

The present status of CIN prevention

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SJRS 2010-Vejle Denmark

Background

- Contrast medium-induced nephrotoxicity (CIN) still remains one of the most clinically important complications following the use of iodine contrast media

Why?

Is CIN a clinical problem in spite of the use of less toxic contrast media?

Increased use of contrast media

- Higher volumes and concentrations to sicker patients
- Increased use of CT and interventional vascular techniques

Reasons for Concern

- With 60 million CM doses/yr, even a low incidence of CM complications affects a large number of patients
- Patients exposed to CM are increasingly elderly, with multiple co-morbidities that increase their risk
- The most common form of CM-induced injury, contrast-induced nephropathy (CIN) can have serious renal and nonrenal consequences

How to avoid

"Luck favours a prepared mind"

Louis Pasteur

How do you prepare your mind

- **What is CIN (CI-AKI)**
- Is CIN dangerous
- Who is the risk patient
- How do I manage the risk

Contrast-Induced Nephropathy (CIN)

Definition

- New onset or exacerbation of renal dysfunction after contrast administration without other identifiable causes:

Increase by >25%

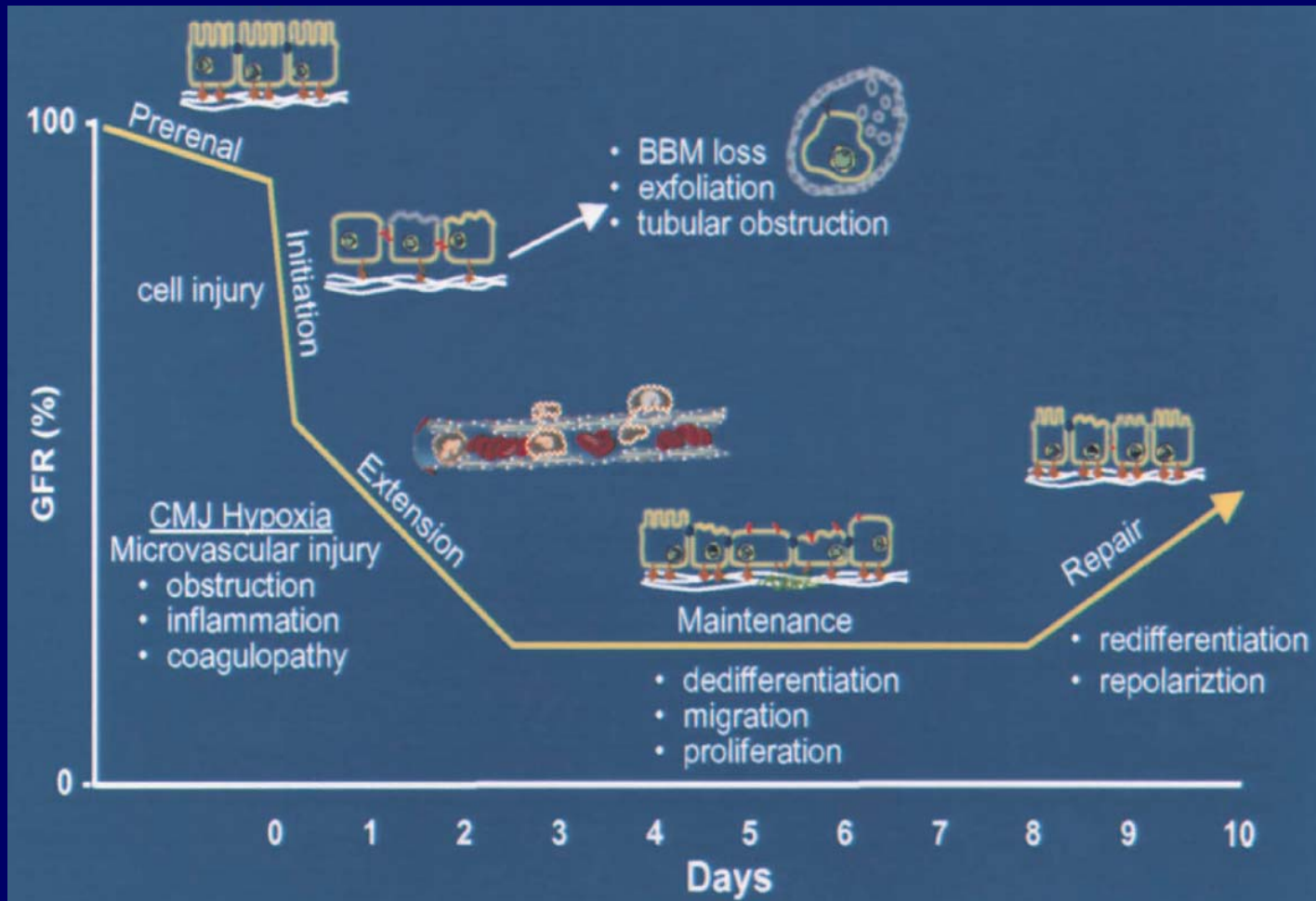
or

Absolute \uparrow of >0.5 mg/dL or $\geq 44.2 \mu\text{mol/L}$

From baseline
serum creatinine

Occurs 24–48 hours post contrast exposure, with creatinine peaking 5–7 days later and normalizing within 7–10 days in most cases

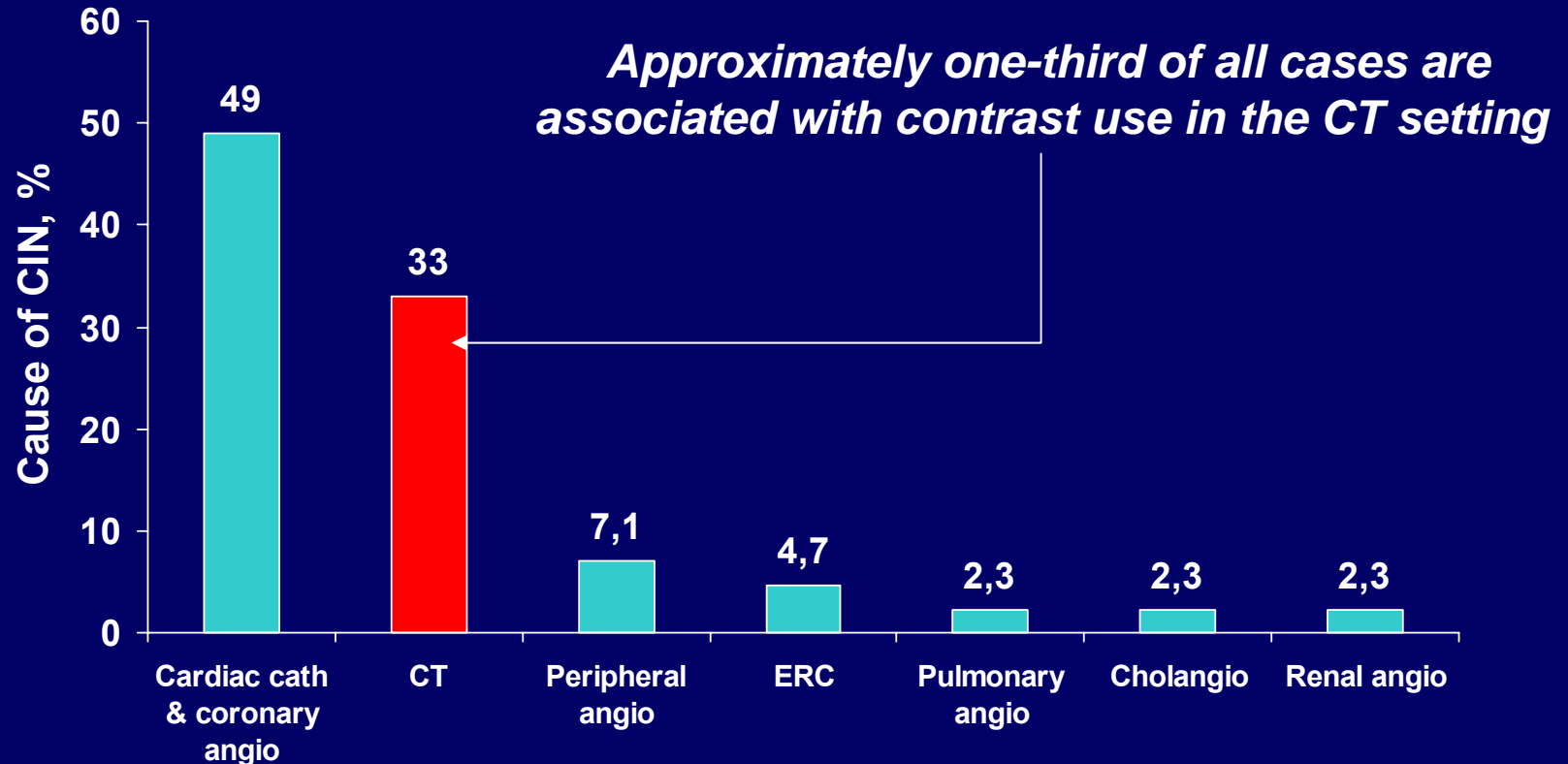
Clinical & cellular phases of ARF



Incidence of CIN

- Third most common cause of hospital-acquired renal failure
- Occurs in less than 1% of general population
- Occurs in 5.5 – 12 % of patients with renal insufficiency
- But, occurs in 50% of patients with both renal insufficiency and diabetes mellitus

Which Contrast Studies Are Most Associated With CIN?



Can “pseudo CIN ”(raise in SCr)
occur
without contrast media?

“Pseudo CIN” without contrast medium

- 32.000 patients – serum creatinine measurements
- Same frequency of CIN with/without contrast media administration

“Pseudo CIN” without contrast medium

- 11500 patients – serum creatinine measurements
- Same frequency of “AKI” without contrast media as after an IOCM (CT study)

CIN with contrast medium

- Differences in randomized controlled studies must be due to "true CIN", but the frequency may be overestimated, especially in not "high-risk patients".
- Occur in experimental animal studies

How do you prepare your mind

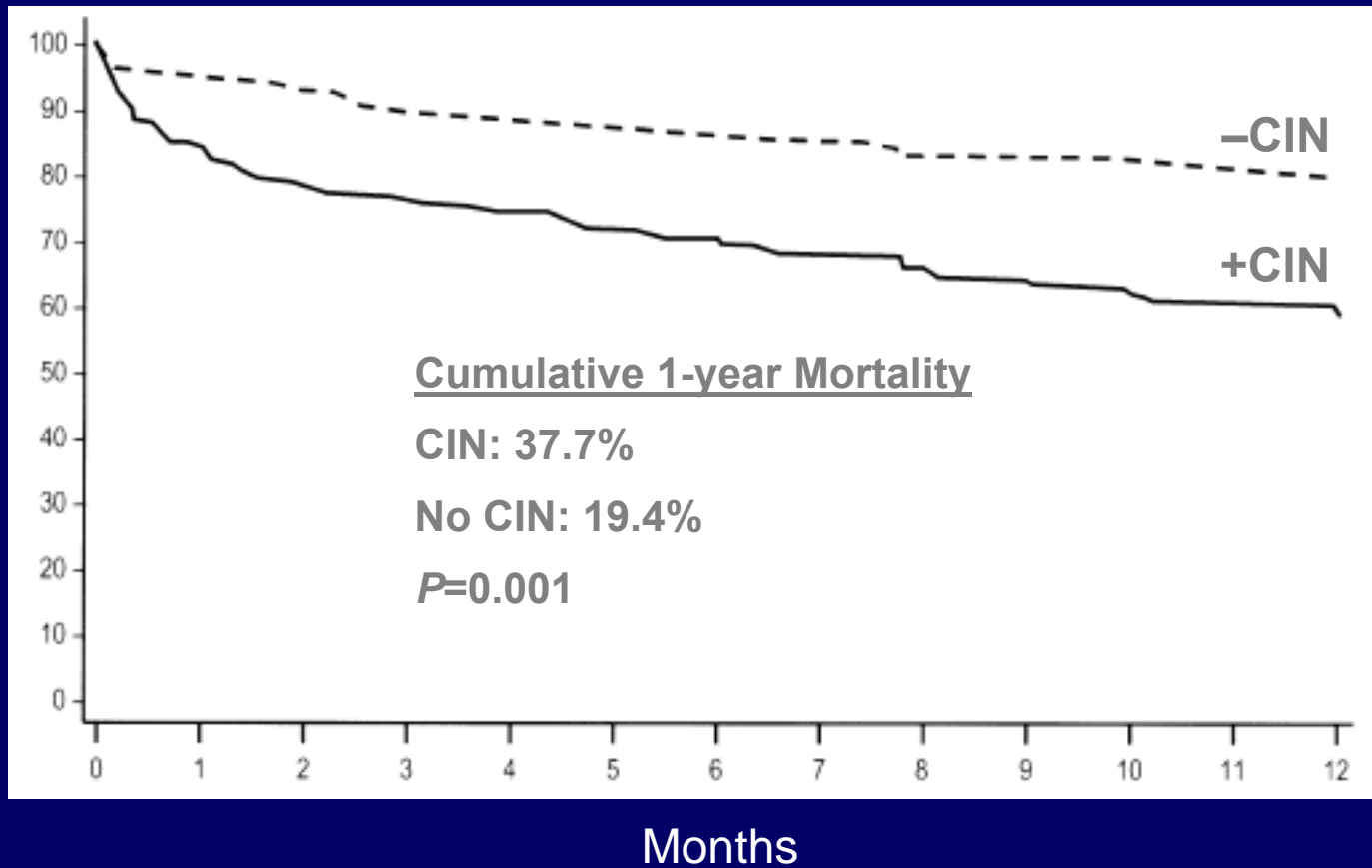
- What is CIN
- **Is CIN dangerous**
- Who is the risk patient
- How do I manage the risk

Contrast-induced nephropathy

- **What does a rise in serum creatinine >0.5mg/dL (>44 μ mol/L) within 48 hours mean ?**
- ... a reasonable surrogate for more relevant outcomes such as need for dialysis, increased length of hospitalization.
- ... a marker for outcome (1-year mortality).

Kaplan Meier 1-year Survival Rates Following CIN

% Event-free Survival



Effect of CIN on In-hospital Outcomes in Patients Undergoing PCI (N=7,230)

	With CIN	Without CIN
Patients without CKD (n=5,250)		
n (%)	688 (13.1%)	4,562
Death	2.5%	0.1%
Cardiac death	2.0%	0%
Major adverse cardiac event	6.8%	0.9%
Postprocedure length of stay, days	3.6 ± 5.1	1.8 ± 2.4
Patients with CKD (n=1,980)		
n (%)	381 (19.2%)	1,599
Death	6.3%	0.8%
Cardiac death	4.0%	0.5%
Major adverse cardiac event	9.3%	1.1%
Postprocedure length of stay, days	6.8 ± 7.1	2.3 ± 2.5

Review of Death Certificates (1999)

Cause of death	%
Renal failure or nephropathy	58
Anaphylactic shock and allergic reactions	19
Cardiopulmonary arrest	10
Respiratory failure	8
Stroke and cerebral hypoxia	4

- 48 certificates collected, 46 did not state the CM name
- 60% women
- Median age 73 y
- Variety of contributing conditions mentioned

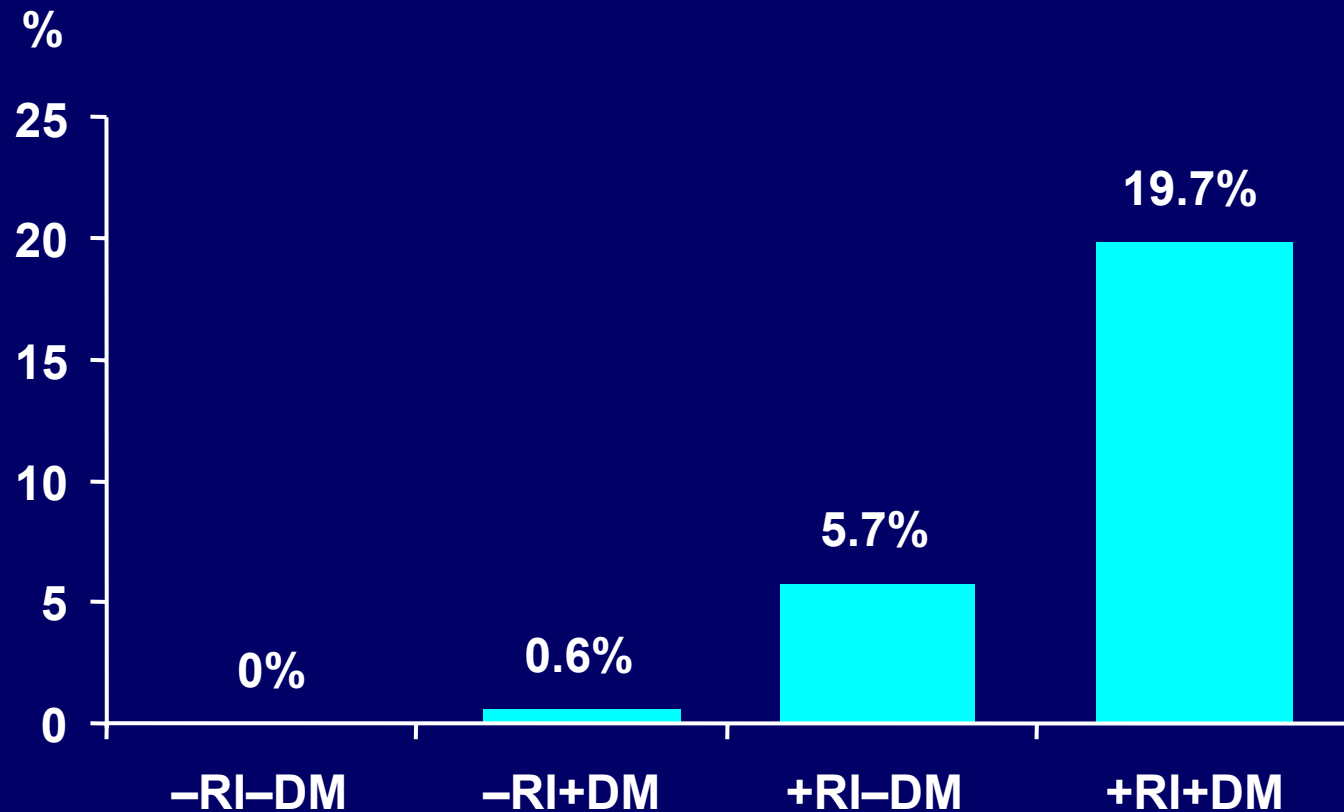
Contrast-Induced Nephropathy (CIN)

- Occurs in ~3% of the general population
 - Responsible for 11% of cases of hospital-acquired renal insufficiency
- $\geq 50\%$ risk for developing CIN in some at-risk patient subsets
- Consequences of CIN
 - Longer hospital stays
 - Increased in-hospital complications
 - Increased mortality

How do you prepare your mind

- What is CIN
- Is CIN dangerous
- **Who is the risk patient**
- How do I manage the risk

Frequency of CIN according to diabetic and renal status (n=1196)



Rudnick et al. (1995)

CIN: Patient-related Risk Factors

Established

- Pre-existing renal impairment with DM
- Pre-existing renal impairment without DM
- Dehydration
- Congestive heart failure
- Old age
- Administration of nephrotoxic drugs

Questionable

- DM without renal impairment
- Hypertension
- Hyperuricemia
- Proteinuria
- Multiple myeloma
- Gender

CIN, contrast-induced nephropathy; DM, diabetes mellitus

Asif A et al. Am J Ther. 2003;10:137-147.

ESUR, Guidelines on Contrast Media version 5.0

Risk factors

- Marked anemia/hypoxia – lack of oxygen
 - Anemia: hematocrit <39% men; <36% women
(WHO definition)
- Any other disease affecting renal function
 - Pancreatitis, sepsis
- Hospitalized - ICU - patient

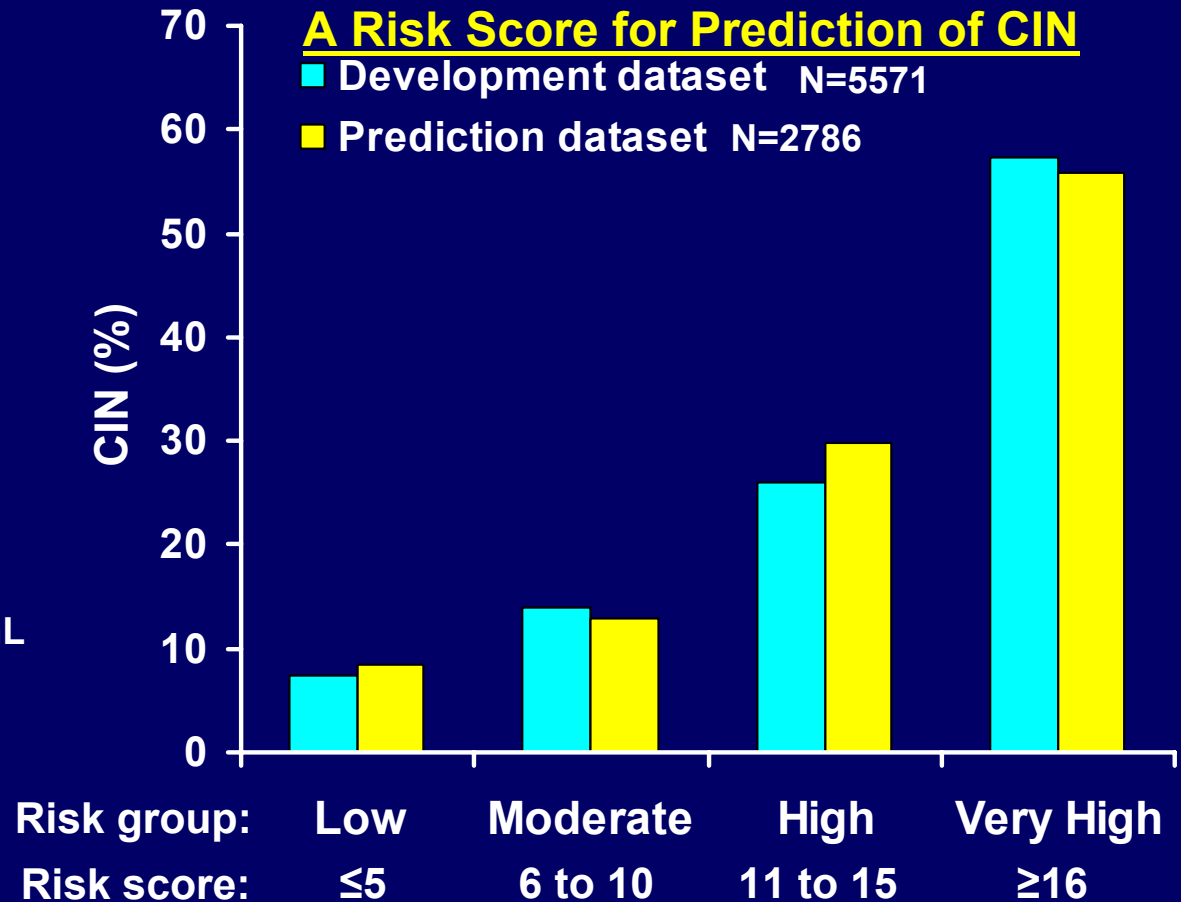
Risk factors

- Repeat CM examinations including MR
- Major surgery

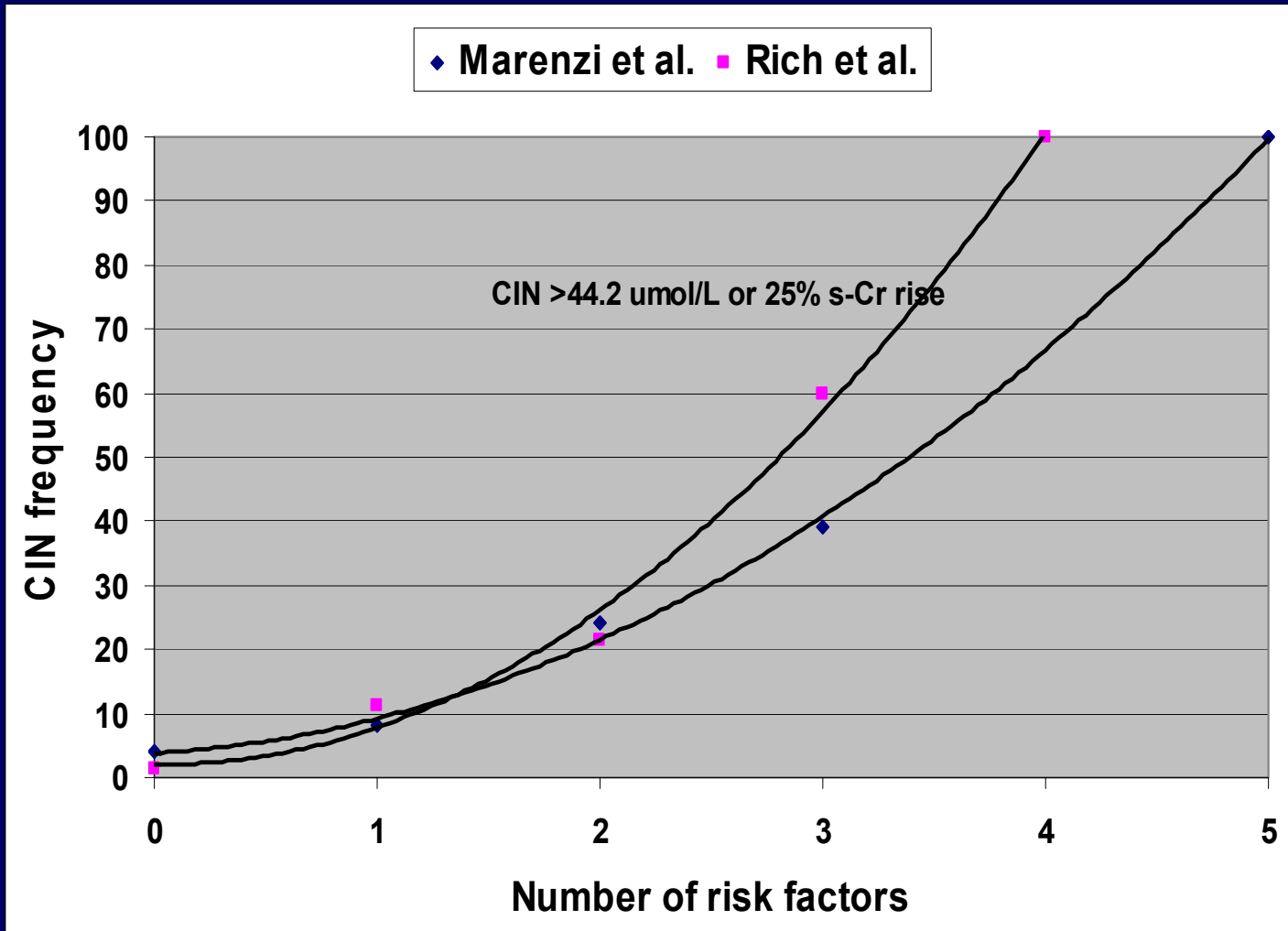
Multiple Risk Markers Create a Very High Risk for CIN

Multivariate Predictors

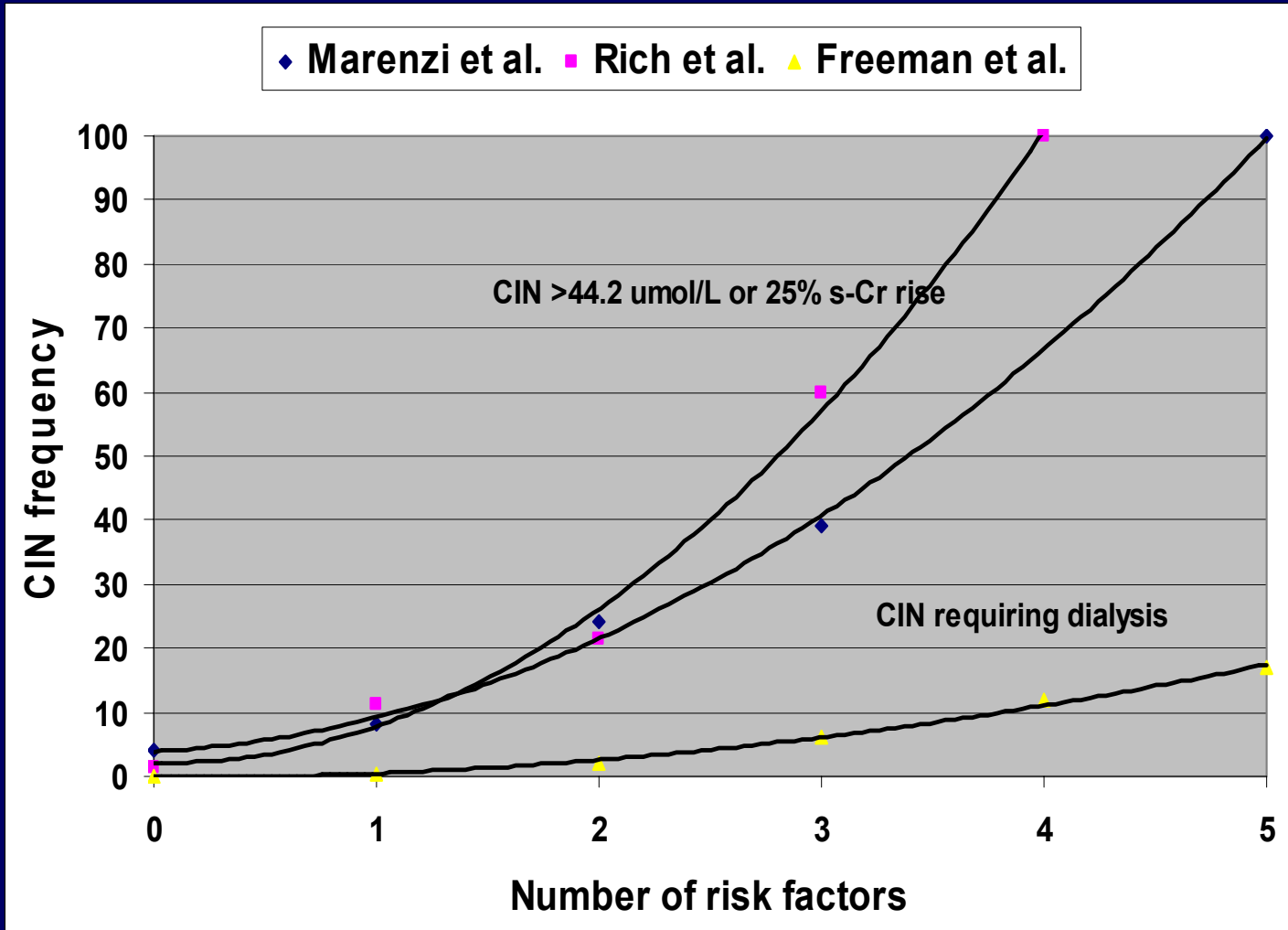
Hypotension	5 points
IABP use	5 points
CHF	5 points
SCr >1.5 mg/dL (>132 $\mu\text{mol/L}$)	4 points
Age >75 y	4 points
Anemia	3 points
Diabetes	3 points
Contrast volume	1 point/100 mL



CIN - number of risk factors



Severe CIN - number of risk factors



Risk stratification

- Renal function
- Contrast medium dose
 - volume *and* concentration
 - 140– 400 mg I/mL, a factor 3 difference
- No. and degree of other risk factors

Summary

- **The increased utilization of contrast media in high-risk patients may result in an increased incidence of contrast induced nephropathy.**
- **Prevention of contrast induced nephropathy is mandatory.**

How do you prepare your mind

- What is CIN
- Is CIN dangerous
- Who is the risk patient
- How do I manage the risk

Prevention

Primary prevention

- Alternative imaging
- Use the least nephrotoxic CM and adapt dose to renal function (ALARA)

Secondary prevention

- Identify risk-patients, plasma volume expansion, pharmacological, withdraw nephrotoxic drugs, RRT-dialysis, hemo-filtration, etc.

Minimising the Risk of CIN In Patients at Risk

- *Withdrawal of nephrotoxic medications*
- Use of adequate hydration
- Pharmacological interventions
- Appropriate selection and use of CM

Which Drugs Are Nephrotoxic?

Definitely avoid

- NSAIDs (both COX-1 and COX-2 inhibitors)
- Aminoglycosides
- Cyclosporin
- FK-506
- Amphotericin B

Unclear risk

- ACE-inhibitors/angiotensin-receptor blockers
- Chronic diuretics

Alamartine E et al. *Eur J Intern Med.* 2003;14:426-431;

Evenepoel P. *Best Pract Res Clin Anaesthesiol.* 2004;18:37-52;

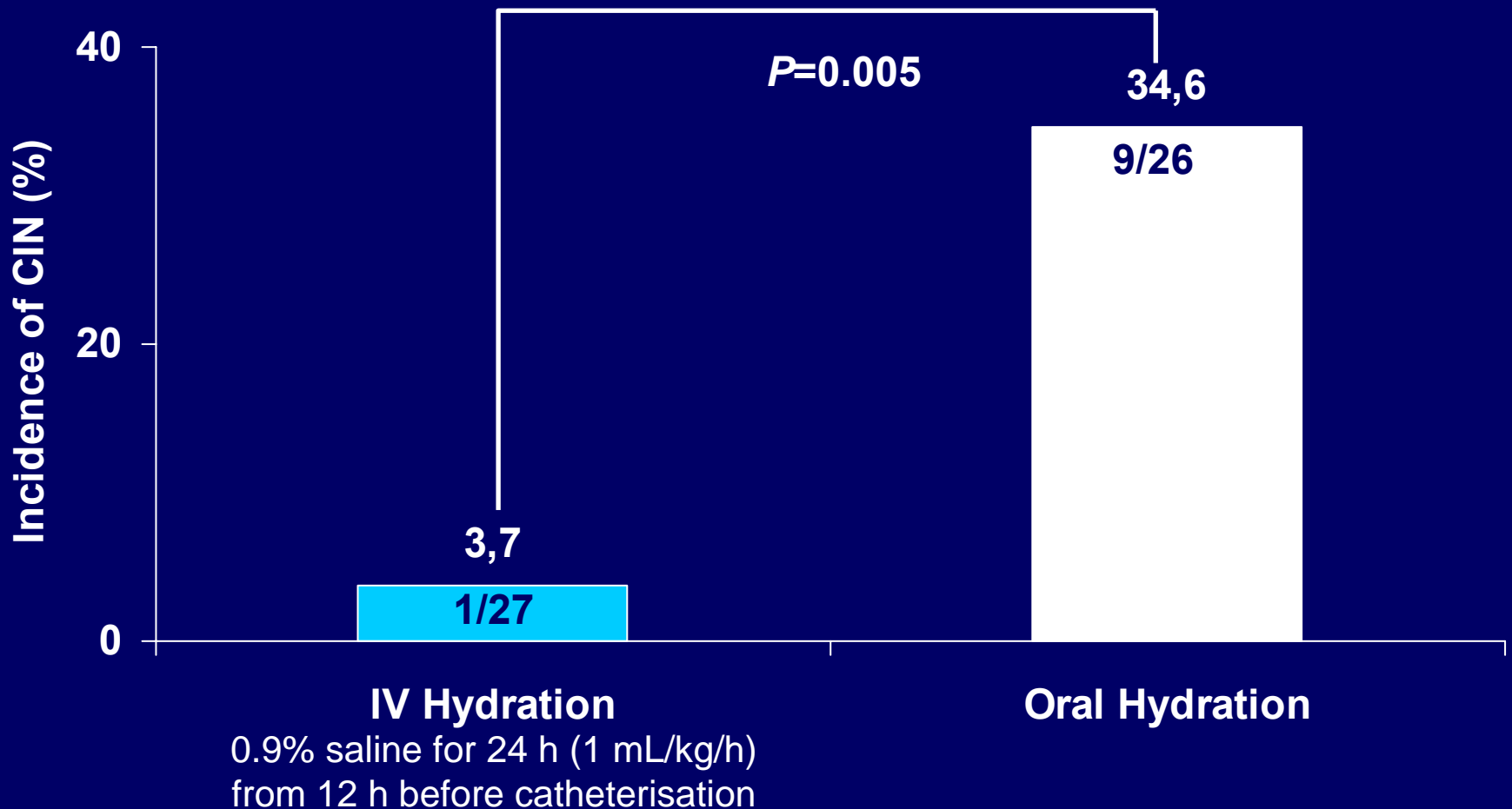
Heyman SN et al. *Invest Radiol.* 1999;34:685-691;

Morcos SK et al. *Eur Radiol.* 1999;9:1602-1613.

Minimising the Risk of CIN In Patients at Risk

- Withdrawal of nephrotoxic medications
- Use of adequate hydration (plasma expansion)
- Pharmacological interventions
- Appropriate selection and use of CM

Incidence of CIN Is Lower with IV Saline Hydration than Unrestricted Oral Fluids



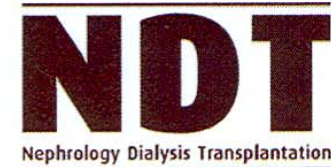
Mean baseline calculated CrCl: 79.6 ± 31.9 mL/min; CIN defined as $44.2 \mu\text{mol/L}$ rise of creatinine over baseline within 48 h

Nephrol Dial Transplant (2006) 21: 2120–2126

doi:10.1093/ndt/gfl133

Advance Access publication 12 April 2006

Original Article



A randomized trial of saline hydration to prevent contrast nephropathy in chronic renal failure patients

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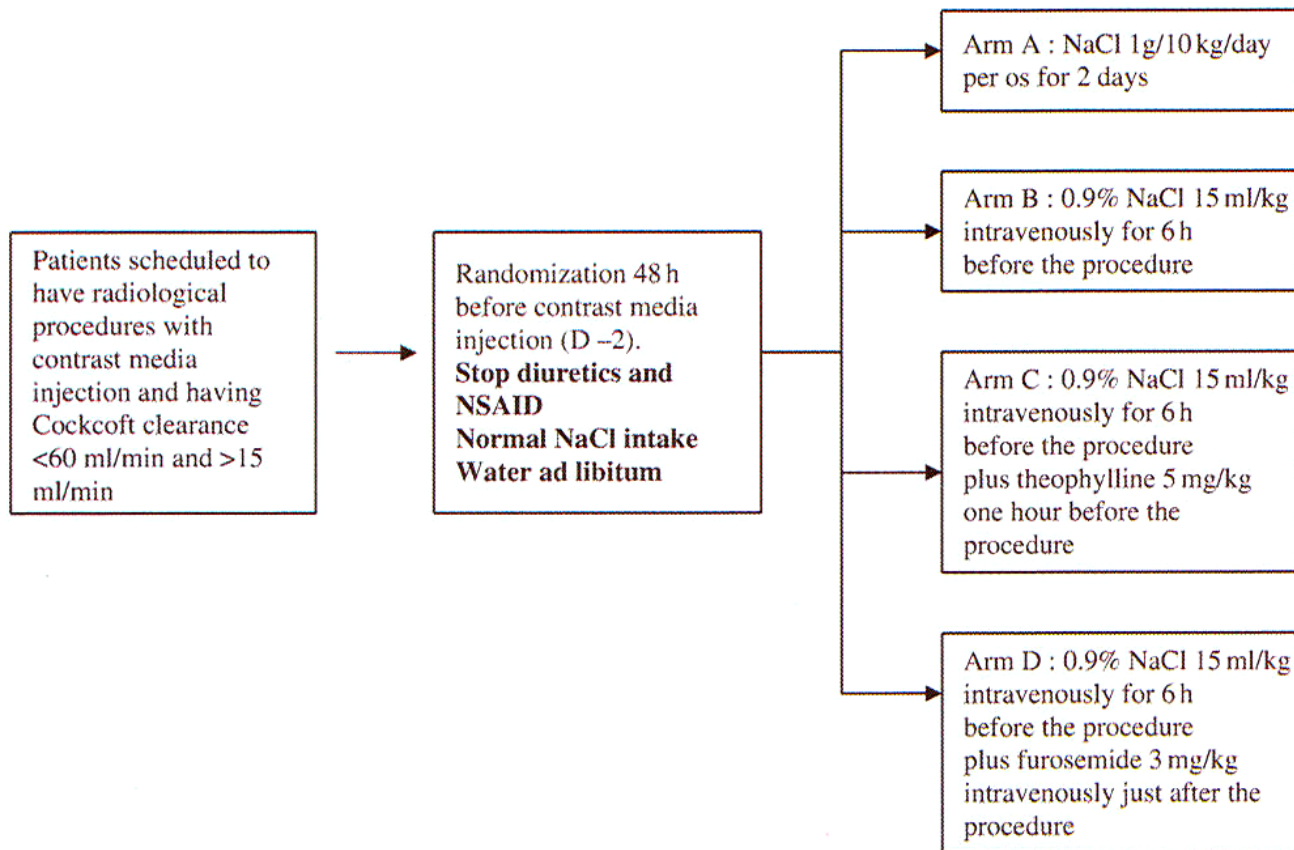


Fig. 1. Study profile.

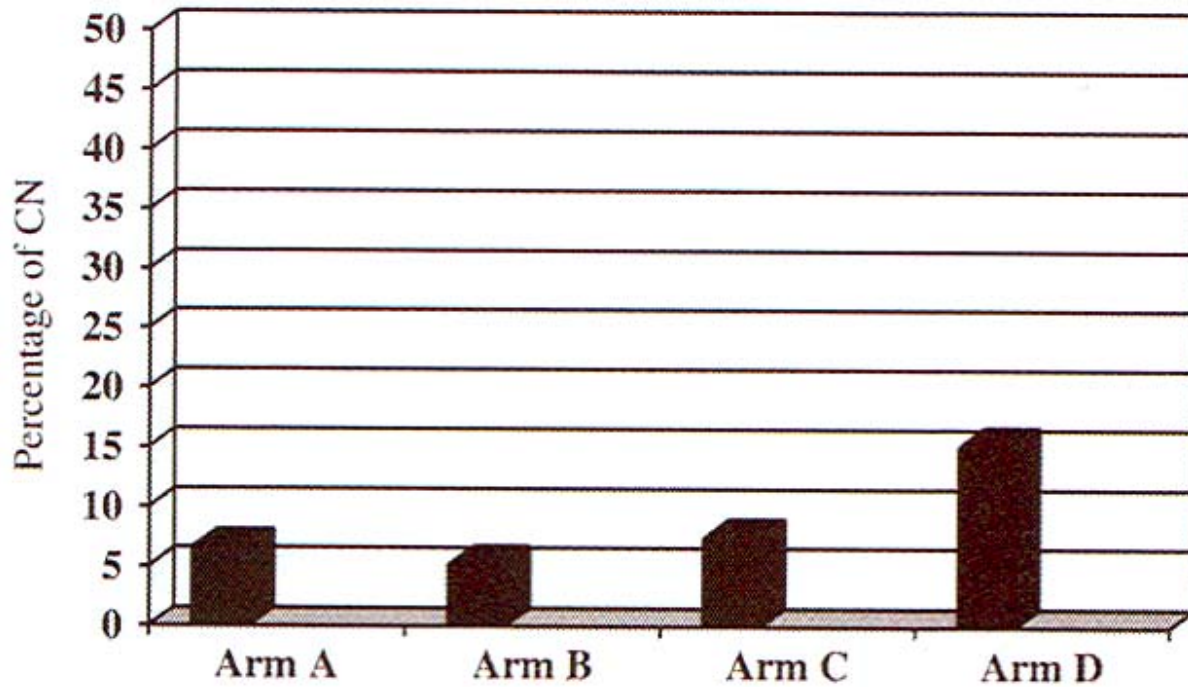
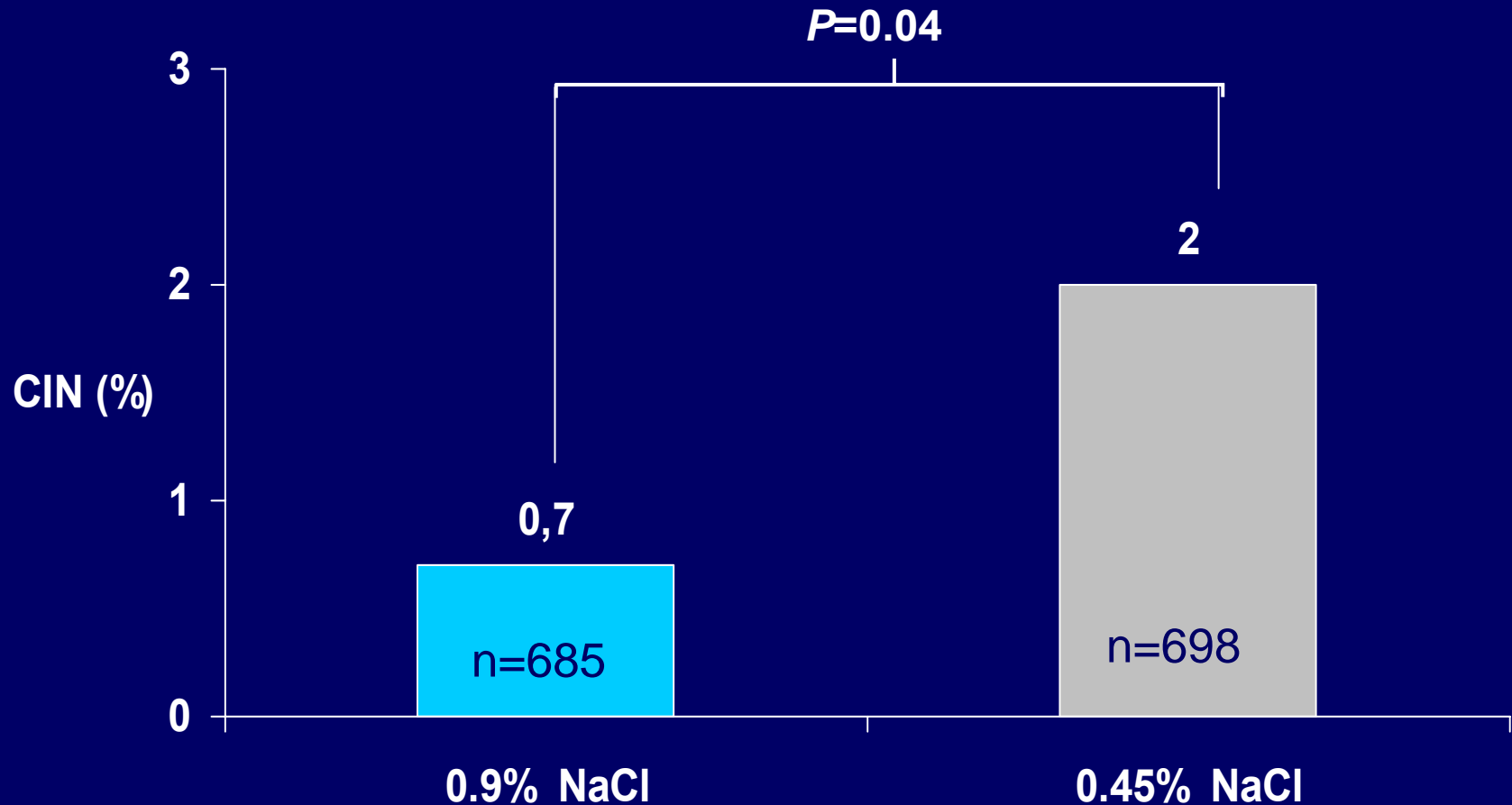


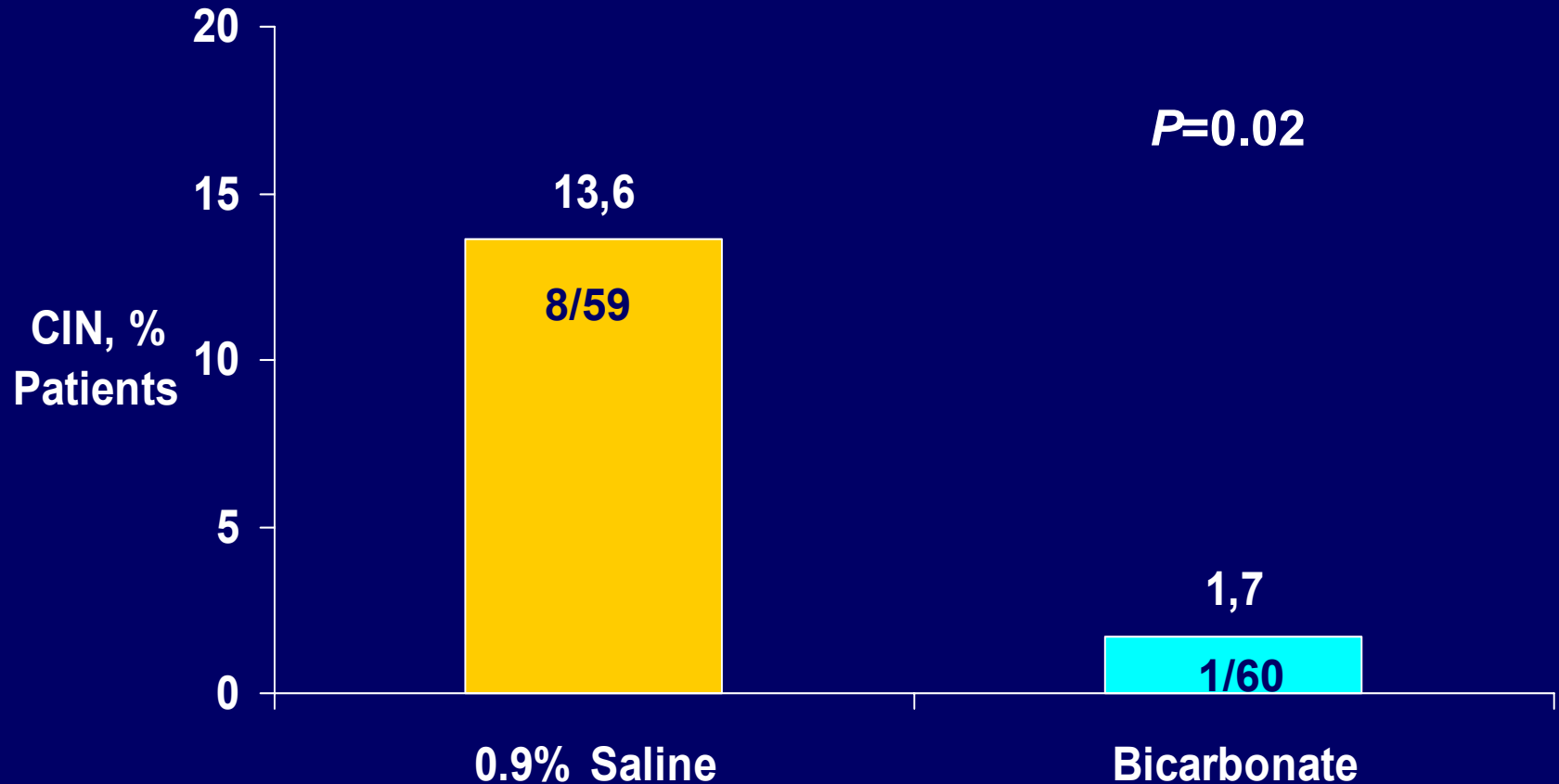
Fig. 2. Prevalence of CN in the four arms of the study.

Prevention of CIN: Normal (0.9%) vs Half-normal (0.45%) IV Saline



CIN defined as 44.2 $\mu\text{mol/L}$ increase in SCr over baseline within 24 or 48 h

Incidence of CIN Is Reduced in Patients Hydrated With NaHCO_3



Review: CIN
 Comparison: 01 Incidence of CIN
 Outcome: 01 CIN incidence

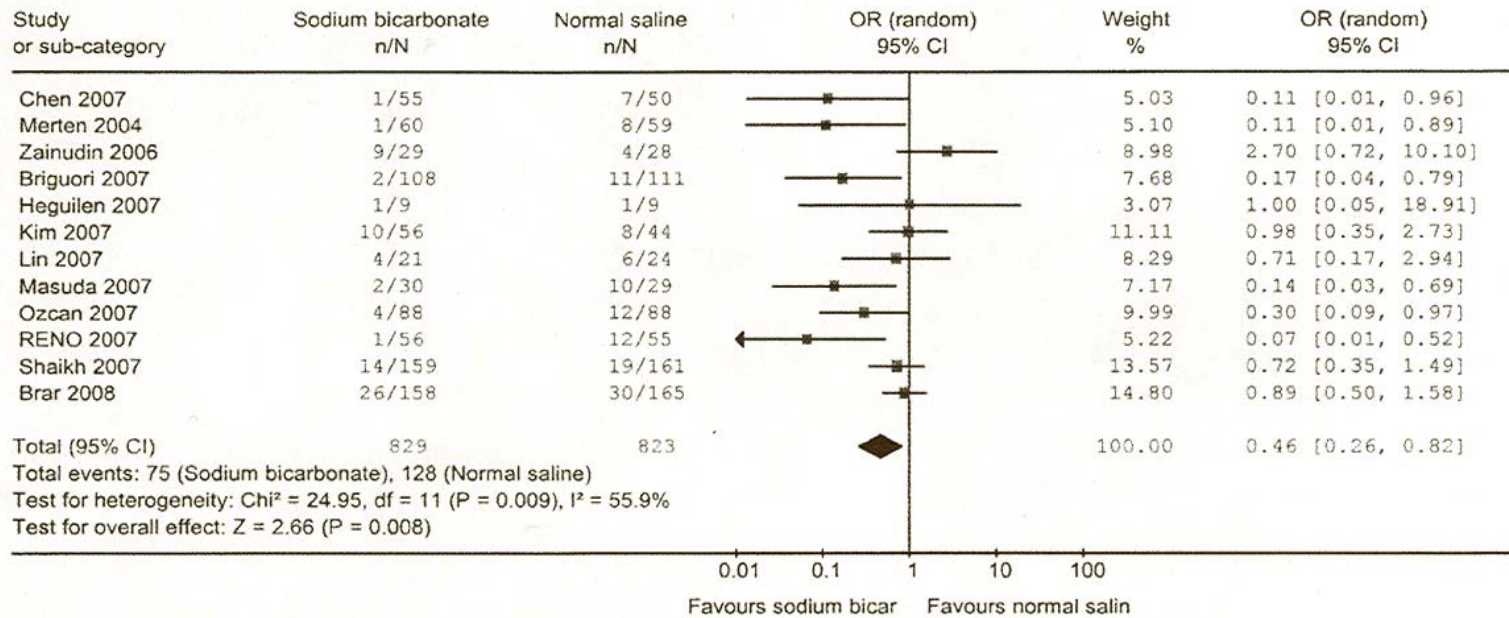
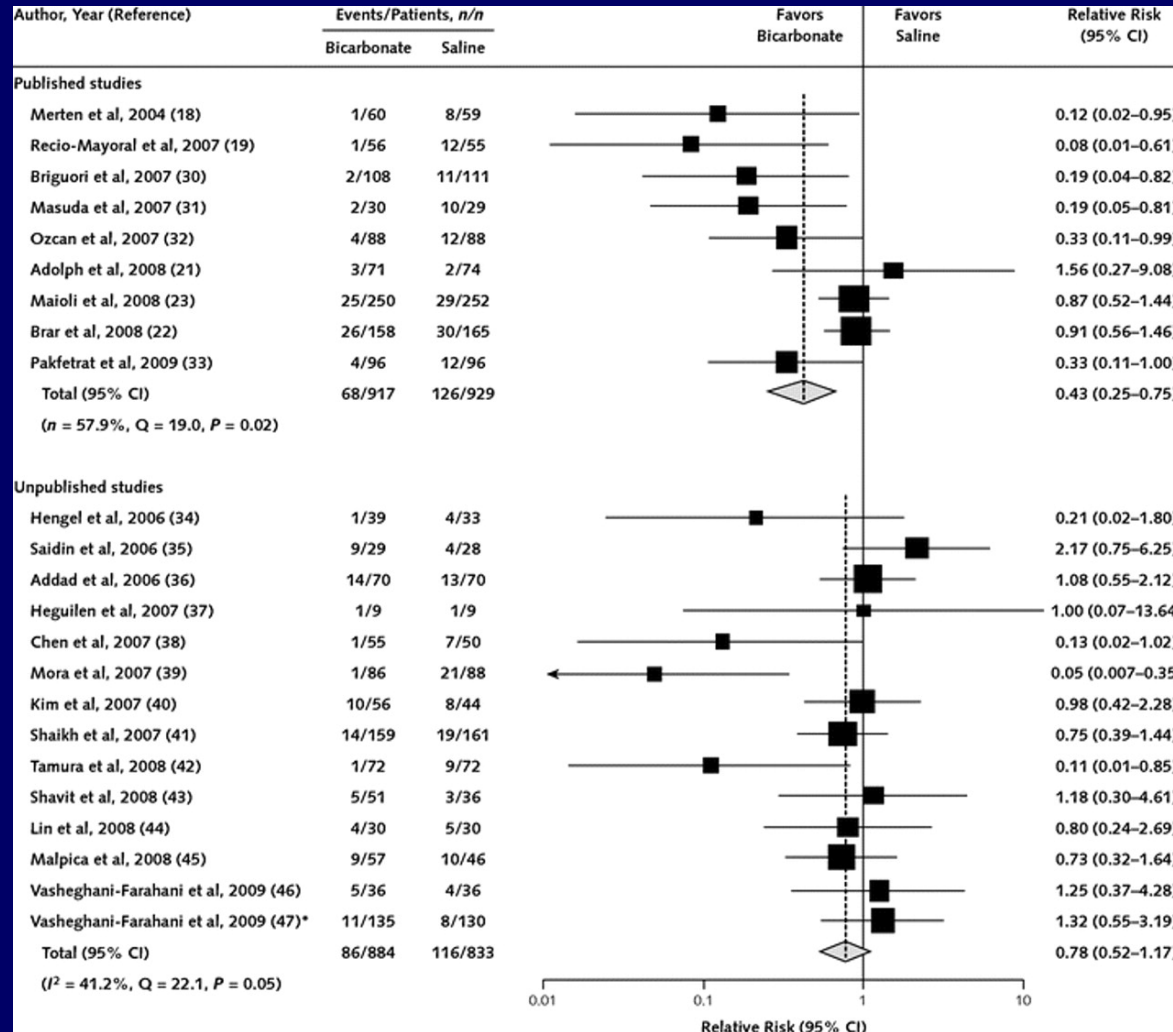


Figure 2. Development of contrast-induced nephropathy (CIN). Abbreviations: CI, confidence interval; OR, odds ratio.

Forest plot of relative risks for contrast-induced nephropathy from 23 studies.* This study has been published since we did our review.



Zoungas S et al. Ann Intern Med 2009;151:631-638

Annals of Internal Medicine

Prophylaxis

Hydration!! (plasma expansion)

- Sodium chloride (0.9% NaCl)
 - ESUR: 100 ml/h 4h before and 24h after
 - SFMR: 1 ml/kg/h 6h prior 12-24h after
taking into account cardiac and renal status
- Intravenous better than per oral
- Fluid list
- Cave forced diuresis

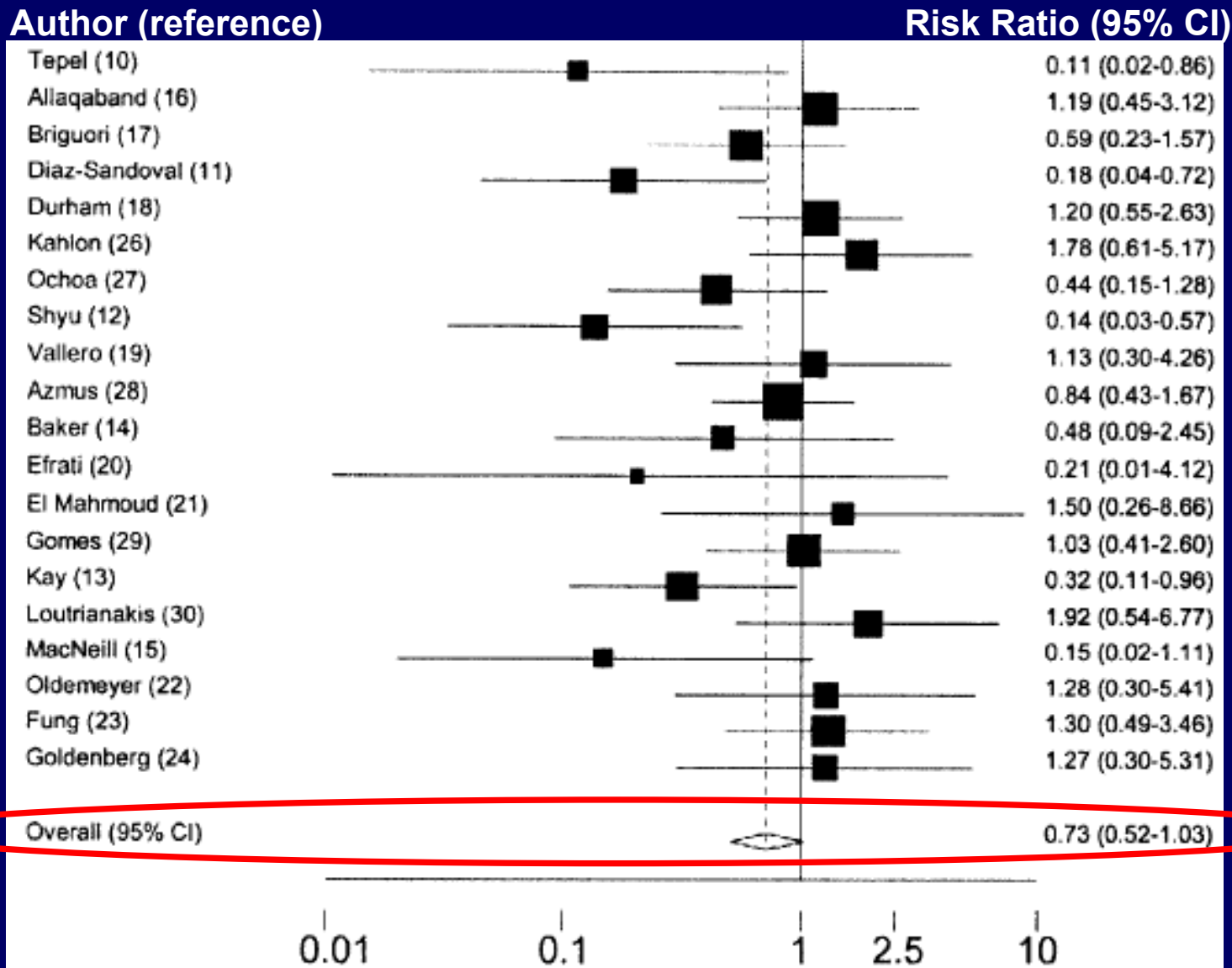
Minimising the Risk of CIN In Patients at Risk

- Withdrawal of nephrotoxic medications
- Use of adequate hydration
- **Pharmacological interventions**
- Appropriate selection and use of CM

Pharmacological Interventions and the Prevention of CIN

- Strategies that do not work
 - Mannitol
 - Furosemide
 - Dopamine
 - Atrial natriuretic peptide
 - Fenoldopam
- Strategies that may work
 - Calcium channel blockers
 - Theophylline
 - Ascorbic acid
 - Prostaglandins
 - **N-acetylcysteine**

Meta-analysis of 20 RCTs Fails to Show a Clear Benefit of NAC



Review: Contrast-Induced Acute Kidney Injury
 Comparison: N-Acetylcysteine and Sodium Bicarbonate versus N-Acetylcysteine
 Outcome: Contrast-Induced Acute Kidney Injury by definition

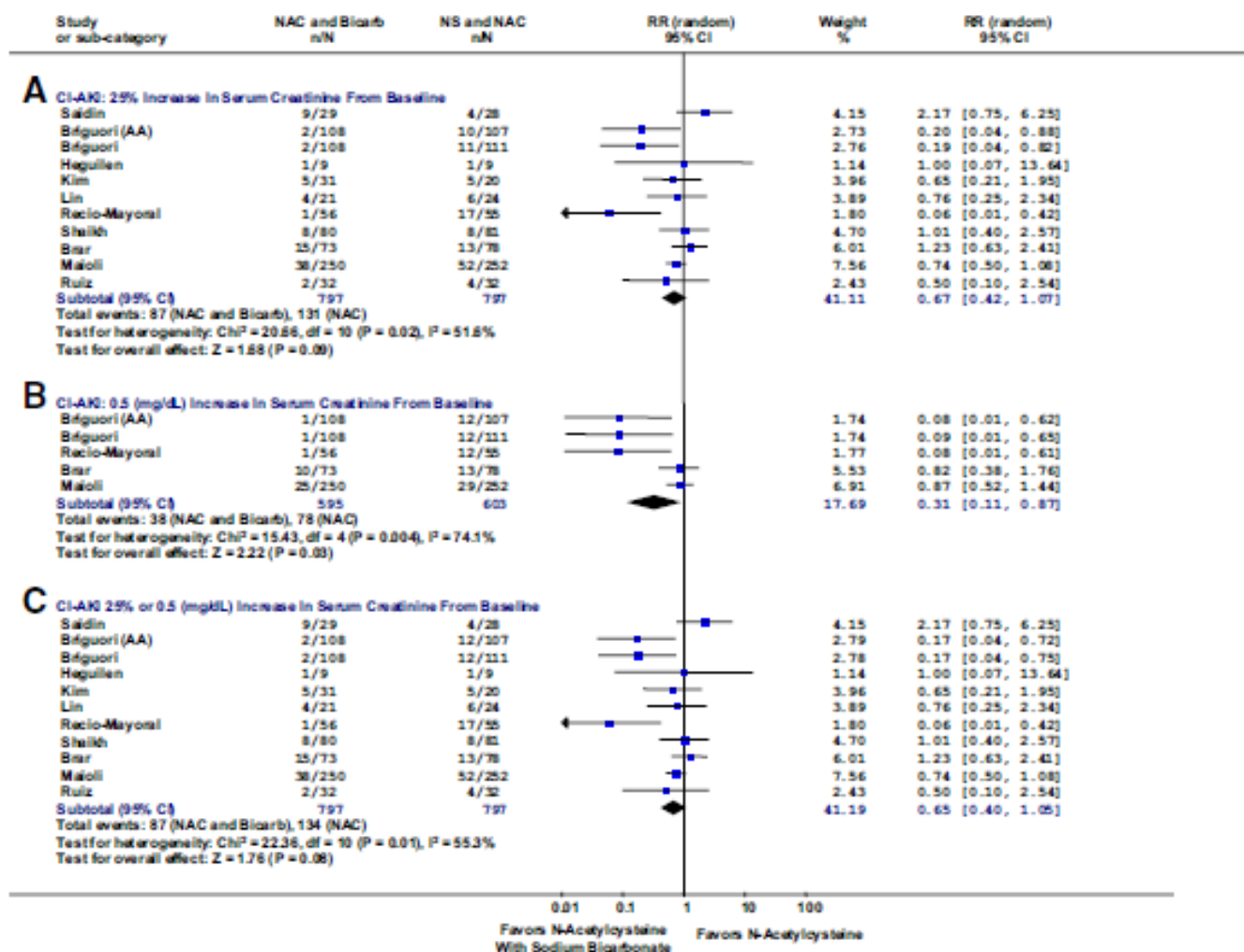


Figure 2. CI-AKI

Individual randomized controlled trials are listed in order by year of publication. Outcome is contrast-induced acute kidney injury (CI-AKI). (A) CI-AKI (25% relative increase in serum creatinine from baseline). (B) CI-AKI (≥ 0.5 mg/dl increase in serum creatinine from baseline). (C) CI-AKI ($\geq 25\%$ or ≥ 0.5 mg/dl increase in serum creatinine from baseline). The size of each square denotes the weight of each trial's relative risk (RR) in calculating the combined RR. The diamond represents the combined RR at the center; opposing points of the diamond represent the 95% confidence intervals (CIs). Treatment: N-acetylcysteine (NAC) plus sodium bicarbonate (Bicarb). AA = N-acetylcysteine plus ascorbic acid; NS = normal saline.

Haemodialysis

- Prophylactic haemodialysis soon after CM has no beneficial effect vs hydration
- Related to the very rapid onset of renal injury after administration of CM

Minimising the Risk of CIN In Patients at Risk

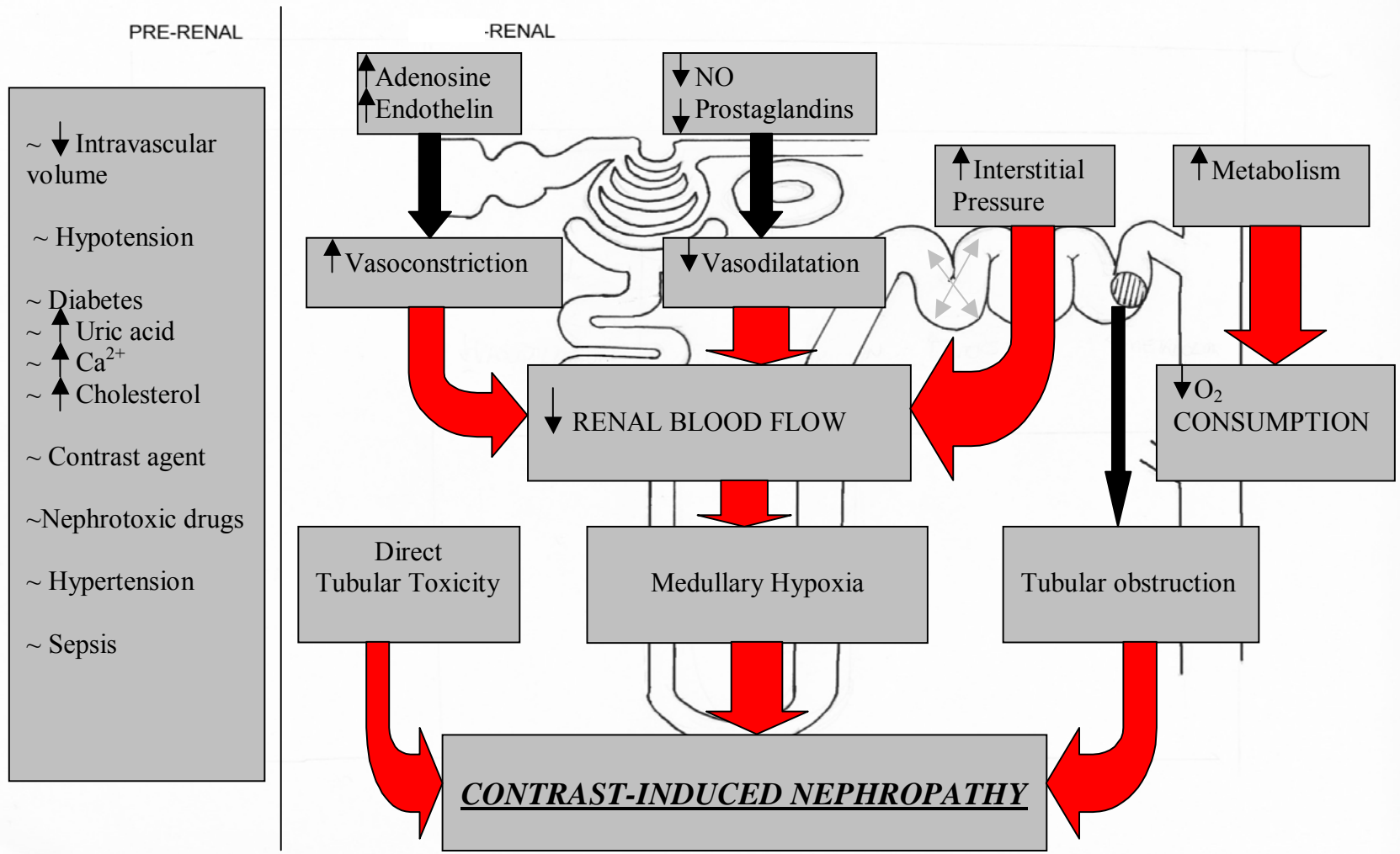
- Withdrawal of nephrotoxic medications
- Use of adequate hydration
- Pharmacological interventions
- **Appropriate selection and use of CM**

Site for action for CIN

- General – vascular?
- Local (kidney)
 - vascular, direct cell toxicity
 - blocking of distal tubules
 - ?

NOT ONE SINGLE CAUSE

Figure 1: Proposed Pathophysiological Mechanisms



Primary prevention

- Select the least nephrotoxic CM
 - What types of CM are there?

CM Classification 300-400 mg I/ml

	High (>1500)	Low (600)	Low (520-915)	Iso-osmolar (290)
Osmolality (mOsm/kg H₂O)	High (>1500)	Low (600)	Low (520-915)	Iso-osmolar (290)
Ionicity	Ionic	Ionic	Non-ionic	Non-ionic
Name	Diatrizoate Iothalamate	Ioxaglate	Iohexol Iopamidol Ioversol Iomeprol	Iodixanol
# Benz. rings	Monomer	Dimer	Monomer	Dimer
Viscosity at 37°C (cP)	≈4.0-9.0	7.5	4.7-13.9	11.4

Stacul F. Eur Radiol. 2001;11:690-697.

American College of Radiology. Manual on Contrast Media, version 5.0; 2004.

Nephrotoxicity of contrast media

- Plausible causes
 - Vascular effect
 - Cytotoxic effect
 - Osmotoxicity
 - Chemotoxicity
 - Viscosity toxicity
 - Ion toxicity

- Is there a difference between low-osmolar and high-osmolar CM
- Is there a difference between iso-osmolar and low-osmolar CM
- Is there a difference between low-osmolar CM

With regard to nephrotoxicity

Level of evidence for conclusions

1. Strong

Two studies with high quality or good systematic overview

High quality = RANDOMIZED controlled study or meta-analysis based on individual patient data.

Wide Range of CIN Incidence Reported in Clinical Trials – Why?

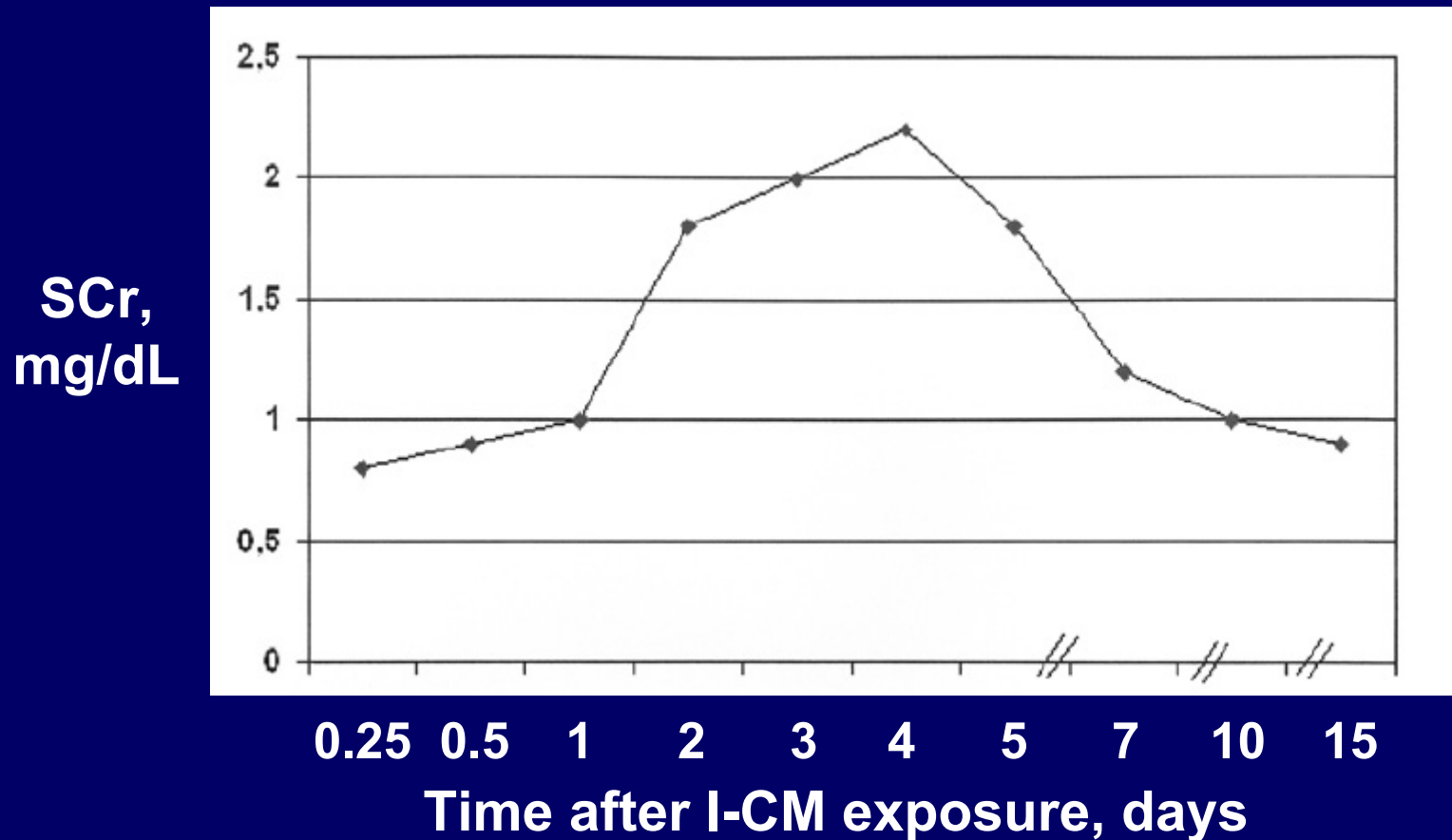
- Difference in number and severity of patient risk factors
- Exclusion vs nonexclusion of patients with other AKI etiologies
- Prospective vs retrospective collection of data
- Definition of CIN used
- Timing of baseline SCr relative to hydration administration
- Presence vs absence of other prophylactic measures
- Type and amount of hydration
- Type and amount of CM used

**At-risk patients
have higher
incidences of CIN**

Determination of CIN: Summary of Effect of Definition and Timing

- Different definitions of CIN will result in different reported incidences
- Timing of postprocedure measurement of SCr can impact the incidence of CIN
 - Single vs multiple measurements
 - Fixed vs random measurements
- Multiple fixed measurements are the most accurate for comparative studies

Time Course of SCr After CM Administration in Patients With CIN



Is there a difference between
different classes of contrast
media?

Nephrotoxicity of contrast media

- Plausible causes

- Vascular effect

- Cytotoxic effect

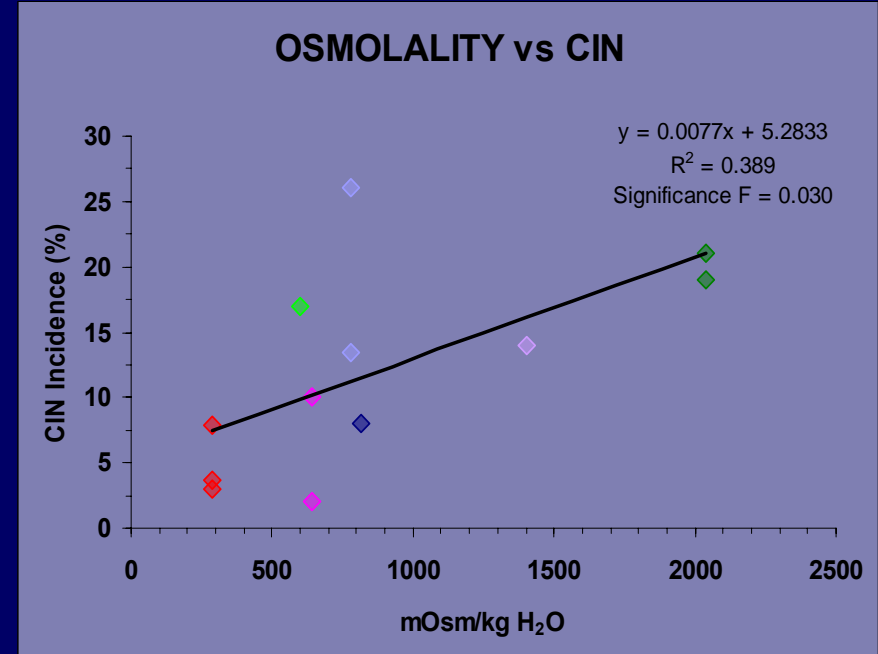
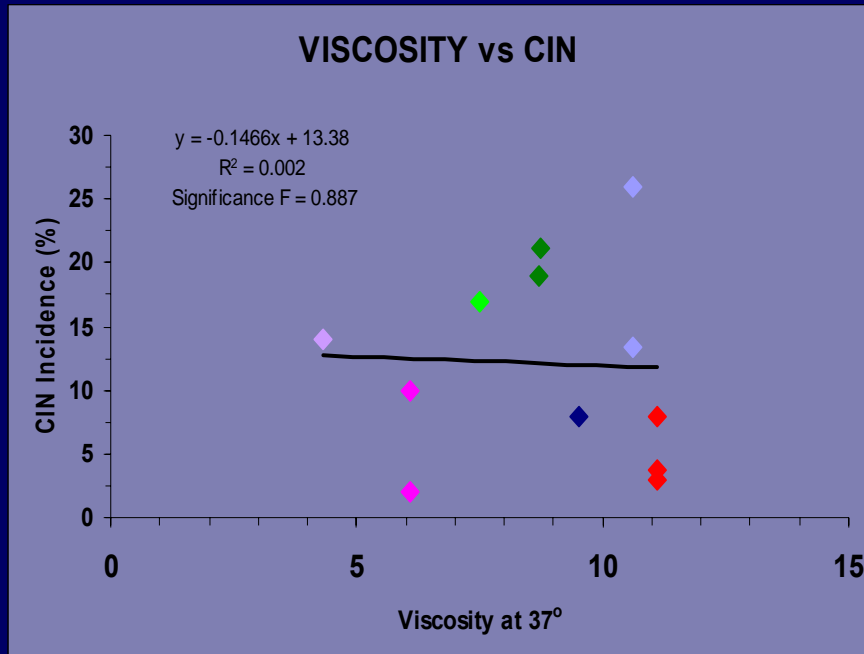
- Osmotoxicity
 - Chemotoxicity
 - Viscosity toxicity
 - Ion toxicity

The role of viscosity

The role of viscosity

- Studies in rats have suggested a role, but no CIN have been reported.
- Studies in pigs have shown no role of viscosity.
- Studies in humans have shown no role of viscosity.

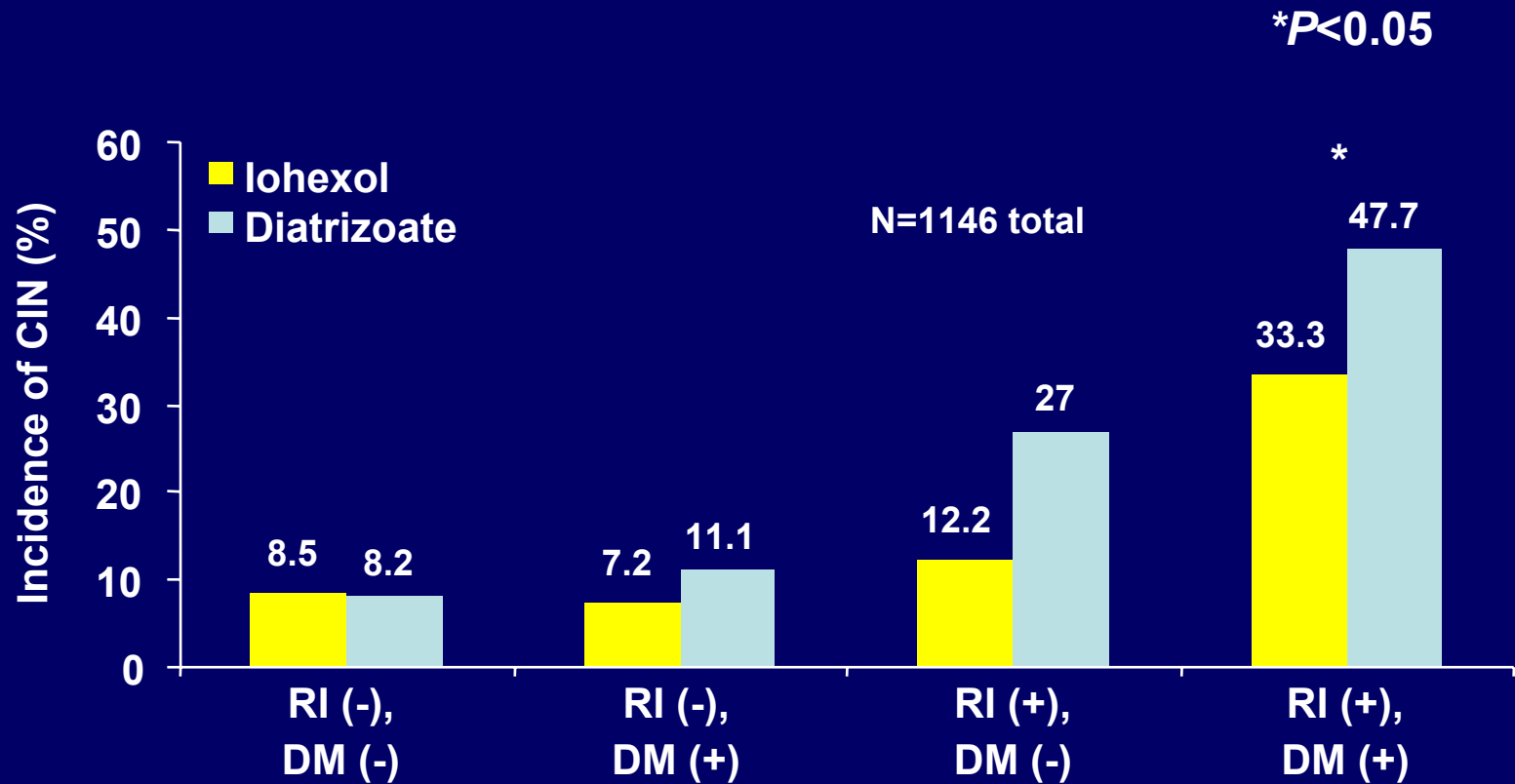
Contrast Media Properties and CIN



*Viscosity and osmolality data taken from Davidson C et al. *Am J Cardiol.* 2006;98(suppl):42K-58K.

The role of osmolality

Low-Osmolar vs High-Osmolar Contrast



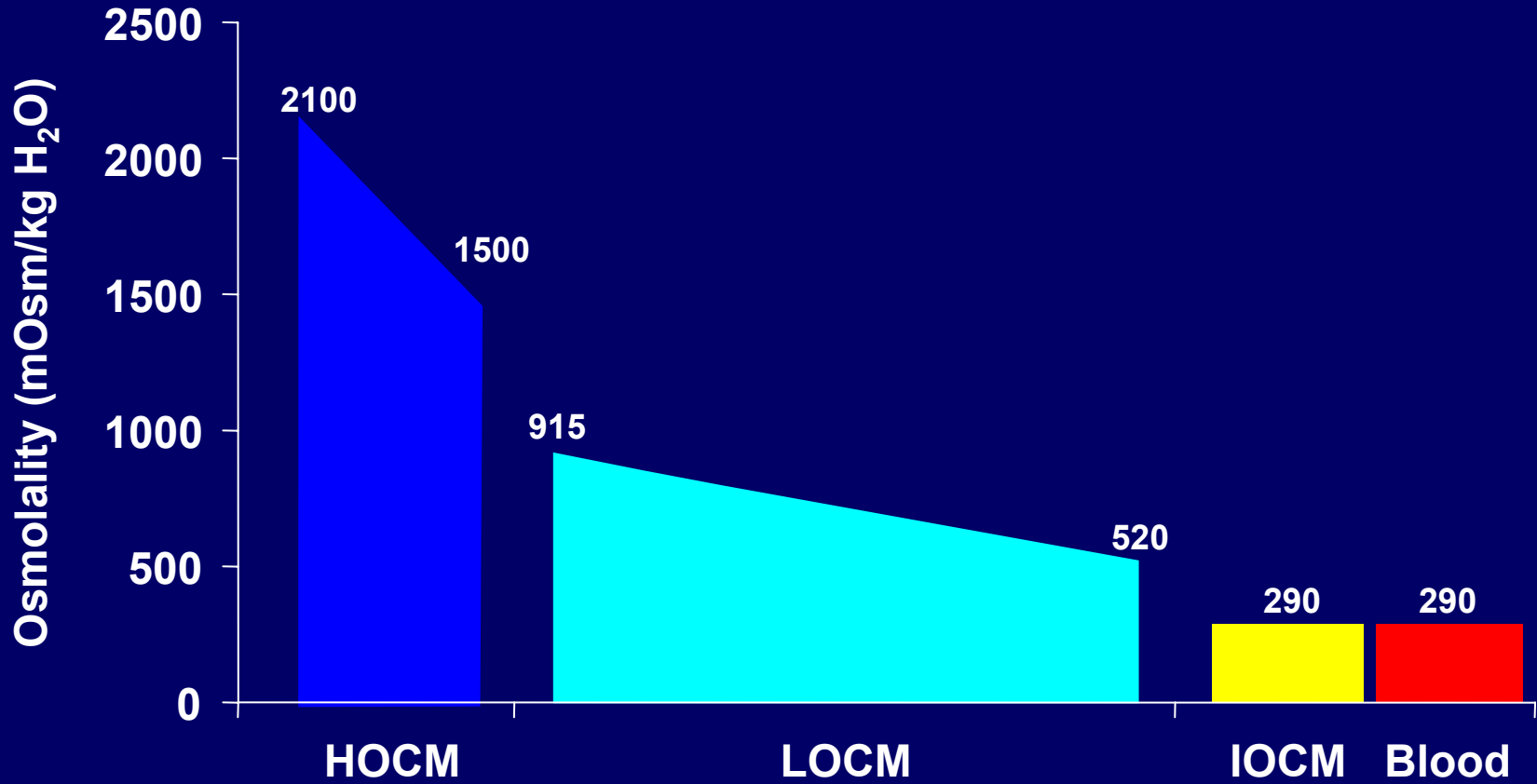
CIN, contrast-induced nephropathy, defined as >0.5 mg/dL increase in SCr within 48 to 72 hours.

RI, baseline SCr >1.5 mg/dL.

Osmotoxicity

- High osmolality is bad
 - Iso-osmolality is good
- How is “low osmolality” in clinical studies?

CM Osmolality



HOCM, high-osmolar CM; LOCM, low-osmolar CM; IOCM, isosmolar CM

RCT

- Statistical difference is superior to no difference
- “No difference” does not automatically imply equality
“Absence of evidence not equal to evidence of absence ”

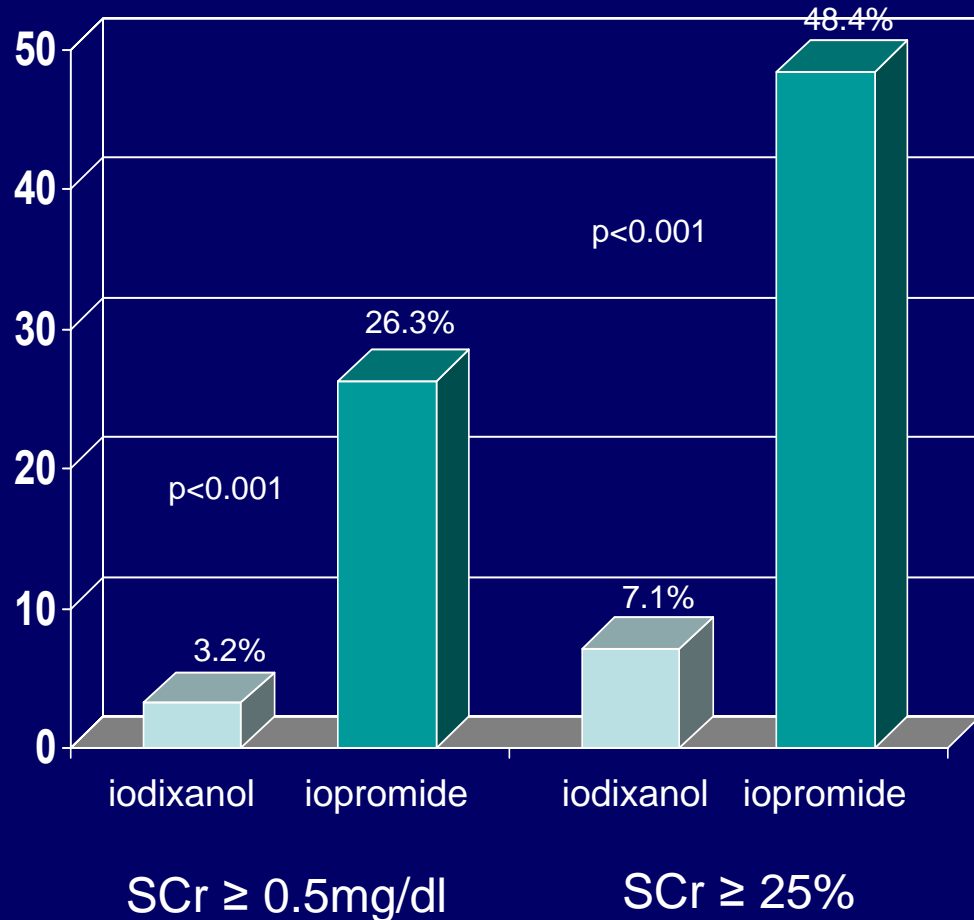
Limitations

Number of and level of risk-patients, sample size, time for measuring Scr and timing and number of postdose SCR measures etc

Clinical Trials Investigating the Impact of Iodixanol on the Kidney

Favours hyperosmolar CM		No statistically significant result	Favours isosmolar iodixanol	
Primary / secondary analysis	Subset analysis		Subset analysis	Primary / secondary
<p>ACTIVE⁷</p> <p>CARE¹³</p>		<p>PREDICT¹²</p> <p>Feldkamp¹⁴</p> <p>IMPACT¹⁵</p> <p>Carraro¹⁶</p> <p>Laskey¹⁷</p>	<p>ICON⁸</p> <p>CONTRAST⁹</p> <p>Hardiek¹⁰</p> <p>VALOR¹¹</p>	<p>Wang¹⁸</p> <p>Hernandez¹</p> <p>Nguyen²</p> <p>Nie³</p> <p>RECOVER⁴</p> <p>NEPHRIC⁵</p> <p>Chalmers⁶</p>
<p>■ Iomeprol</p>	<p>■ Ioversol</p>	<p>■ Iopamidol</p>	<p>■ Ioxaglate</p>	<p>■ Iopromide</p> <p>■ Iohexol</p>

Largest CIN Study to Date



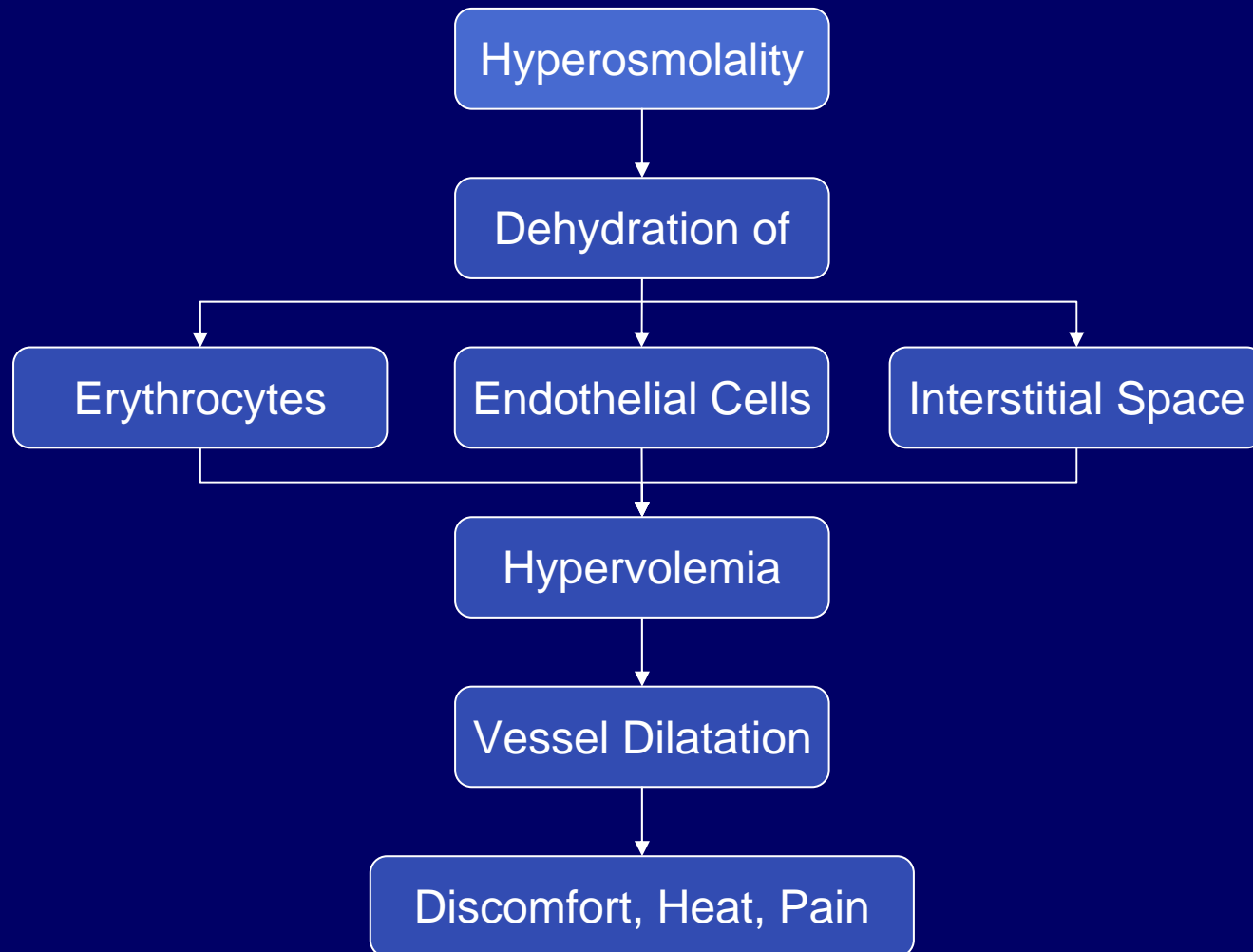
- 1706 high-risk pts
 - Renally impaired
 - CrCl 30-60 mL/min
 - Older adults
 - ≥60 years
- Coronary angiography ± PCI
- CIN
 - ≥0.5 mg/dL ↑ in SCr
 - ≥25% ↑ in SCr
 - Fixed time point for SCr measurements

- Is there a difference between low-osmolar and high-osmolar CM .**YES**
- Is there a difference between low-osmolar CM.
We Don't know-very little evidens and studies
- Is there a difference between iso-osmolar and low-osmolar CM. **Still under debate**
- **With regard to nephrotoxicity**

Minimising Patient Risk

- Patient comfort
- Cardiac safety
- Renal safety

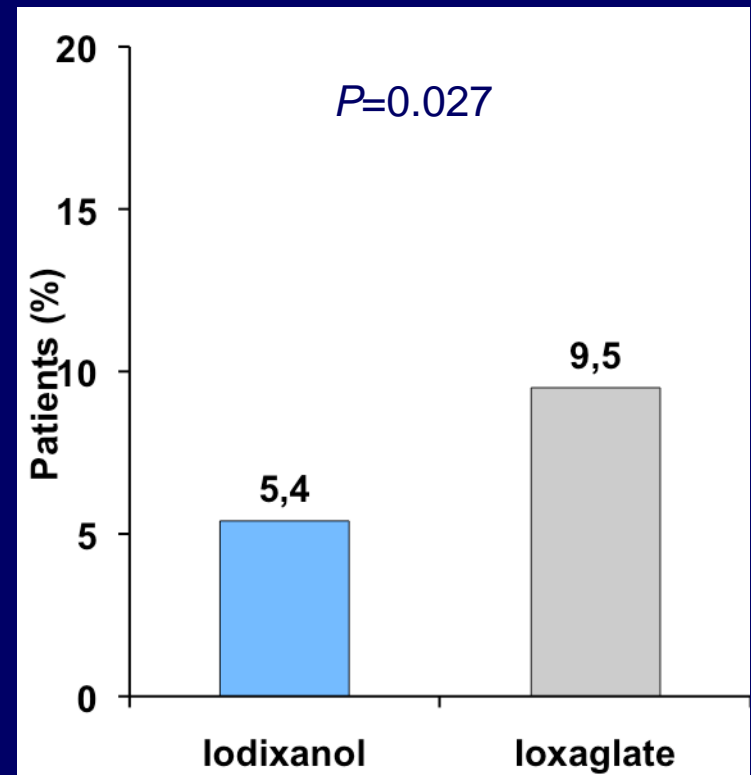
Contrast Medium Hyperosmolality and Patient Comfort



Cardiac safety

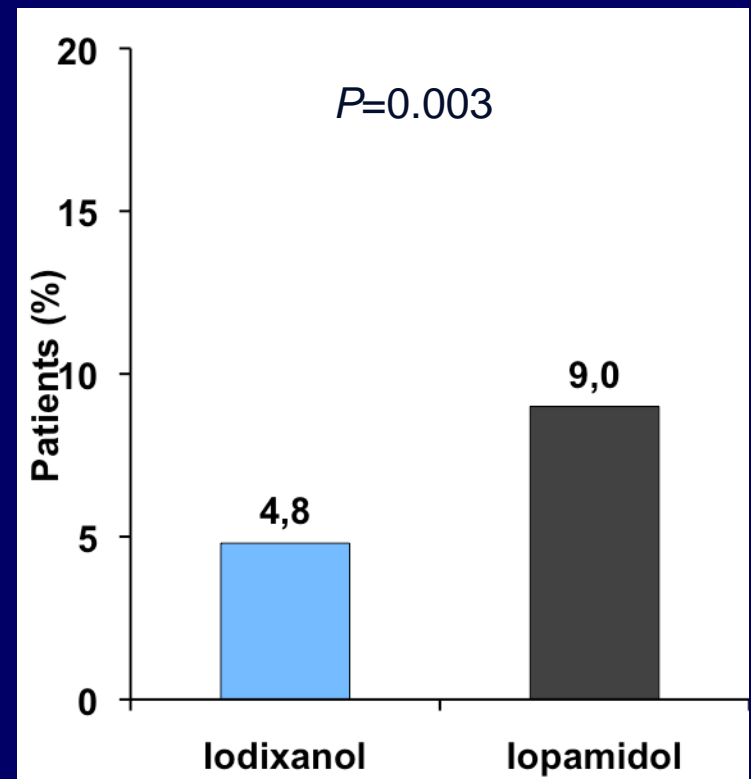
COURT Trial: Primary Clinical Outcomes Following High-risk PTCA

Incidence of MACE



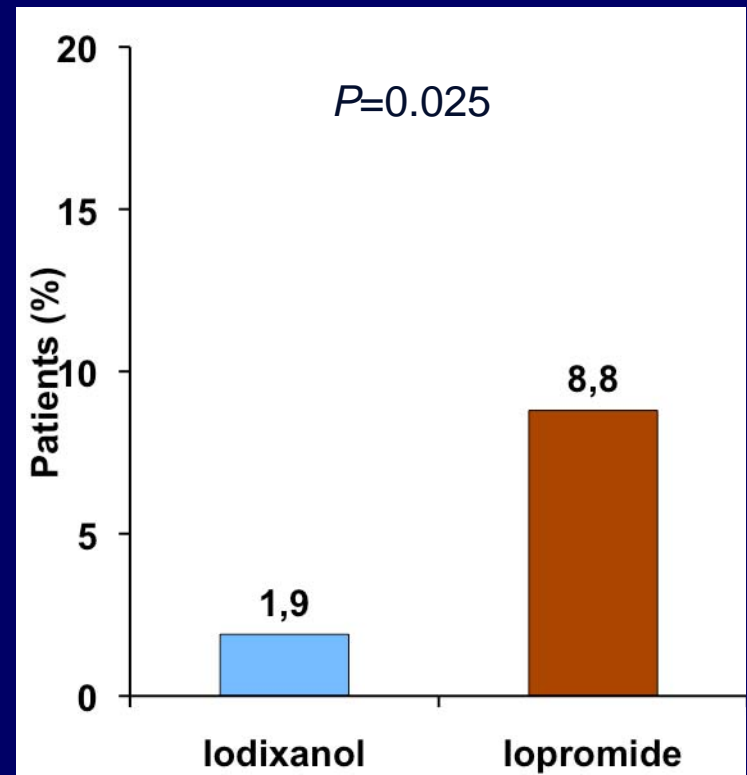
VICC Trial: CV Outcomes Following PCI

Incidence of MACE



CV Outcomes Following Coronary Angiography ± PCI

Incidence of MACE



Renal safety

Overall conclusion-IOCM vs LOCM

- A difference matters. CIN matters
- Iso-osmolality is always correct. Either better than or equal to low-osmolar CM.
- No studies have shown differences between the low-osmolar.
- Some studies have not shown inferiority of some LOCM to IOCM.
- Better studies needed

Contrast medium induced nephropathy

To avoid CIN

Contrast medium dose should be
adjusted to renal function

Renal function

- Serum (plasma) creatinine
- Generally regarded as a POOR predictor of GFR

Shemesh et al. Limitations of creatinine as a filtration marker in glomerulopathic patients. Kidney Int 1985;28:830-838.

Safe CM dose relative GFR

A gram-iodine/GFR ratio = 1:1

seems to imply a relatively low risk of CIN
providing GFR is not <30 mL/min (severe renal
impairment) and in the absence of multiple risk
factors

Gram-iodine/GFR ratio

N=391

CIN frequency

- All patients 17%
 - hemodialysis/-filtration (CIN patients) 2 (12)%
- Gram-iodine/GFR ratio $\geq 1:1$ 25%
- Gram-iodine/GFR ratio $< 1:1$ 3%
 - LVEF $\geq 50\%$ (normal cardiac function) 0%
 - LVEF $< 50\%$ (decreased cardiac function) 8%
- Gram-iodine/GFR ratio 1:1 4-7%
 - LVEF = 50%, no shock, GFR 30-90 mL/min

Conclusion

- I. Always consider alternative imaging method
 - II. Identify risk patients-stratify
 - III. Discontinuing use of nephrotoxic drugs
 - IV. The incidence of CIN may be reduced by:
 - Using the lowest dose of CM possible
 - Correlating dose to renal function
 - Choosing an iso-osmolar or (some) low-osmolar contrast media
 - Use adequate hydration-isotonic Saline
- No strong evidence that the use of bicarbonate or NAC are of value

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