≥ 1.0 mg/dl from baseline (0 hour) within 48 to 72 hours after contrast administration.

Rudnick MR et al, Kidney Int 1995; 47: 254-261

LOCM (iomeprol) vs. IOCM (iodixanol)

randomized 324 patients with CKD undergoing coronary angiography

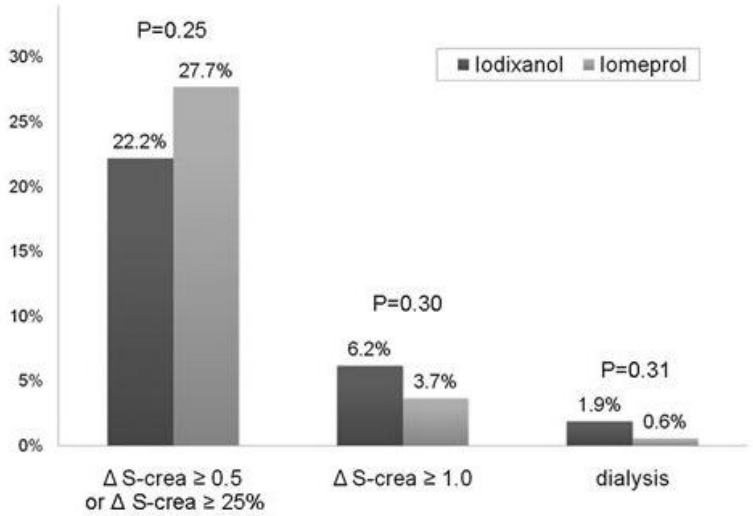


Figure 3. CIN associated with the use of iodixanol (black bars) or iomeprol (gray bars). The incidence of CIN as defined as a increase of *S*-creatinine of >0.5 mg/dL or >25% of the value before contrast exposure is shown on the left. The bars in the center display the incidence of severe CIN as defined as a increase of *S*-creatinine of ≤1 mg/dL. The bars on the right reveal the rate of dialysis that was required subsequent to PCI.

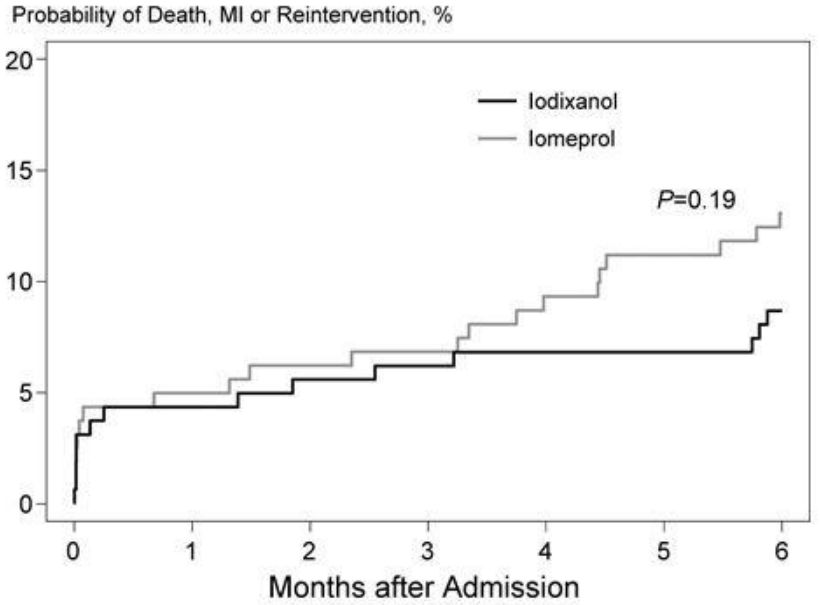


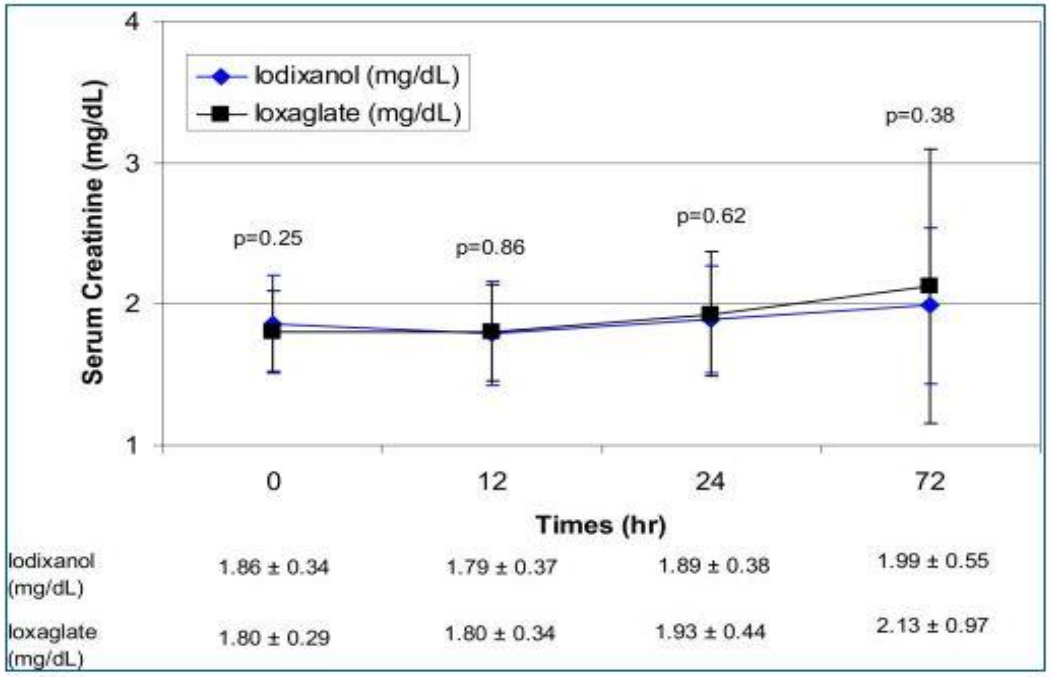
Figure 5. Kaplan–Meier curves showing the incidence of major adverse coronary events during the 6-month follow-up.

rates of CIAKI were not different between the two groups (22.2% with iodixanol vs. 27.8% with iomeprol)

Wessely R et al.Circ Cardiovasc Interv 2:430-437, 2009

LOCM (ioxaglate) vs. IOCM (iodixanol)

- **ICON study in high risk patients (CKD)**
  - **Randomized, multicenter trial**
  - **Comparing iodixanol to ioxaglate**
  - **146 patients with moderate CKD undergoing CAG**

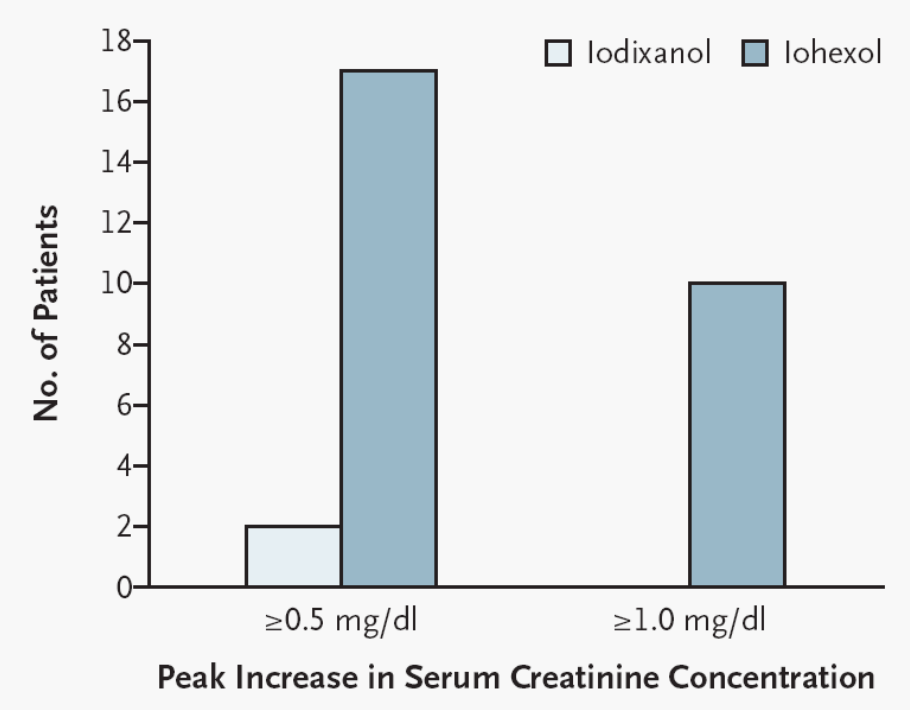


	0	12	24	72
Iodixanol (mg/dL)	1.86 ± 0.34	1.79 ± 0.37	1.89 ± 0.38	1.99 ± 0.55
Ioxaglate (mg/dL)	1.80 ± 0.29	1.80 ± 0.34	1.93 ± 0.44	2.13 ± 0.97

Mehran R et al. JACC Cardiovasc Interv 2:415-421, 2009

LOCM (iohexol) vs. IOCM (iodixanol)

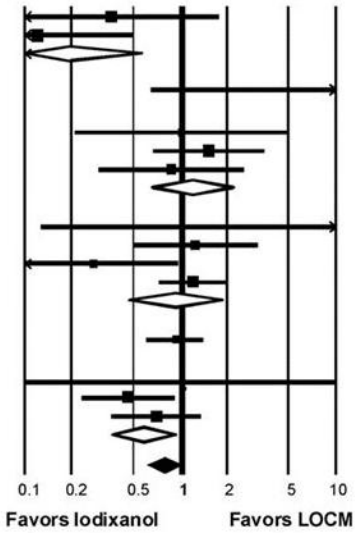
- **Randomized, double blind, prospective multicenter trial**
  - **Comparing iodixanol to iohexol**
  - **129 patients with diabetes with moderate CKD undergoing angiography**



Aspelin P et al, NEJM 2003; 348:491-499

Meta-analysis: LOCM vs. IOCM (iodixanol)

Type of LOCM	Study	Year	RR	95% CI		p-Value
	Chalmers	1999	0.36	0.07	1.75	0.203
	NEPHRIC	2003	0.12	0.03	0.50	0.003
Iohexol		$I^2 = 0.059\%$	**0.19**	**0.07**	**0.56**	**0.002**
Iomeprol	ACTIVE	2008	**11.60**	**0.65**	**206.14**	**0.095**
		$I^2 = 0\%$				
	IMPACT	2006	1.01	0.21	4.86	0.987
	CARE	2007	1.51	0.67	3.41	0.321
	PREDICT	2008	0.87	0.30	2.52	0.799
Iopamidol		$I^2 = 0\%$	**1.20**	**0.66**	**2.18**	**0.555**
	Carraro	1998	3.00	0.13	71.00	0.496
	Feldkamp	2006	1.24	0.50	3.10	0.641
	Nguyen	2008	0.28	0.08	0.95	0.041
	Juergens	2008	1.19	0.73	1.95	0.477
Iopromide		$I^2 = 61.051\%$	**0.93**	**0.47**	**1.85**	**0.843**
Ioversol	VALOR	2008	**0.92**	**0.60**	**1.39**	**0.683**
		$I^2 = 0\%$				
	Andersen	1993	1.06	0.07	16.25	0.969
	RECOVER	2006	0.46	0.23	0.91	0.025
	ICON	2006	0.70	0.36	1.33	0.275
Ioxaglate		$I^2 = 0\%$	0.58	0.37	0.92	0.022
Overall			**0.79**	**0.62**	**1.01**	**0.063**



This meta-analysis including 2,763 subjects suggests that iodixanol, when compared with LOCM overall, is not associated with less CI-AKI. The relative renal safety of LOCM compared with iodixanol may vary based on the specific type of LOCM.

Reed M et al, JACC Cardiovasc Interv 2009; 2:645-654

HOCM vs. LOCM vs. IOCM

- The primary benefit of nonionic (LOCM) contrast agents
  - ✓ Seen in high-risk patients (eg, serum Cr ≥1.5 mg/dL [132 µmol/L] or a GFR <60 mL/min per 1.73 m^2), particularly if they are diabetic

- The iso-osmolal nonionic contrast agent (iodixanol)
  - ✓ Appears to reduce the risk of contrast nephropathy in high-risk patients such as diabetic patients with renal insufficiency
  - ✓ similar risk of CIAKI when compared to other low osmolal nonionic agents except ioxehol.

Contrast-induced AKI

1) Definition
2) Pathogenesis
3) Risk Factors
4) **Prevention of Contrast-induced AKI**
   - Radiocontrast agents
   - **Hydration**
   - Hemodialysis
   - N-Acetylcysteins
5) Recommendations

Hydration

Most cost-effective & accepted preventive method

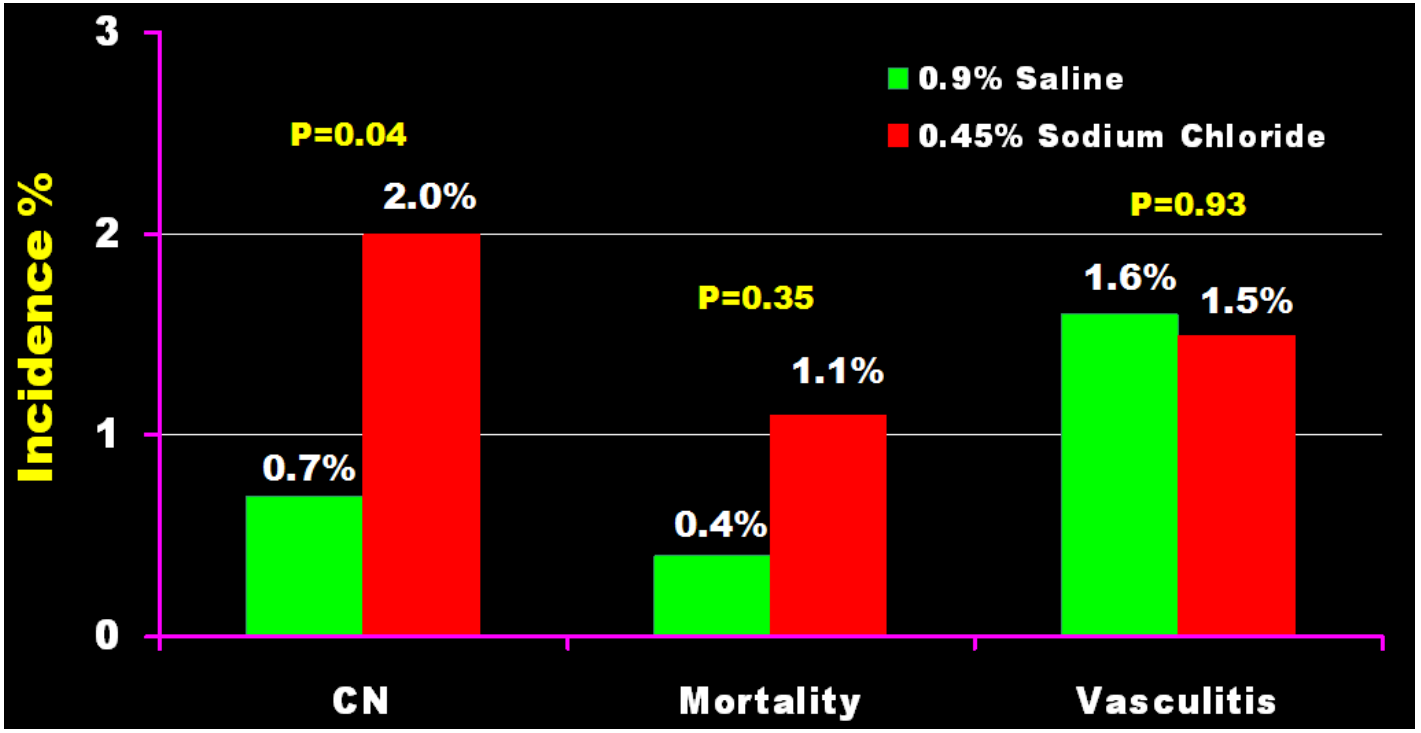
- ✓ **Optimal hydration solution : ?**

  0.45% vs. 0.9% NaCl *vs.* $NaHCO_3$

- ✓ **Route of hydration : ? iv *vs.* oral**
- ✓ **Amount of hydration : ?**
- ✓ **Duration of hydration : ?**

Hydration with isotonic saline may be superior to one-half isotonic saline

- prospective randomized trial of **1620 patients**
- **either isotonic or one-half isotonic** saline at a rate of 1 mL/kg per hour
- Contrast nephropathy: defined as an increase in serum creatinine of at least 0.5 mg/dL within 48 hours



Mueller C, Arch Int Med 2002; 162:329–336.

Intravenous bicarbonate

Isotonic sodium bicarbonate versus isotonic sodium chloride have noted either equivalent or better outcomes with sodium bicarbonate.

Table 3 Clinical trials comparing i.v. isotonic bicarbonate and i.v. isotonic saline to prevent contrast-induced acute kidney injury

Authors	Number of patients	Diabetes	Baseline SCr (mg/dl)	Definition of 1° outcome	Frequency of CIAKI bicarbonate	Frequency of CIAKI saline	Dialysis	Death	PRI/RH	Assumed effect size of bicarbonate
Positive studies										
Briguori *et al.* [92]	219	52%	2.0	↑SCr ≥25%	1.9%	9.9%	1%	NA	NA	86%
Masuda *et al.* [93]	59	31%	1.3	↑SCr ≥0.5 mg/dl or ≥25%	6.6%	34.5%	7%	3%	NA	85%
Merten *et al.* [94]	119	48%	1.7–1.9	↑SCr ≥25%	1.7%	13.6%	0%	NA	NA	66%
Ozcan *et al.* [95]	176	45%	1.4	↑SCr ≥0.5 mg/dl or ≥25%	4.2%	16.6%	1%	NA	NA	NR
Pakfetrat *et al.* [96]	192	30%	1.1	[b]	4.2%	12.5%	NA	NA	NA	NR
Recio-Mayoral *et al.* [97]	111	30%	1.0	↑SCr ≥0.5 mg/dl	1.8%	21.8%	4%	4.5%	NA	85%
Negative studies										
Adolph *et al.* [19]	145	34%	1.5–1.6	↑SCr ≥0.5 mg/dl or ≥25%	4.2%	2.7%	0%	NA	NA	87%
Brar *et al.* [98]	353	44%	1.5	↓eGFR ≥25%	13.3%	14.6%	2% [b]	2% [a]	19% [a]	66%
Maioli *et al.* [99]	502	24%	1.2	↑SCr ≥0.5 mg/dl	10%	11.5%	<1%	1%	NA	50%
Vasheghani *et al.*[c] [100]	265	22%	1.6–1.6	↑SCr ≥0.5 mg/dl or ≥25%	7.4%	5.9%	NA	NA	NA	71%

Intravenous bicarbonate

- **Prefer the administration of isotonic sodium bicarbonate**
  - **Bolus of 3 mL/kg of isotonic bicarbonate for 1 hour prior to the procedure**
  - **Continued at a rate of 1 mL/kg /hour for 6 hours after the procedure**
  - **Isotonic bicarbonate : 150 meq of sodium bicarbonate**

    + 850 mL of sterile water

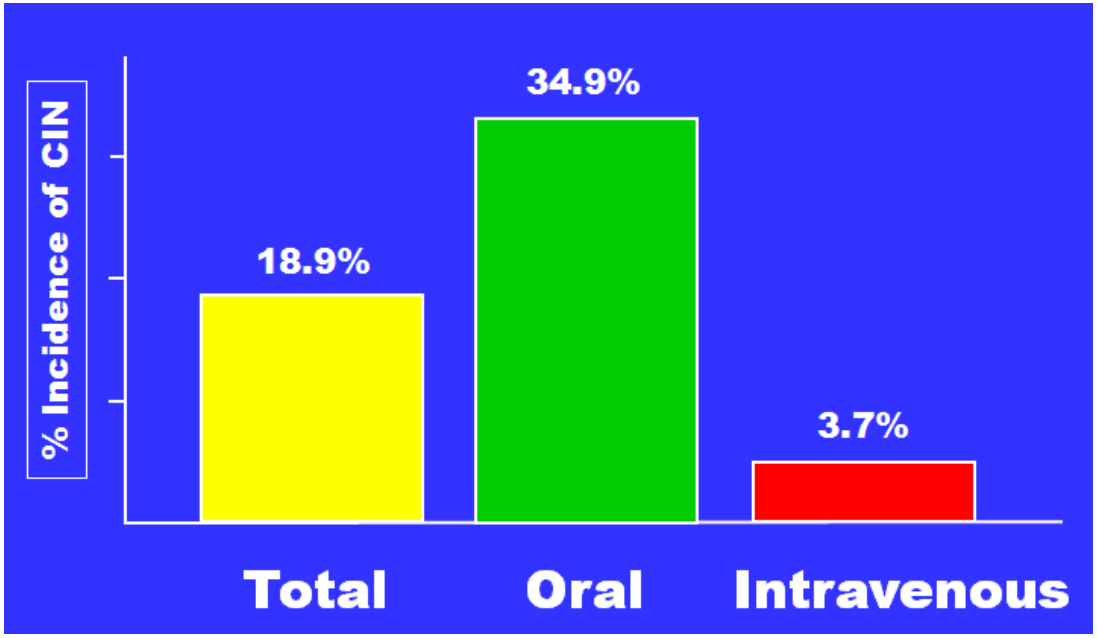
UpToDate 19.2

Zoungas et al. Ann Intern Med 2009;151:631

Oral vs. P/S hydration

- **unrestricted oral fluids (ie, no salt) found a much higher rate of acute renal failure after contrast than those given isotonic saline**.

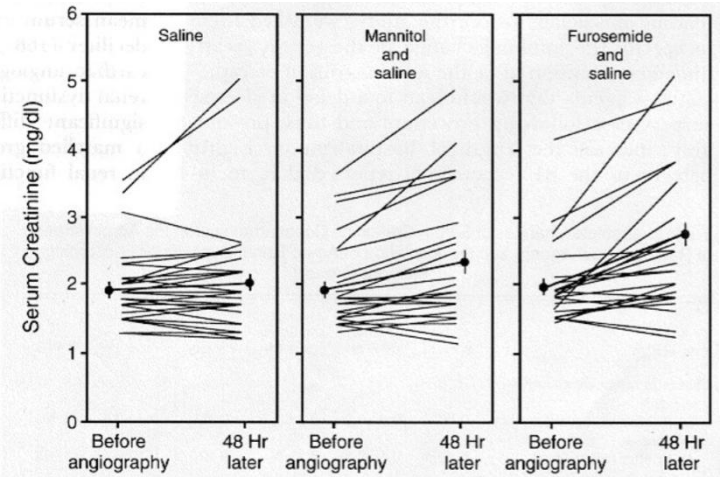
- In this trial**, 53** patients, **unrestricted oral fluids vs. normal saline at 1 mL/kg** per hour beginning 12 hours prior to the scheduled catheterization.



Trivedi et al. Nephron Clin Prac 2003;93:C29

Diuretics

- Half saline 1ml/kg/hr : half saline + mannitol : half saline + furosemide 12hrs before procedure and after 12hrs
- **The incidence of AKI** was **lowest** in the group treated **with saline alone**.
- **Mannitol was of no added benefit**
- **Furosemide therapy slightly increased the risk**.



Variable	P Value	Saline (N = 28)	Mannitol and Saline (N = 25)	P Value	Furosemide and Saline (N = 25)	P Value
Change in serum creatinine — mg/dl						
24 Hr after radiocontrast agent	0.003†	0.0±0.2	0.2±0.2	0.01‡	0.3±0.4	0.002‡
48 Hr after radiocontrast agent	0.021†	0.1±0.5	0.3±0.4	0.10‡	0.5±0.6	0.01‡
Incidence of acute renal dysfunction — no. of patients (%)	0.05§	3 (11)	7 (28)	0.16¶	10 (40)	0.02¶

Solomon et al. NEJM 1994;331:1416

Diuretics and Hydration

Summary — The following conclusions can be drawn from the current literature:

- Prophylactic diuretics or mannitol do not appear to be beneficial for the prevention of contrast-induced acute renal failure.
- Intravenous hydration is superior to oral hydration.
- Oral hydration with water alone should not be used.
- Hydration with isotonic saline solution is superior to one-half normal saline, and isotonic sodium bicarbonate may be superior to isotonic saline.

Contrast-induced AKI

1) Definition
2) Pathogenesis
3) Risk Factors
4) **Prevention of Contrast-induced AKI**
   - Radiocontrast agents
   - Hydration
   - **Hemodialysis**
   - N-Acetylcysteins
5) Recommendations

Contrast-Medium Elimination

Reference	Period of dialysis	Elimination (% of contrast-medium)
Matzkies 99	3h	58% (high-flux-membrane)
	3hr	62% (low-flux-membrane)
Matzkies 2000 2h	2h	57% (Cuprophane membrane)
	2h	66% (Polysulfone membrane)
		68% (Polysulfone membrane + ultrafiltraion)
Lorusso 2001	2h	70%
Sterner 2000	4h	79%
Ueda 96	4h	81%
Moon 95	6h	77%
Lehnert 98	3h	32%
Waaler 90	4h	36%
Baars 84	4.4h	50%
Kierdorf 89	3h	60%
Bahlmann 73	12h	85%

Huber W et al, Invest Radiol 2002; 37:471-481

Prevention of CIN with Hemodialysis

Treatment group	Incidence of RCN	Diabetes mellitus		Incidence of RCN
HD n=15	n=8 (53%)	Present	n=7	n=4 (57%)
		Absent	n=8	n=4 (50%)
No HD n=15	n=6 (40%)	Present	n=6	n=3 (50%)
		Absent	n=9	n=3 (33%)

HD eliminates contrast medium effectively, but it may not influence the incidence or outcome of contrast induced nephropathy.

Lehnert T et al, NDT 1998;13: 358-361

Prevention of CIN with Hemodialysis

412 patients with baseline S_{Cr} values of 1.3–3.5 mg/dl undergoing elective coronary angiography

TABLE 2
Multivariate analysis by logistic regression with crude and adjusted OR for contrast media-induced nephropathy (CIN) within 72 h

	Patients, n (% of all)	CIN within 72 h, n (%)	Crude OR			Adjusted OR		
			OR	95% CI	P	OR	95% CI	P
Therapy								
Hydration only	139 (33.7)	10 (7.2)	1		0.003	1		0.006
Hydration plus dialysis	134 (32.6)	22 (16.4)	2.534	1.151–5.579		2.862	1.065–7.690	
Hydration plus *N*-acetylcysteine	139 (33.7)	6 (4.3)	0.582	0.206–1.648		0.565	0.164–1.950	

Holscher B et al. Can J Cardiol 2008; 24:845–850.

Hemodialysis and Hemofiltration

Summary

- do NOT recommend routine hemofiltration or hemodialysis for the prevention of contrast nephropathy in patients with stage 3 and 4 CKD.
- More data are needed in stage 5 CKD, as in the last trial, before any firm recommendation can be made.
- consider the prophylactic use of hemodialysis in patients with stage 5 CKD, provided that a functioning access is already available.
- We would not place a temporary access for prophylactic hemodialysis in these patients.

Contrast-induced AKI

1) Definition
2) Pathogenesis
3) Risk Factors
4) **Prevention of Contrast-induced AKI**
   - Radiocontrast agents
   - Hydration
   - Hemodialysis
   - **N-Acetylcysteins**
5) Recommendations

Pharmacological Interventions

- ***N-Acetylcysteine***

  - ✓ Scavenge reactive oxygen species (ROS)
  - ✓ Reduce the depletion of glutathione
  - ✓ Stimulate the production of vasodilatory mediators(nitric oxide)
  - ✓ Well tolerated and relatively inexpensive
  - ✓ Accompanied by isotonic fluid hydration and use of a low or iso-osmolal contrast agent

Pharmacological Interventions

- **N-Acetylcysteine**

Table 2 Randomized clinical trials comparing *N*-acetylcysteine and placebo to prevent contrast-induced acute kidney injury

Authors	NAC dose	Number of patients	Definition 1° outcome	% CIAKI NAC	% CIAKI control	Dialysis	Death	PRI/RH	Assumed effect size NAC
Positive studies									
Baker *et al.* [58]	[a]	80	↑ SCr ≥25%	5	21	0%	NR	NR	[b]
Balderramo *et al.* [59]	1200 mg po × 2	61	↑ SCr ≥0.5 mg/dl	3	7.1	NR	NR	NR	90%
Diaz-Sandoval *et al.* [60]	600 mg po × 4	54	↑ SCr≥25%/0.5 mg/dl	8	45	NR	NR	NR	NR
Drager *et al.* [61]	600 mg po × 4	24	Mean Δ CrCl	NR	NR	NR	NR	NR	NR
Kay *et al.* [62]	600 mg po × 4	200	↑ SCr ≥25%	4	12	0%	0%	NR	[b]
MacNeill *et al.* [63]	600 mg po × 5	43	↑ SCr ≥25%	5	32	NR	NR	NR	NR
Marenzi *et al.* [64]	[c]	352	↑ SCr ≥25%	11.6	33	2.6%	6%	NR	50%
Miner *et al.* [65]	[d]	171	↑ SCr ≥25%	9.6	22.2	2%	5.5%	9.4%	50%
Ochoa *et al.* [66]	1000 mg po × 2	80	↑ SCr ≥25%/0.5 mg/dl	8	25	NR	NR	NR	[b]
Shyu *et al.* [67]	400 mg po × 4	121	↑ SCr ≥0.5 mg/dl	3.3	24.6	0.8%	NR	NR	[b]
Tepel *et al.* [57]	600 mg po × 4	83	↑ SCr ≥0.5 mg/dl	2	12	0%	NR	NR	NR
Negative studies									
Allaqaband *et al.* [68]	600 mg p.o. × 4	80	↑ SCr ≥0.5 mg/dl	17.7	15.3	NR	NR	NR	NR
Amini *et al.* [69]	600 mg p.o. × 4	87	↑ SCr ≥25%/0.5 mg/dl	11.1	14.3	NR	NR	NR	90%
Azmus *et al.* [70]	600 mg p.o. × 4	399	↑ SCr ≥25%/↓eGFR 50%	7.1	8.4	0.5%	NR	NR	65%
Briguori *et al.* [71]	600 mg p.o. × 4	183	↑ SCr ≥25%	6.5	11	0.5%	NR	NR	NR
Carbonell *et al.* [72]	600 mg i.v. × 4	216	↑ SCr ≥25%/0.5 mg/dl	10.3	10.1	0%	3.7%	NR	NR
Coyle *et al.* [73]	600 mg p.o. × 4	137	mean Δ SCr	NR	NR	NR	NR	NR	[b]
Durham *et al.* [74]	1200 mg p.o. × 2	79	↑ SCr ≥0.5 mg/dl	26.3	22	2.5%	NR	NR	NR
Fung *et al.* [75]	400 mg p.o. × 6	91	↑ SCr ≥25%/↓eGFR 50%	13.3	17.4	0%	NR	NR	90%
Goldenberg *et al.* [76]	600 mg p.o. × 6	80	↑ SCr ≥0.5 mg/dl	10	8	0%	0%	NR	90%
Gomes *et al.* [77]	600 mg p.o. × 4	156	↑ SCr ≥0.5 mg/dl	10.4%	10.1	1.3%	4.5%	NR	50%
Kefer *et al.* [78]	1200 mg i.v. × 2	104	↑ SCr ≥25%/0.5 mg/dl	3.8	5.9	0%	NR	NR	NR
Oldemeyer *et al.* [79]	1500 mg p.o. × 4	96	↑ SCr ≥25%/0.5 mg/dl	8.2	6.4	0%	NR	NR	NR
Rashid *et al.* [80]	1000 mg i.v. × 1	94	↑ SCr ≥25%/0.5 mg/dl	6.5	6.3	NR	NR	NR	90%
Sandhu *et al.* [81]	600 mg p.o. × 4	106	↑ SCr ≥0.5 mg/dl	5.7	0	NR	NR	NR	NR
Webb *et al.* [82]	500 mg i.v. × 1	487	↓ CrCl >5 ml/min	23.3	20.7	0%	2.5%	NR	50%

Pharmacological Interventions

➢ *N-Acetylcysteine*

- There is great heterogeneity and conflicting results in the available clinical trials and meta-analyses examining the effectiveness of acetylcysteine in the prevention of contrast nephropathy.
- The overall direction of the data is toward benefit and the agent is well tolerated and relatively inexpensive.
- We recommend administration of acetylcysteine to patients at high risk.
- This must be accompanied by isotonic fluid hydration and use of a low or iso-osmolal contrast agent.

Kshirsagar et al. J Am Soc Nephrol 2004;15:761
Fishbane S. Clin J Am Soc Nephrol 2008;3:281

Pharmacological Interventions

- **N-Acetylcysteine (Muteran®)**

  - ✓ **600 mg orally twice daily (m/c)**
  - ✓ **600 mg and 1200 mg twice daily suggested slightly better outcomes with the higher dose**
  - ✓ **Preferred dose**
    - **1200 mg administered orally twice daily on the day before and the day of the procedure to patients at risk for contrast nephropathy**

Marenzi et al. NEJM 2006;354:2773
Briguori et al. Eur Heart J 2004;25:206

Summary (1)

- **Patients at increased risk of contrast nephropathy**
  - **NOT using high osmolal agents (1400 to 1800 mosmol/kg)**
  - **Iodixanol or nonionic low osmolal agents such as iopamidol or ioversol rather than iohexol**
  - **Lower doses of contrast and avoid repetitive, closely spaced studies (eg, < 48 hours apart)**
  - **Avoid volume depletion and NSAIDs.**

Summary (2)

- **Patients at increased risk of contrast nephropathy**
  - **Bolus of 3 mL/kg of isotonic bicarbonate for 1 hour prior to the procedure, and continued at a rate of 1 mL/kg /hour for 6 hours after the procedure.**
  - **Isotonic saline at a rate of 1 mL/kg/hour, begun at least 2 and preferably 6 to 12 hours prior to the procedure, and continuing for 6 to 12 hours after contrast administration**

Summary (3)

- **Patients at increased risk of contrast nephropathy**
  - **Acetylcysteine be administered the day before and the day of the procedure, based upon its potential for benefit and low toxicity and cost**
  - **1200 mg orally twice daily rather than 600 mg twice daily the day before and the day of the procedure.**
  - **NOT using mannitol or other diuretics prophylactically.**
  - **NOT performing prophylactic hemofiltration or hemodialysis after contrast exposure.**

Thank your for your attention !