Contrast Induced Nephrotoxicity

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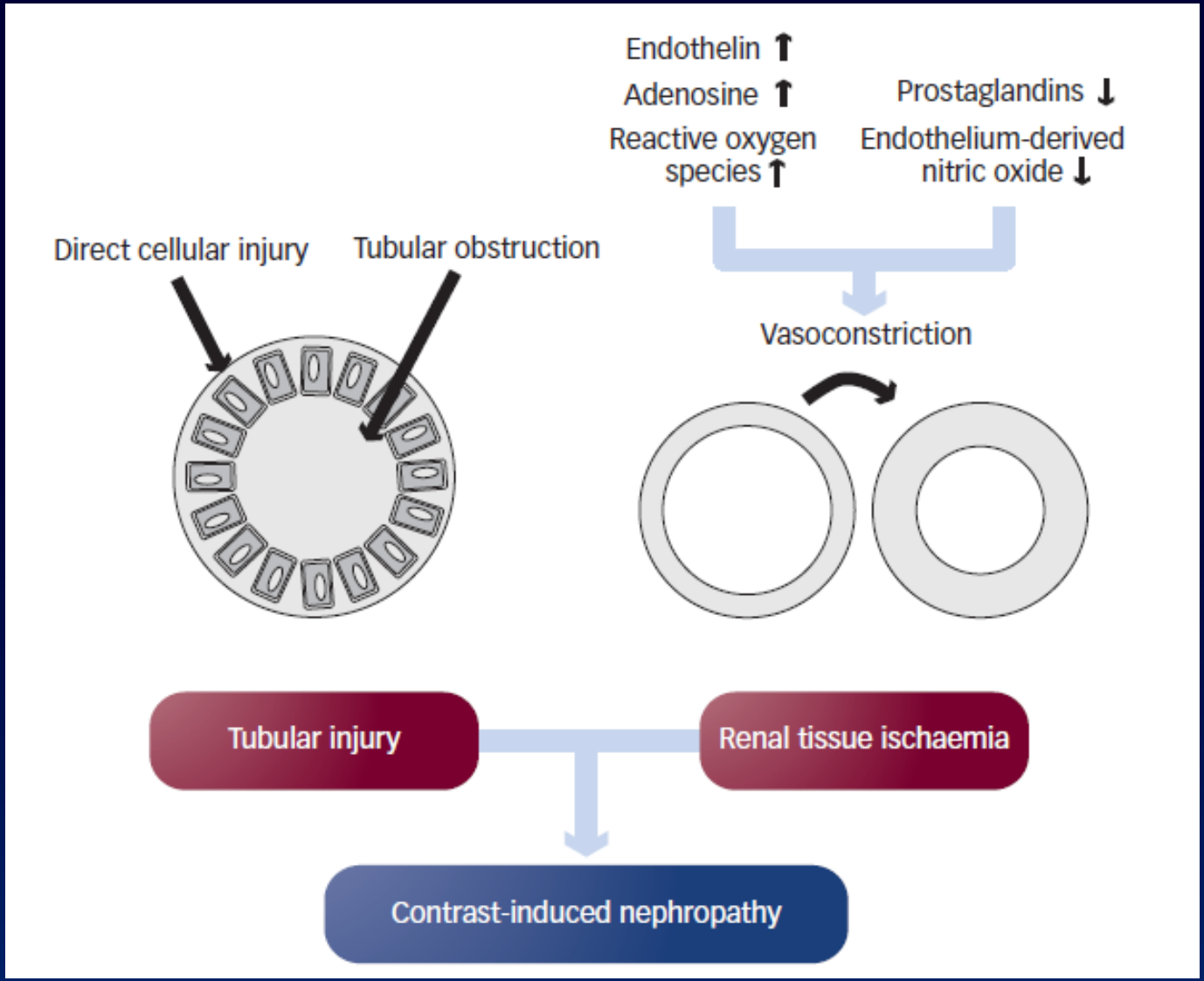
Major Causes of CIN



Definition

0.3 mg/dL change in Cr

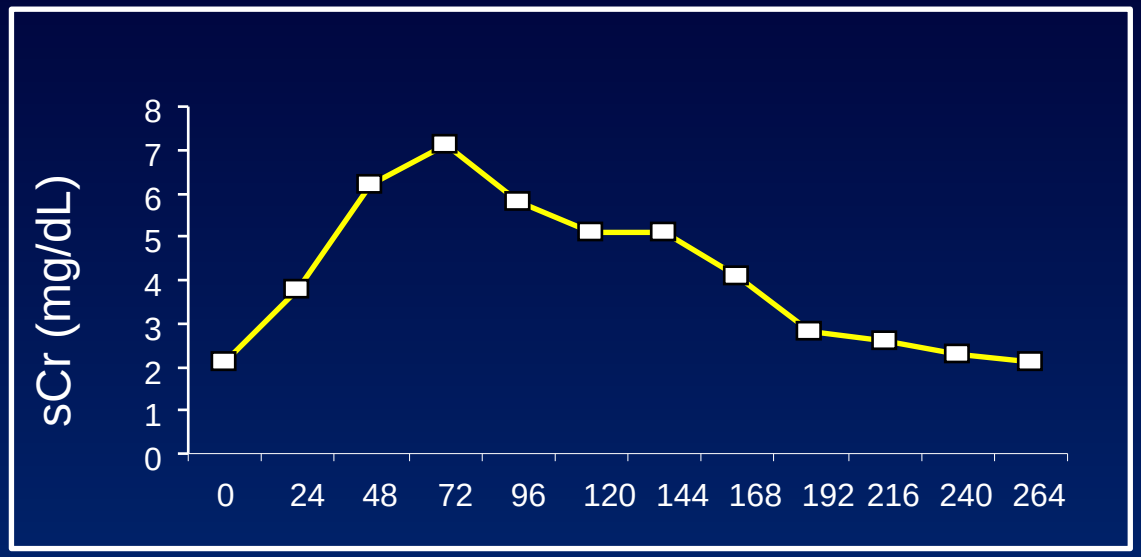
>25% change in eGFR

>25% change in CrCl

0.5 mg/dL change in Cr

>25% change in Cr

- 0.5mg/dL ↑ or 25%↑ compared to baseline serum Cr in 48~72 hours after injection



eGRF

CrCl

Cystatin C

Risk Factors

Fixed risk factors	Modifiable risk factors
Age	Contrast volume
Diabetes Mellitus	HTN
Pre-existing renal failure	Anemia & blood loss
Advenced CHF	Dehydration
Low EF	ACE inhibitor
AMI	Diuretics
Cardiogenic shock	NSAIDs
Renal transplantation	Nephrotoxic antibiotics
	IABP

Strategies Assessed for Prevention of CIN

Hydration

Pharmacological agents

Non-pharmacological therapies

Hydration

Normal Saline

½Normal Saline

Bicarbonate

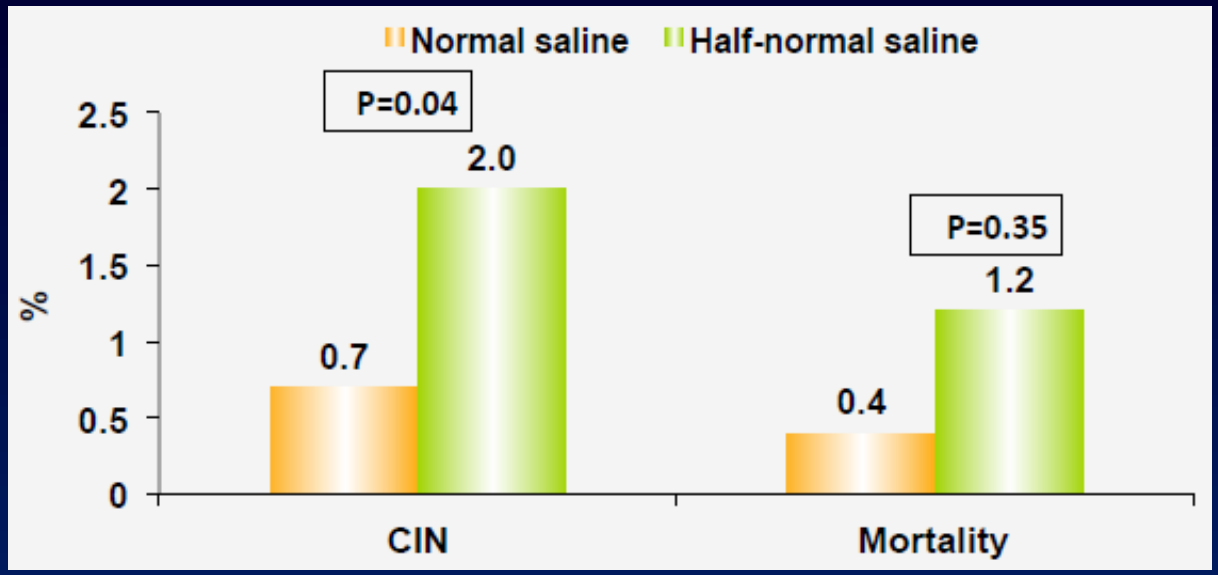
Forced diuresis

Matched hydration

Consecutive 1,620 pa&ents undergoing elec&ve or urgent coronary angiography at 1 site in Switzerland

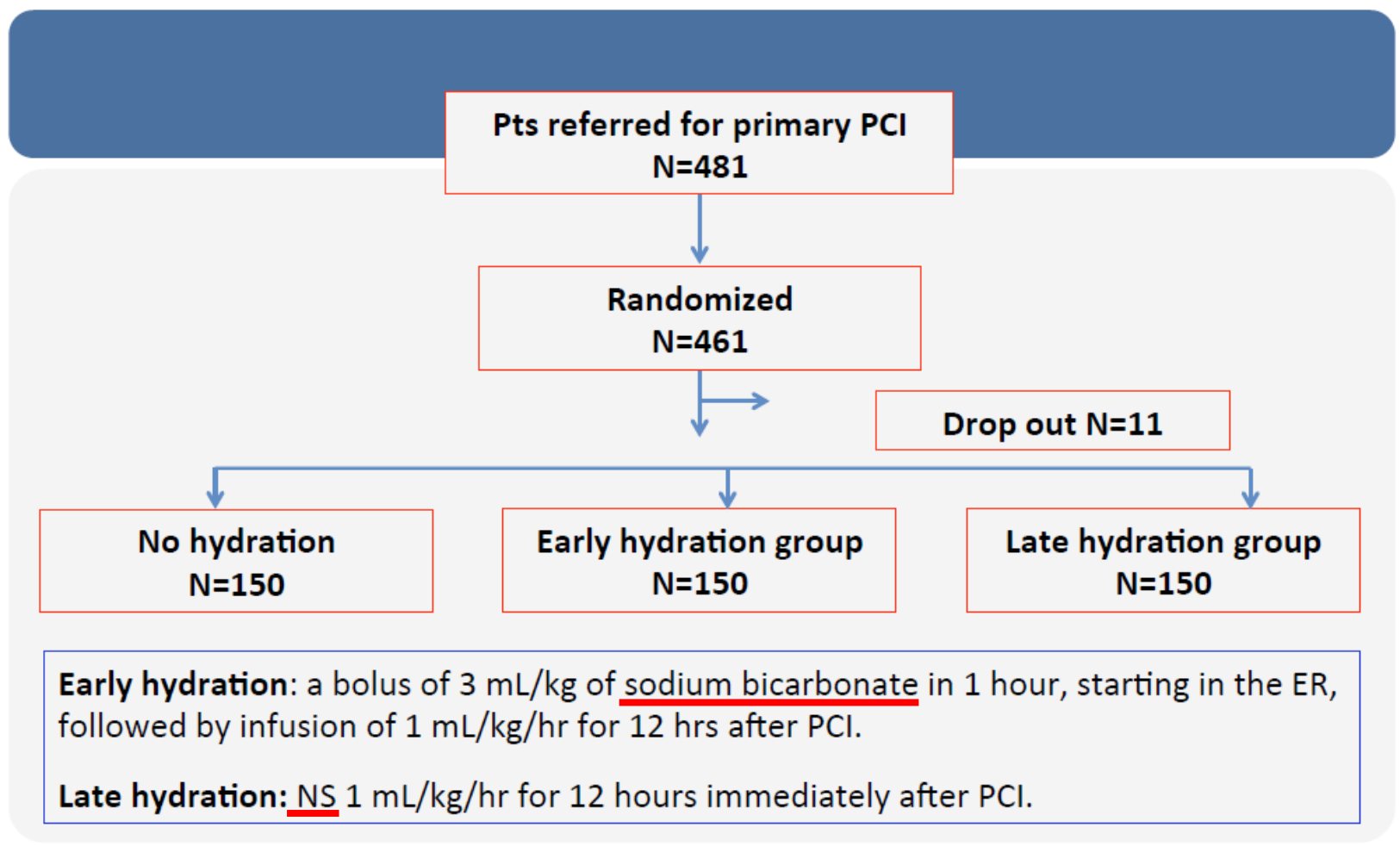
Hydra&on with isotonic saline N=809

Hydra&on with half-isotonic saline N=811

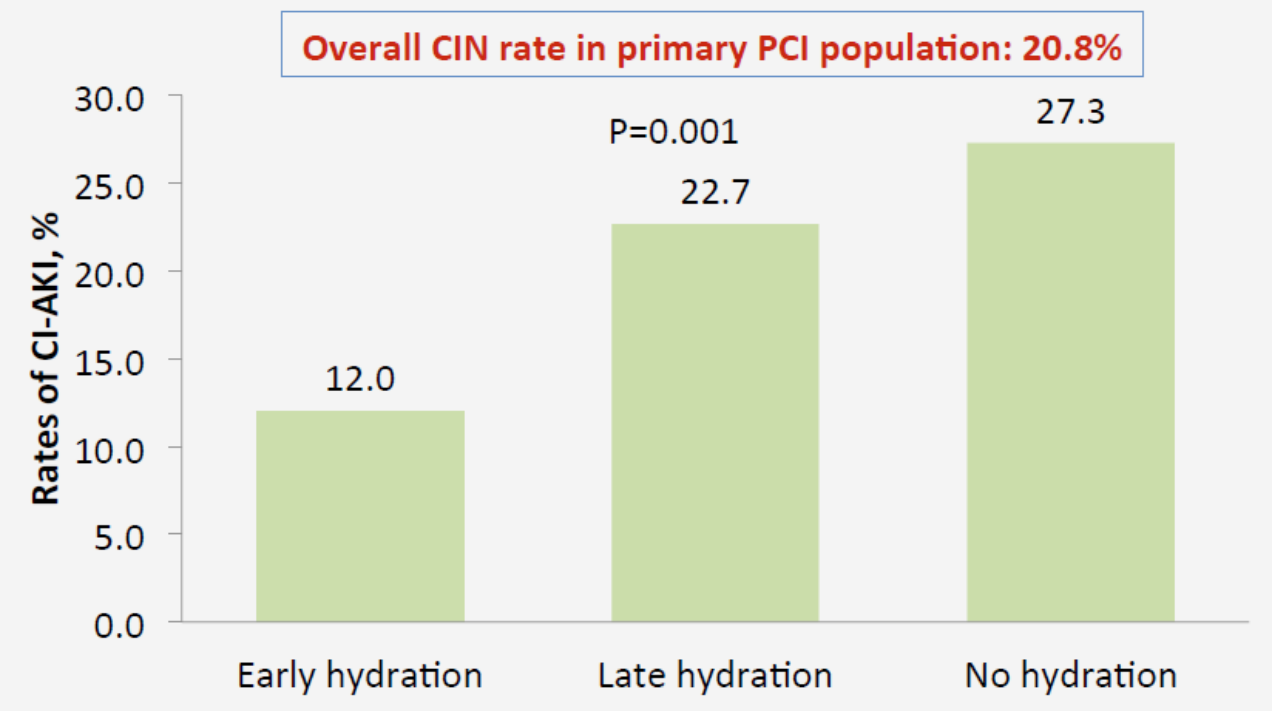


Mueller C et al Arch Intern Med , 2002, 162:329-336

Effects of Hydration on CIN After Primary Angioplasty



Maioli et al, Circ Cardiovascular Interv. 2011;4:456-462



3-Day Outcomes	Early (n = 150)	Late (n = 150)	Control (n = 150)	P Value for Trend
SCr Increase of ≥ 25% or 0.5 mg/dL	12.0%	22.7%	27.3%	0.001
eGFR Decrease > 25%	6.0%	10.3%	15.6%	0.007

There was a trend toward reduced in-hospital death with early (2.0%) vs. late or no hydration (3.3% and 5.3%, respectively; P = 0.12)

Maioli et al, Circ Cardiovascular Interv. 2011;4:456-462

Prevention of CIN with Sodium Bicarbonate

Patients With Baseline Serum Creatinine >1.8 mg/dl who Underwent Contrast Exposure (Iopamidol in All) N=137

Sodium Chloride Hydration (154 mEq/L of Sodium Chloride) N=68

Sodium Bicarbonate Hydration (154 mEq/L of Sodium Bicarbonate) N=69

Endpoints	Sodium Chloride N=59	Sodium Bicarbonate N=60	P value
Incidence of CIN (%)	13.6%	1.7%	0.02
Incidence of CIN (↑SCr 0.5 mg/dL)	11.9%	1.7%	0.03

Merten GJ et al. JAMA, 2004;291:2328-2334

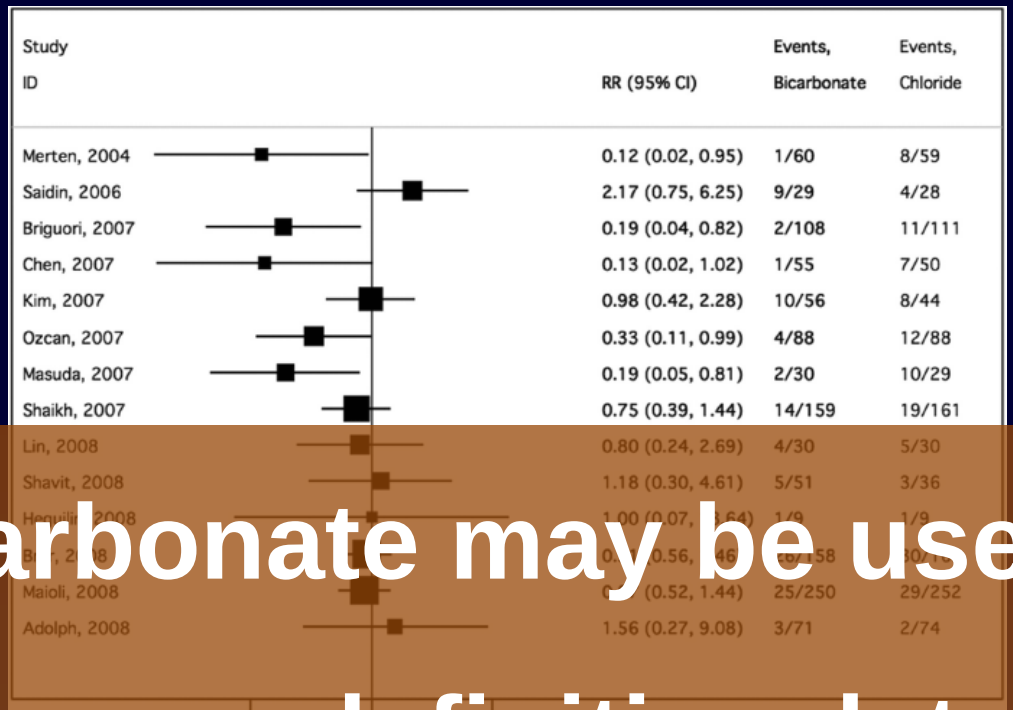
Meta-Analysis

Sodium Bicarbonate for the Prevention of CIN

Dates: 1966 to 2008

Randomized Trials

Number of patients: 2,290



Sodium bicarbonate may be useful, but need more definitive data

Summary: No overall benefit, but trend driven by studies with extreme treatment effects

Brar S S et al. CJASN 2009;4:1584–1592

Contrast Media

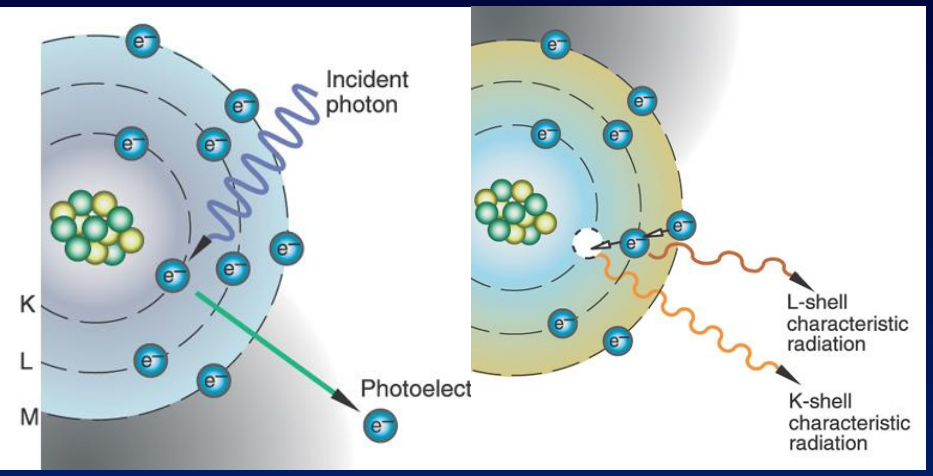
Osmolarity, Hydrophilicity, Viscosity

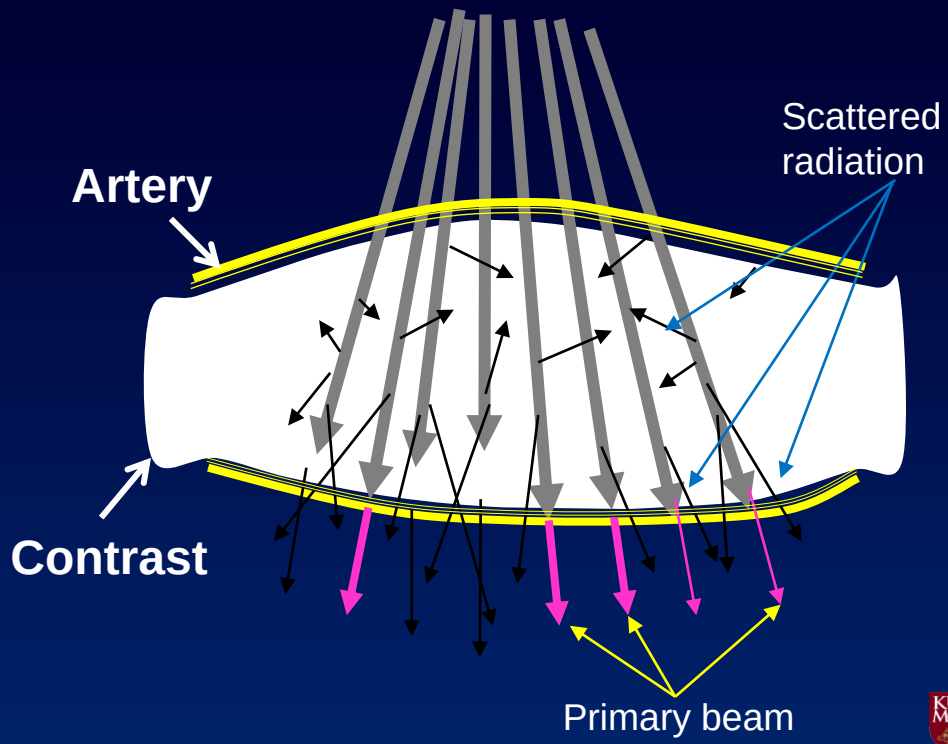
	Type	Iodine mg/ml	Osmolality mOsm/kg	Viscosity cps
High Osmolar	• Ionic Monomer	325	1843	2.75
	• Ionic Monomer	306	1530	5.0
Low Osmolar	• Ionic Dimer	320	580	7.5
	• Non-ionic Monomer	300	616	4.7
Iso Osmolar	• Non-ionic Dimer	300	320	8.1
	• Non-ionic Dimer	320	290	11.4

Contrast Media

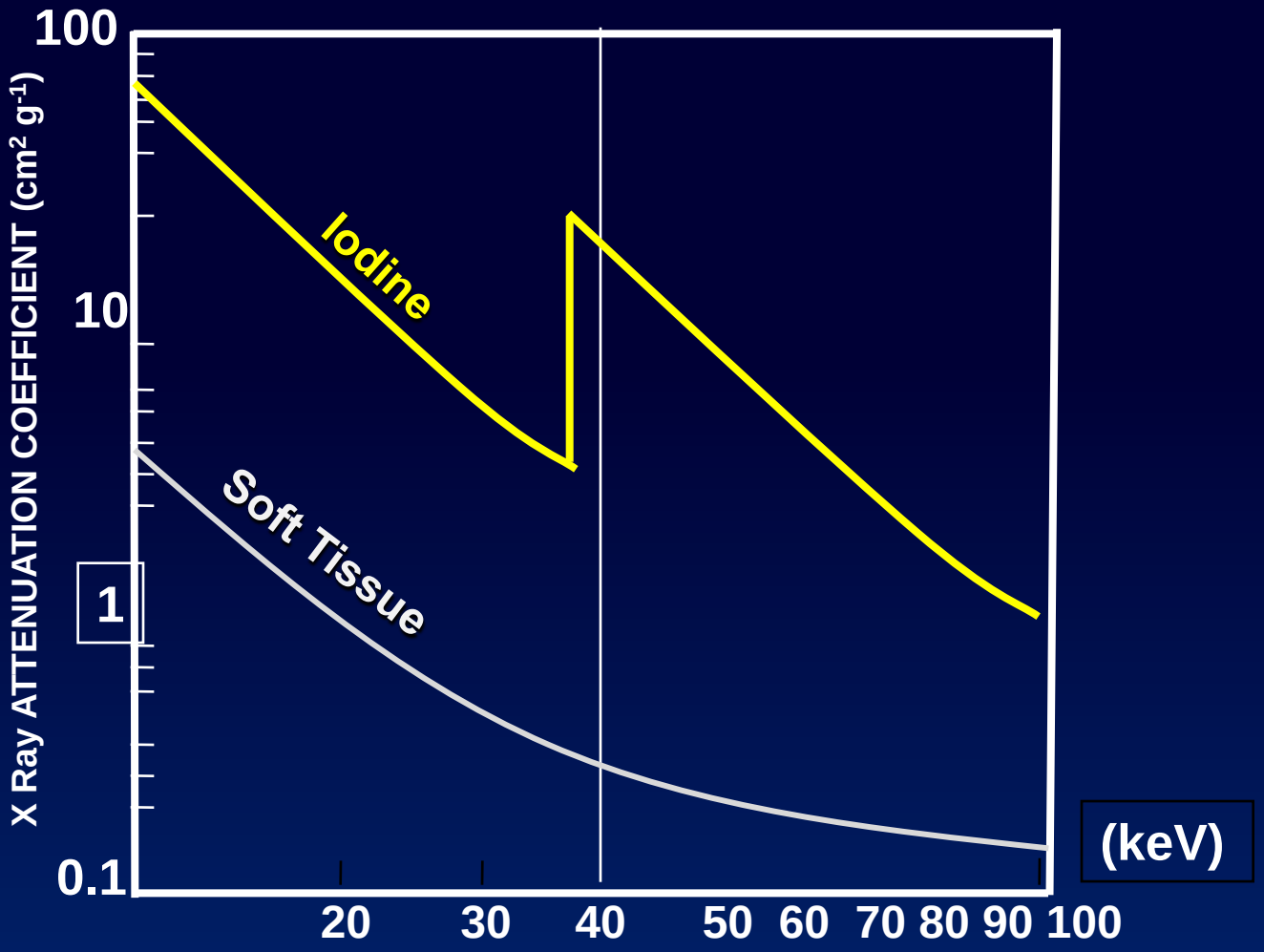
- Physics of CM : attenuation
  - Binding energy of K shell of "I" : 33.2 keV
  - Similar to mean energy level of polychromatic radiation

    using general X-ray beam generator
  - Photoelectric absorption

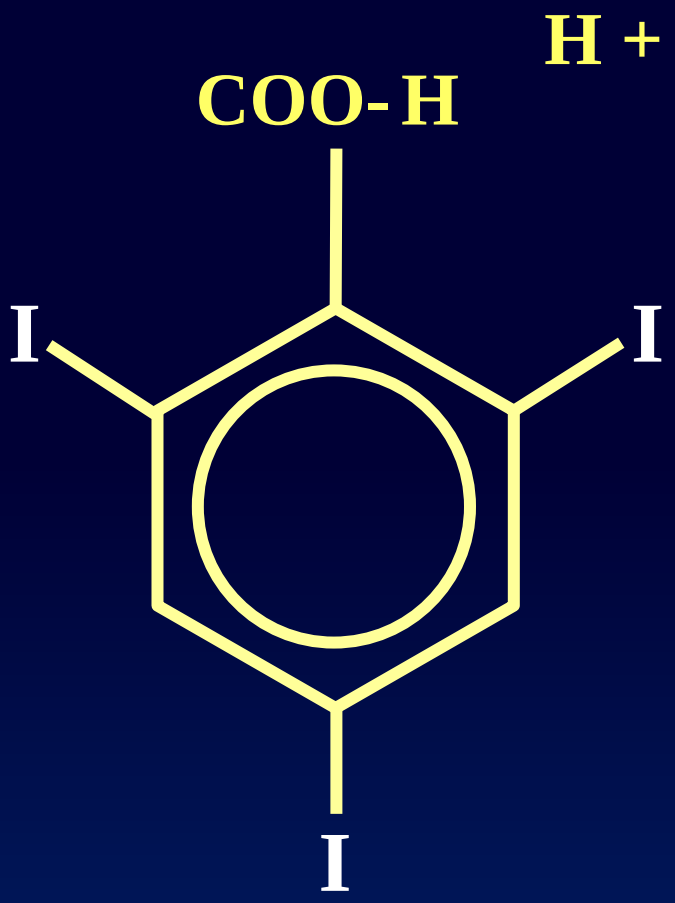




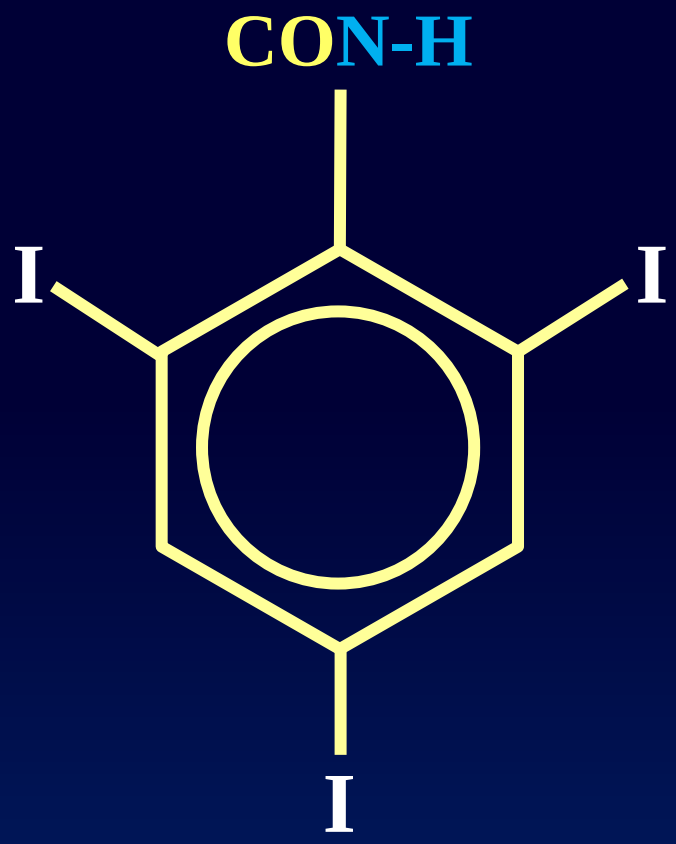
X Ray absorption characteristics of iodine, barium and body soft tissue



Structure of iodine CM

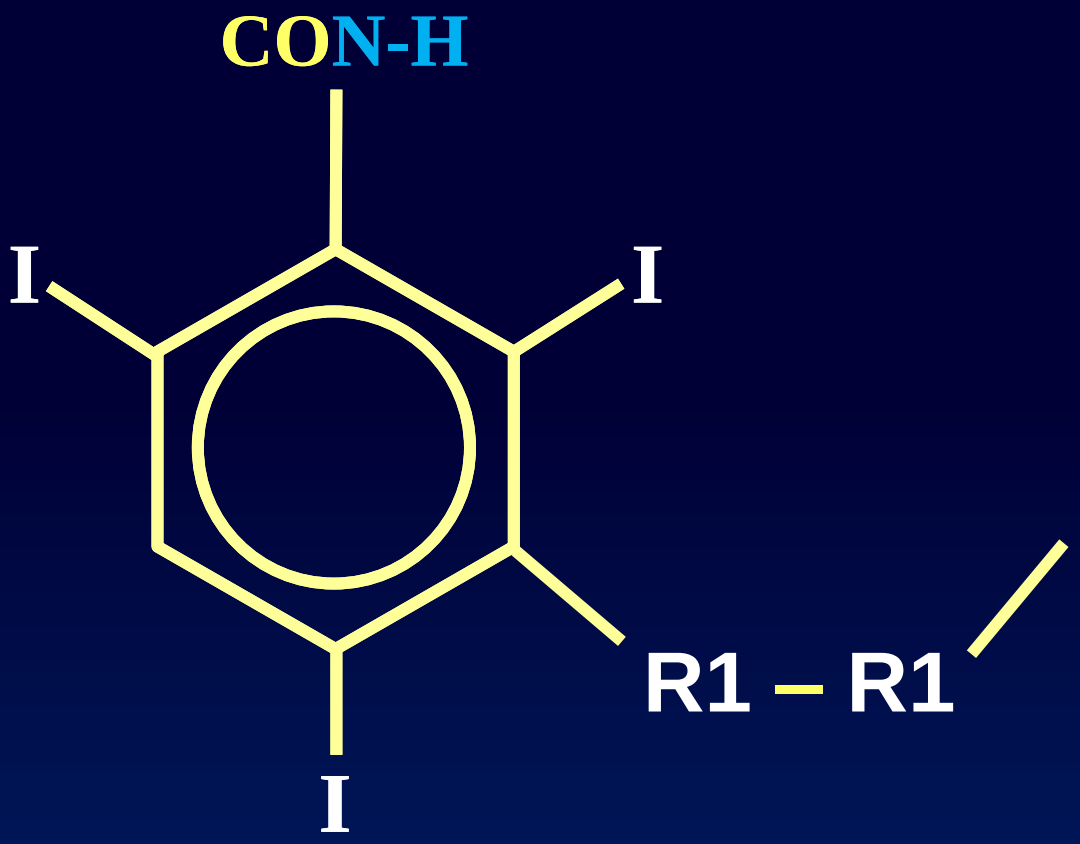


Ionic Monomer



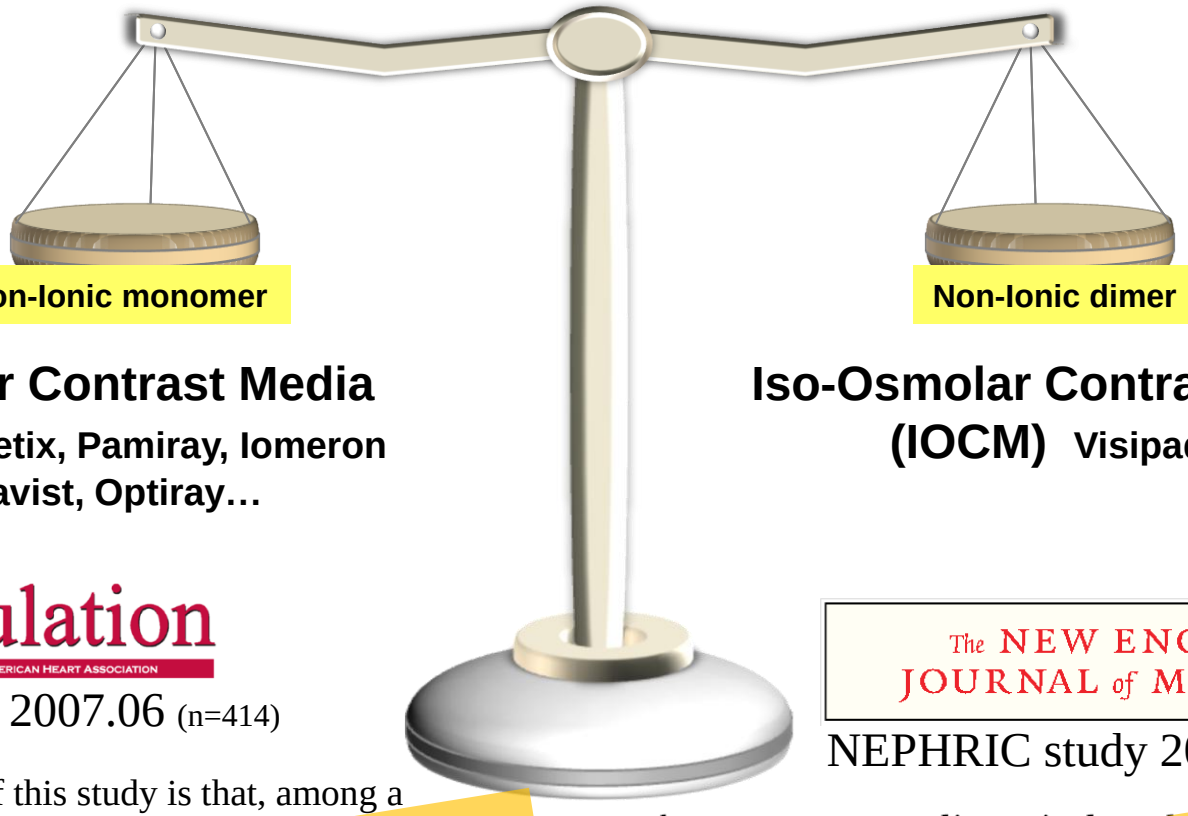
Non-Ionic Monomer

Structure of iodine CM



Non-Ionic dimer

High-Osmolar Contrast Media, HOCM



Non-Ionic monomer

Non-Ionic dimer

Low-Osmolar Contrast Media (LOCM) Xenetix, Pamiray, Iomeron Ultravist, Optiray…

Iso-Osmolar Contrast Media (IOCM) Visipaque

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

CARE study 2007.06 (n=414)

The major finding of this study is that, among a population of high-risk patients who underwent cardiac catheterization procedures, no significant difference existed in the occurrence of CIN between the low-osmolality monomer iopamidol-370 (796 mOsm/kg) and the iso-osmolality dimer iodixanol-320 (290 mOsm/kg).

N-acetylcysteine O

ICON study *J Am Coll Cardiol Intv*. 2009;2(5):415-421.

The NEW ENGLAND JOURNAL of MEDICINE

NEPHRIC study 2003.02 (n=129)

that contrast-medium–induced nephropathy will develop in high-risk patients [illegible] significantly reduced [illegible] iodixanol, an iso-osmolar contrast medium, is used rather than a low-osmolar nonionic contrast medium.

Supported by Amersham Health.

N-acetylcysteine X

RECOVER study *J Am Coll Cardiol, 2006;48(5):924–30.*

Drugs to Prevent CIAKI

N-Acetylcysteine…?

Pharmacological agents

Improvement of renal hemodynamics:

Dopamine, Fenoldopam, Theophylline, PGE1, ANP, L-Arginine, Nitrendipine ,Endothelin Receptor Antagonists

Antioxidants: NAC, Ascorbic Acid

Prevention of renal cell apoptosis: Atorvastatin

N-acetylcysteine(NAC)

The New England Journal of Medicine

PREVENTION OF RADIOGRAPHIC-CONTRAST-AGENT–INDUCED REDUCTIONS IN RENAL FUNCTION BY ACETYLCYSTEINE

MARTIN TEPEL, M.D., MARCUS VAN DER GIET, M.D., CAROLA SCHWARZFELD, ULF LAUFER, M.D., DIETER LIERMANN, M.D., AND WALTER ZIDEK, M.D.

In conclusion, prophylactic oral administration of the antioxidant acetylcysteine at a dose of 600 mg twice daily on the day before and on the day of administration of the contrast agent, together with hydration with saline, is an effective means of preventing renal damage induced by a nonionic, low-osmolality contrast agent in patients with chronic renal insufficiency.

July 20, 2000 Tepel M., van der Giet M., Schwarzfeld C., et al. N Engl J Med 2000; 343:180-184

Tepel et al. (NEJM 2000) first described its efficacy in preventing CIN

The NEW ENGLAND JOURNAL of MEDICINE

N-Acetylcysteine and Contrast-Induced Nephropathy in Primary Angioplasty

Giancarlo Marenzi, M.D., Emilio Assanelli, M.D., Ivana Marana, M.D., Gianfranco Lauri, M.D., Jeness Campodonico, M.D., Marco Grazi, M.D., Monica De Metrio, M.D., Stefano Galli, M.D., Franco Fabbiocchi, M.D., Piero Montorsi, M.D., Fabrizio Veglia, Ph.D., and Antonio L. Bartorelli, M.D.

In conclusion, we found that N-acetylcysteine reduced the severity of contrast-medium–induced nephropathy in patients with acute myocardial infarction treated with primary angioplasty. The effect appears to be dose-dependent and is accompanied by a significantly improved in-hospital outcome. The mechanisms underlying the improvement in the in-hospital clinical outcome have not been completely elucidated, and studies of potential extrarenal effects of N-acetylcysteine are warranted.

NEJM 2006;354:2773

항산화제인 N-acetylcysteine(NAC)가 CIN을 예방한다는 연구가 보고

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.

Ann Intern Med 2008; 148, 284-294

Summarizing the Literature

29 trials for renal protection with NAC, 2000-6

Positive n=14

Author	N-Acetylcysteine Dose
Tepel et al (1)	600 mg orally twice daily for 48 h
Diaz-Sandoval et al (9)	600 mg orally twice daily for 48 h
Briguori et al (7)	600 mg orally twice daily for 48 h
Shyu et al (47)	400 mg orally twice daily for 48 h
Kay et al (40)	600 mg orally twice daily for 48 h
Baker et al (5)	150 mg/kg IV before and 50 mg/kg IV after
Tadros et al (72)	600 mg orally twice daily 3 doses
MacNeill et al (53)	600 mg orally twice daily 5 doses
Efrati et al (54)	1,000 mg orally twice daily for 48 h
Briguori et al (44)	Single dose, 600 mg orally twice daily for 48 h; double dose, 1,200 mg orally twice daily for 48 h
Ochoa et al (55)	1,000 mg orally 1 h prior and 4 h after
Miner et al (56)	2,000 mg orally twice daily, 3 doses; if randomized 1 day earlier or two doses if same day
Drager et al (57)	600 mg orally twice daily for 4 days (first dose 48 h before procedure)
Marenzi et al (4)	600 mg IV before, 600 mg orally twice daily for 48 h 1,200 mg IV before and 1,200 mg orally twice daily for 48 h

Negative n=15

Allaqaband et al (58)	600 mg orally twice daily for 48 h
Durham et al (59)	1,200 mg orally 1 h before and repeat 3 h after
Goldenberg et al (60)	600 mg orally three times daily for 48 h
Oldemeyer et al (51)	1,500 mg orally twice daily for 48 h
Boccalandro et al (45)	600 mg orally twice daily for 48 h
Kefer et al (61)	1,200 mg IV 12 h before, repeat with contrast agent
Webb et al (48)	500 mg IV 1 h before
Fung et al (62)	400 mg orally twice daily for 48 h
Rashid et al (49)	1,000 mg IV before, 1000 mg IV after
Gomes et al (41)	600 mg orally twice daily for 48 h
Gulel et al (13)	600 mg orally twice daily for 48 h
Azmus et al (46)	600 mg orally twice daily for 48 h and 1 day after
Kotlyar et al (50)*	300 mg IV 1–2 h before and 2–4 h after 600 mg IV 1–2 h before and 2–4 h after
Coyle et al (42)	600 mg orally twice daily for 48 h
Carbonell et al (43)	600 mg orally twice daily for 48 h

Stentstrom et al. J Vasc Interv Radiol 2008; 19:309-318

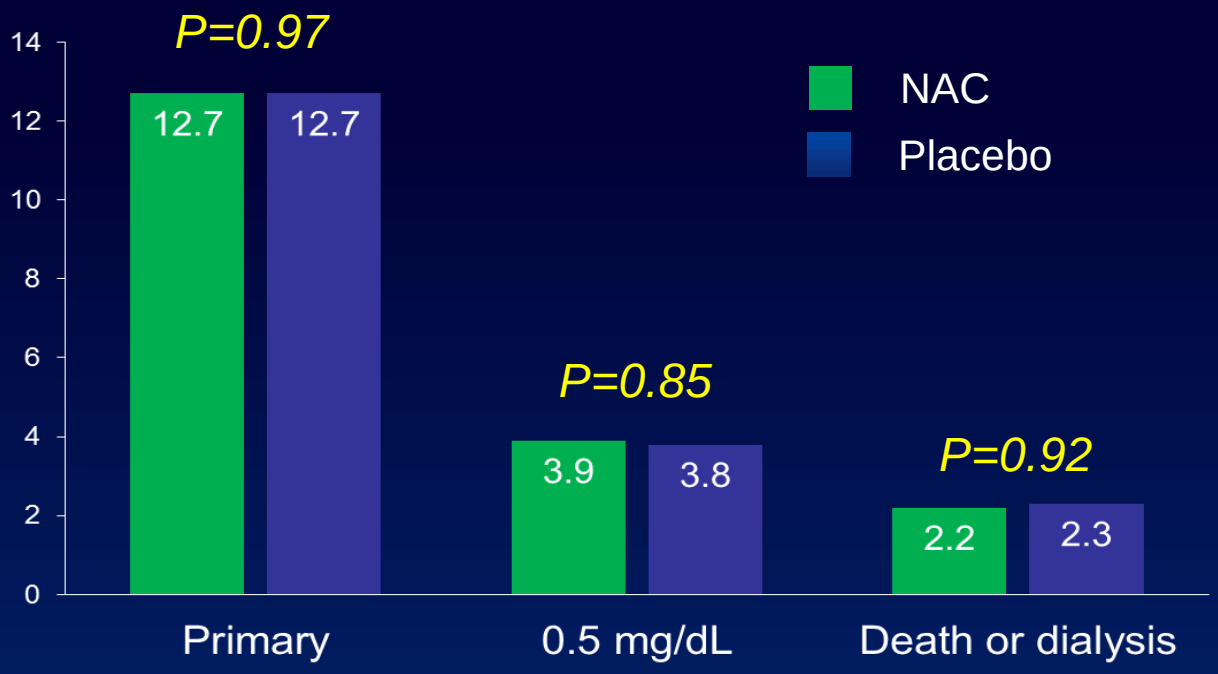
ACT Trial

Acetylcysteine for Contrast-Induced Nephropathy Trial

2,308 Patients undergoing an angiographic procedure with at least one of the following risk factors:

Age > 70 years;

Chronic Renal Failure;
Diabetes Mellitus;
Heart Failure or LVEF <0.45;
Shock



ACT Investigators. Circulation 2011. 124(11);1250-9

N-acetylcysteine(NAC)

Since then a multitude of trials published with highly conflicting results (largest trial 487 patients) A number of meta-analysis published

- potential to reduce the nephrotoxicity of contrast medium

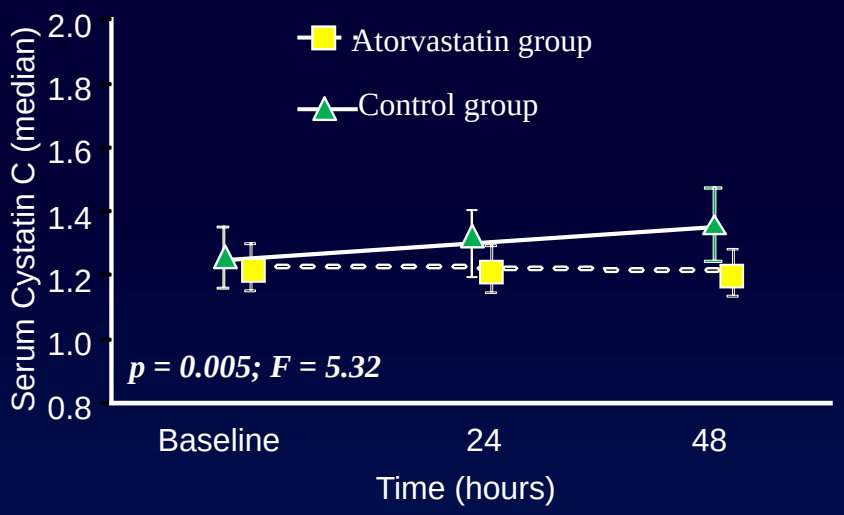
  : Antioxidant and Vasodilatory effect

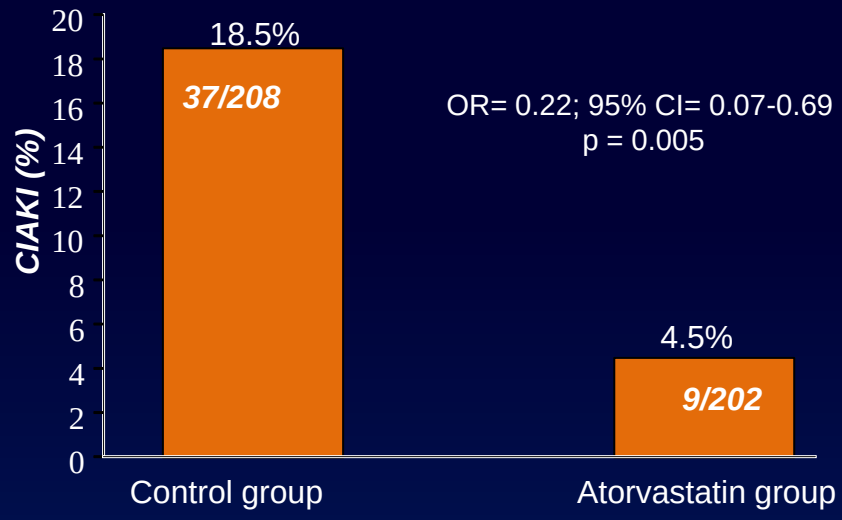
- recent meta-analyses : benefit for N-acetylcysteine

  (pooled odd ratio, 0.54 ~ 0.73 for contrast nephropathy)

More data needed for strong recommendation !!

Statins & CIN



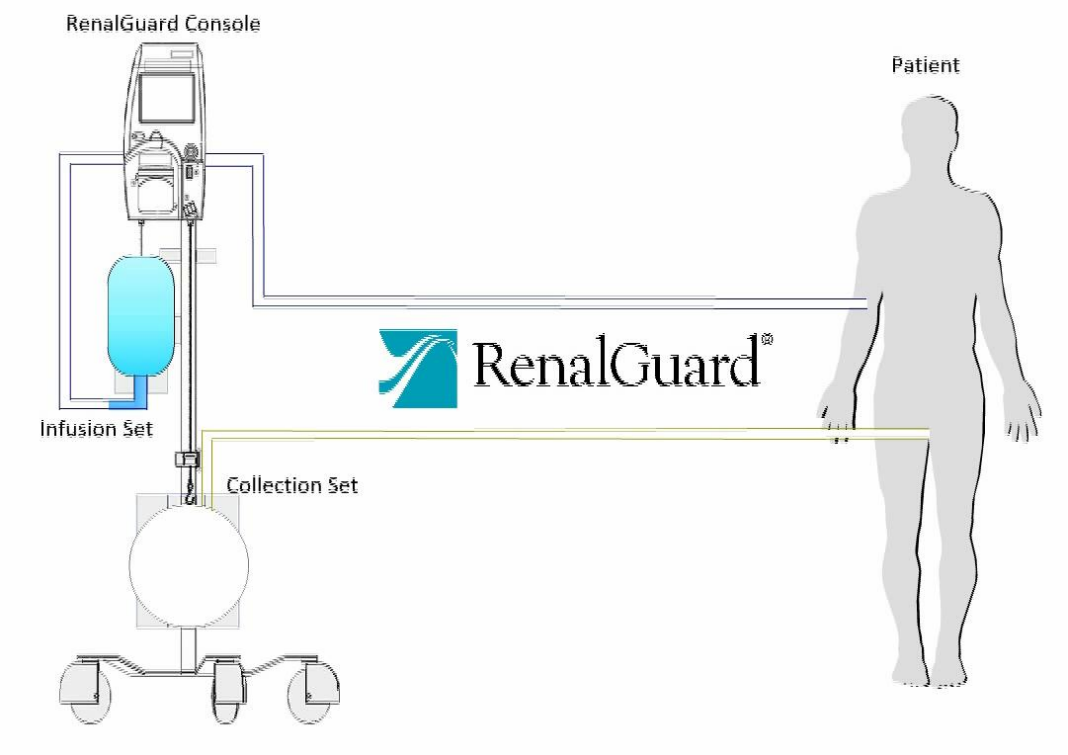


Quintavalle C et al. Circulation 2012 (in press)

Failed CIN Preventive Measures

- Fenoldopam (Dopamine agonist)
- Diuretics (Furosemide and Mannitol)
- Aminophylline
- Hemodialysis
- Endothelin Antagonists
- Calcium channel blockers

RenalGuard System



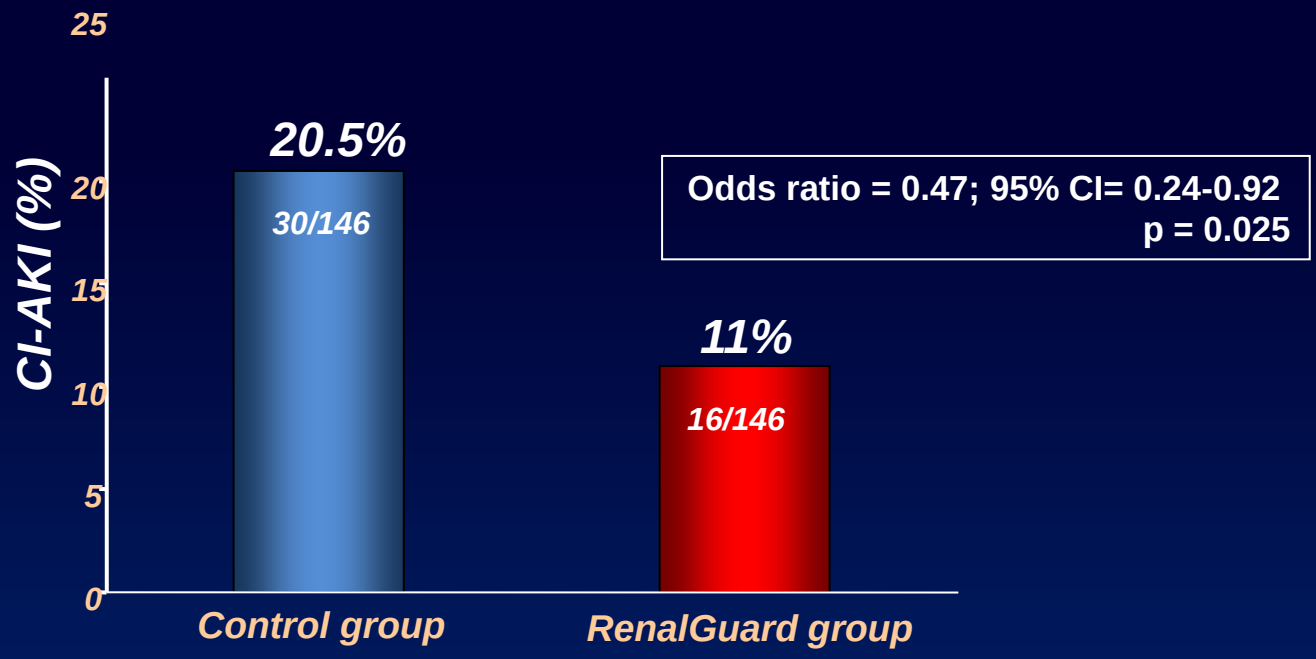
The Console measures the **volume of urine** in the collection set and infuses an **equal volume of hydration** fluid to match the patient's urine output

REMEDIAL II

Prospective, randomized, double-arm, multicenter clinical study

REnal Insufficiency Following Contrast **MEDIA** Administration II Tria**L**

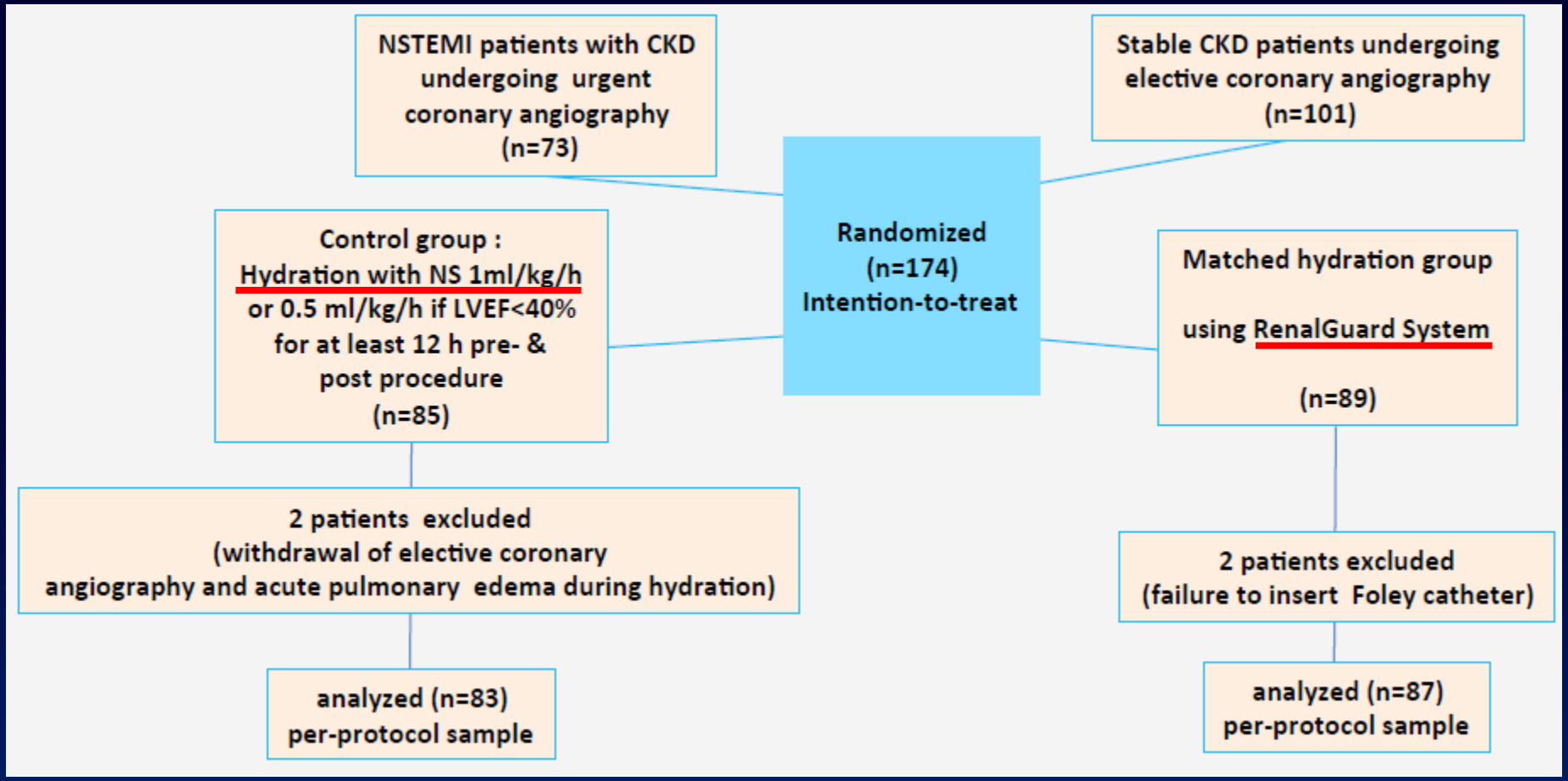
(risk score ≥11 and/or eGFR≤30 ml/min/1.73 m_2)



Briguori C et al, Circulaton 2011;124:00-7

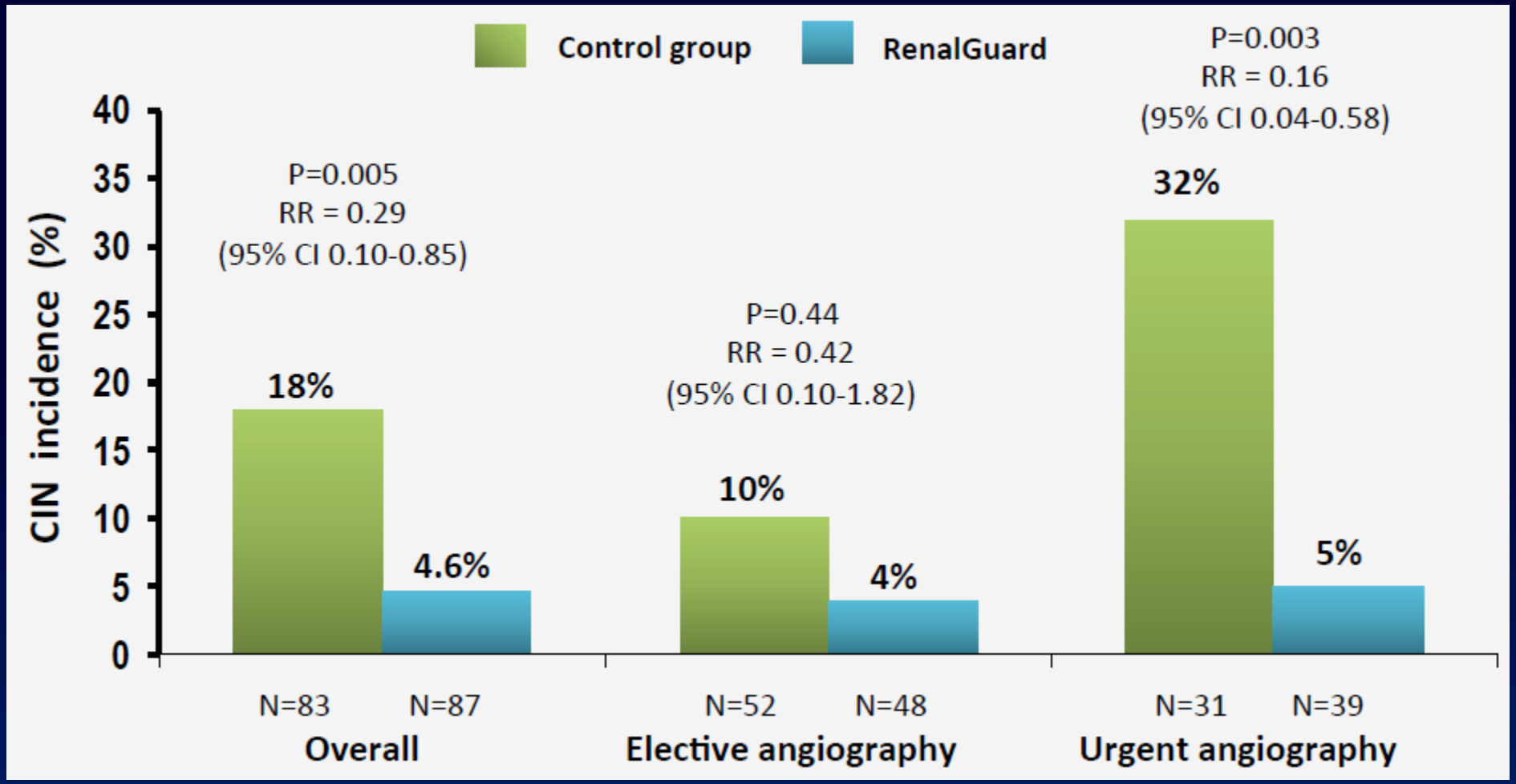
The MYTHOS trial

Consecu6ve CKD pa6ents (eGFR<60ml/min/1.73m2) undergoing coronary angiography between September 1, 2008 and September 15, 2010



Marenzi G et al, J Am Coll Cardiol Intv 2012;5:90-7

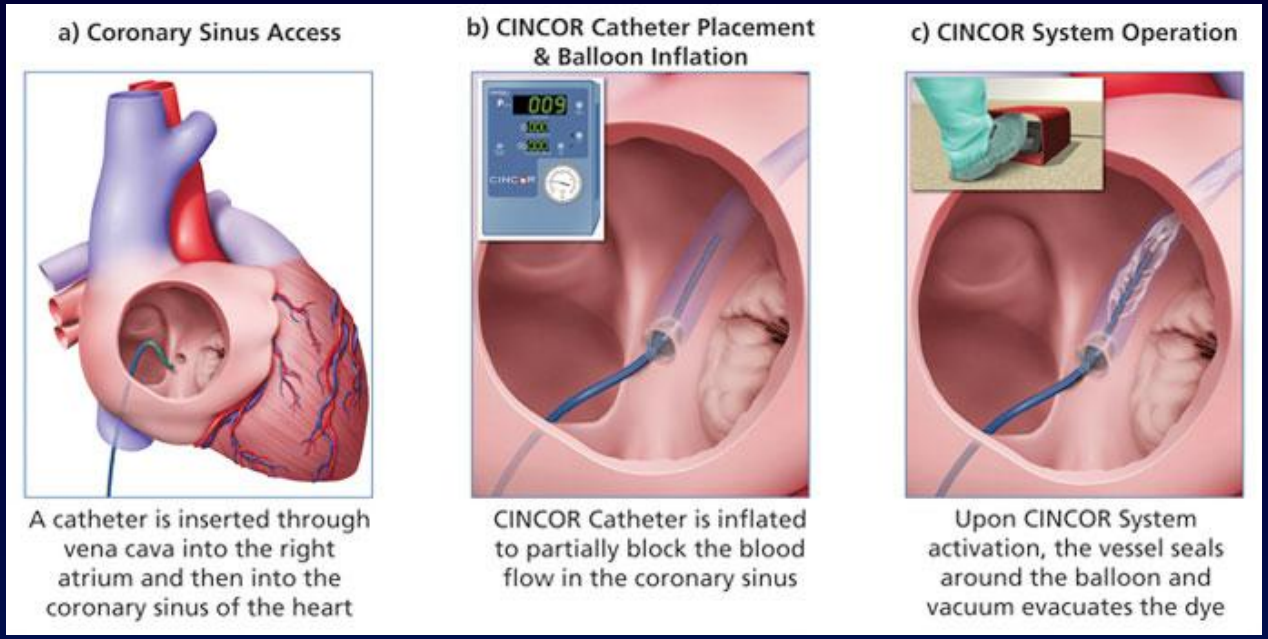
MYTHOS: Incidence of CIN

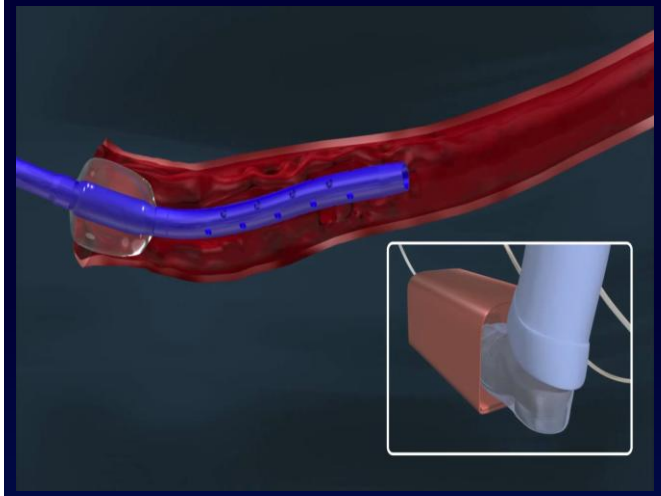


Marenzi G et al, J Am Coll Cardiol Intv 2012;5:90-7

New therapies for prevention of Contrast induced-acute kidney injury

CINCOR™ Contrast Removal System





This is a catheter and vacuum system that is designed to directly capture and remove a significant quantity of the dye as it leaves the coronary sinus before it makes its way to the kidneys.

CINCOR™ Pivotal Trial

1. Demonstrate a reduction in the incidence of CIN in subjects in which the CINCOR™ System group compared to the control group receiving standard of care medical practice 96 hours post-procedure

2. Demonstrate the safety of the CINCOR™ System by evaluating bleeding/transfusion events. Through 30 days post-procedure

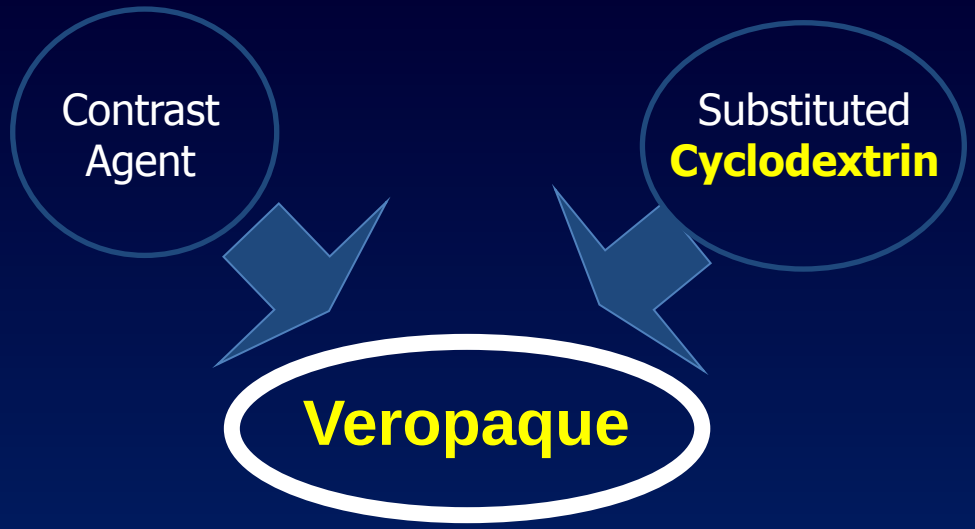
Estimated Enrollment: 600

Study Start Date: December 2012

New Contrast Media to avoid Contrast Induced AKI

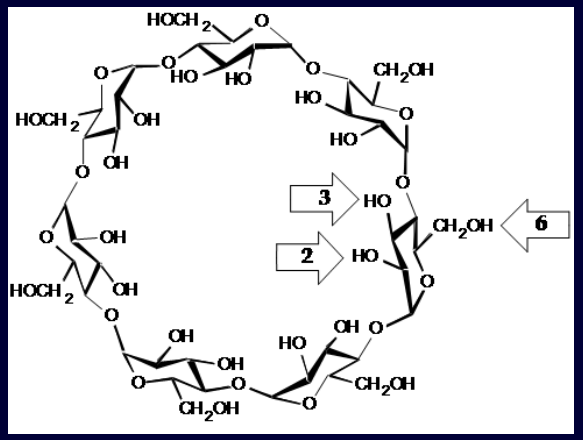
Scientists at Verrow found a way to prevent direct tubular toxicity of methotrexate

VEROPAQUE: A kidney safe X-ray contrast agent



Cyclodextrins

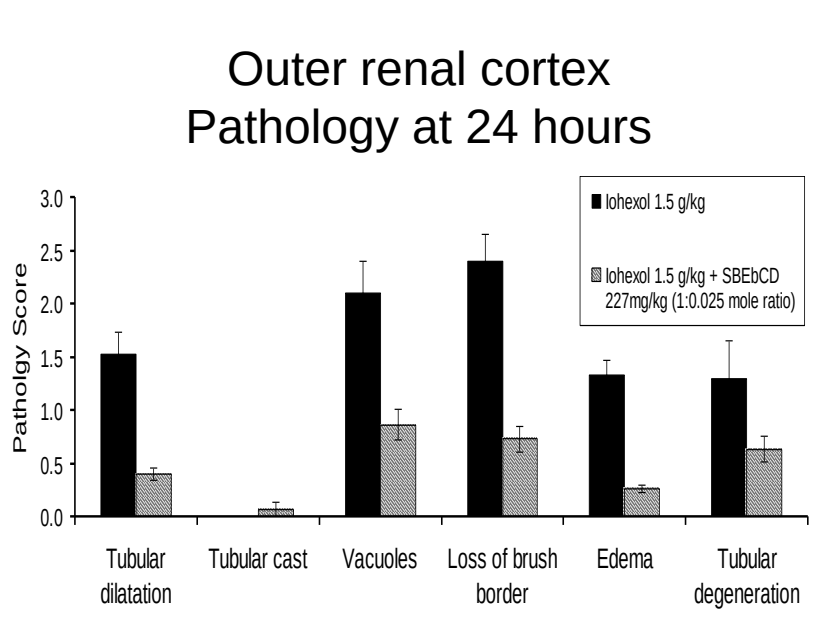
Naturally occurring oligosaccharides containing 6, 7, or 8 glucopyranose units in a donut shape with hydrophobic pocket

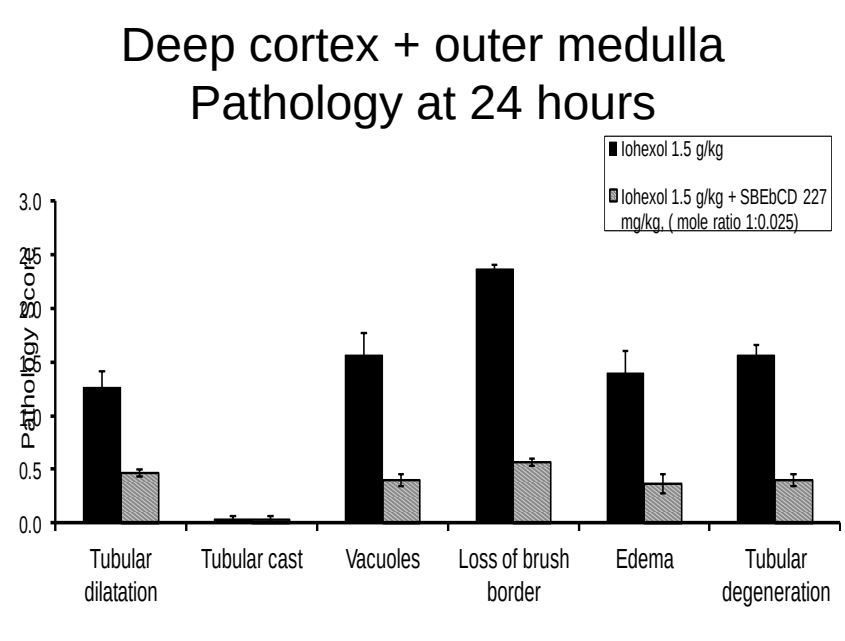


- Function as solubilizers by including insoluble drug molecule in the pocket
- Unsubstituted (natural) cyclodextrins are toxic when given IV
- Only two specific substituted cyclodextrins have been found safe enough for parenteral administration and are used in FDA approved drug products
- Previously thought to be inert excipients

Reduction in Pathology Scores

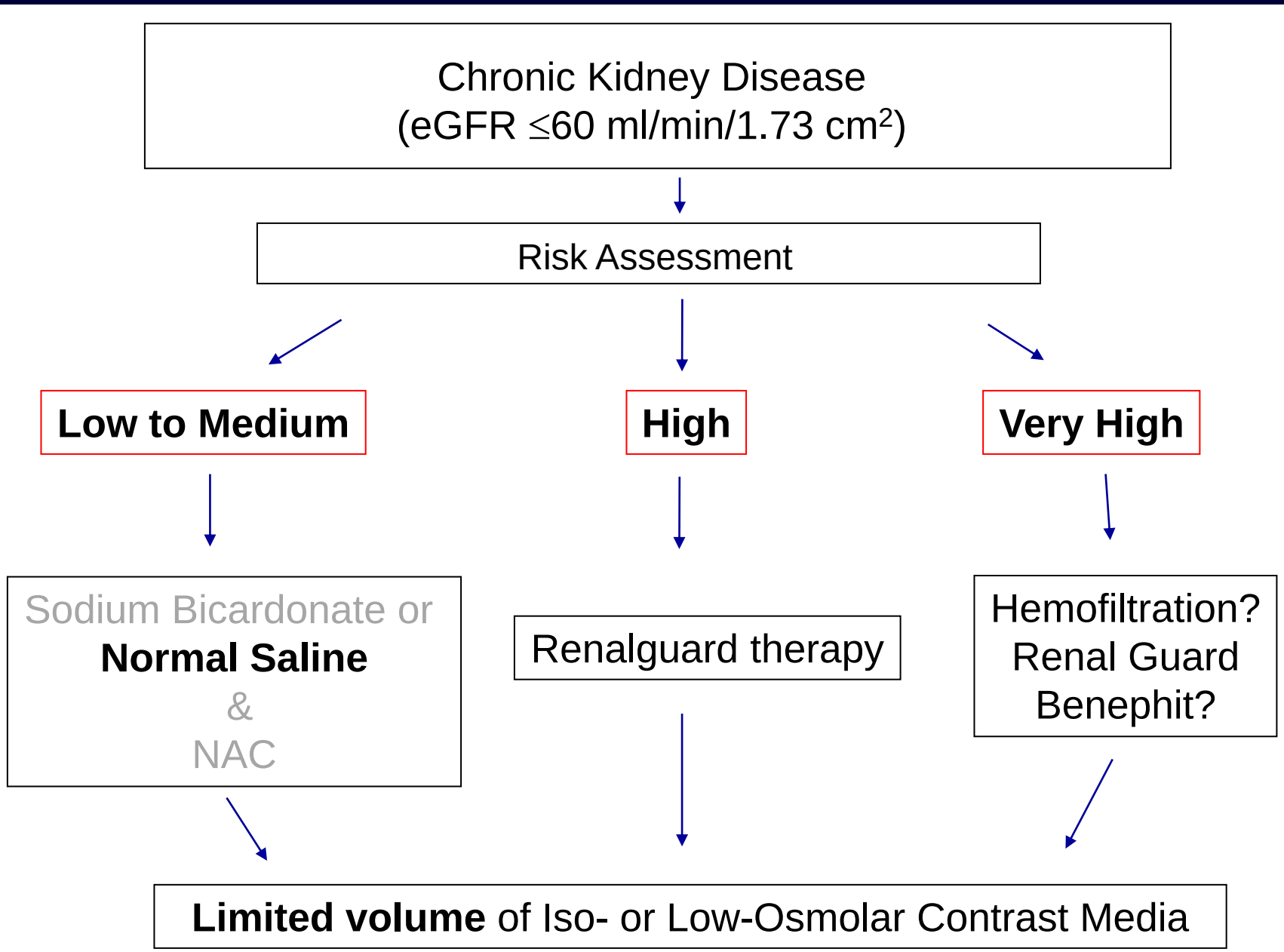
- **The kidney damage was quantitated**
- Two regions in each kidney (outer cortex and deep cortex)
- Five arbitrary fields per region @ 40x magnification
- Six parameters scored from 0 to 4
- Operator blinded to treatment





70% Reduction in Overall Pathology Scores

(Over 400 animals studied)


Chronic Kidney Disease
(eGFR ≤60 ml/min/1.73 cm2)
Risk Assessment
Low to Medium
High
Very High
Sodium Bicardonate or
Normal Saline
&
NAC
Renalguard therapy
Hemofiltration?
Renal Guard
Benephit?
Limited volume of Iso- or Low-Osmolar Contrast Media

Conclusions

- **IV Hydration pre-PCI (12 hours recommended)**
- Eliminate risk factors if possible
- D/C nephrotoxic drugs (NSAIDS, antibiotics, etc)
- No role for NAC or sodium bicarbonate (in the absence of new data)
- Use lower volume of CM (Low or Iso-osmolar CM)
- Biomarkers to identify patients at risk as well as diagnose CIN earlier