

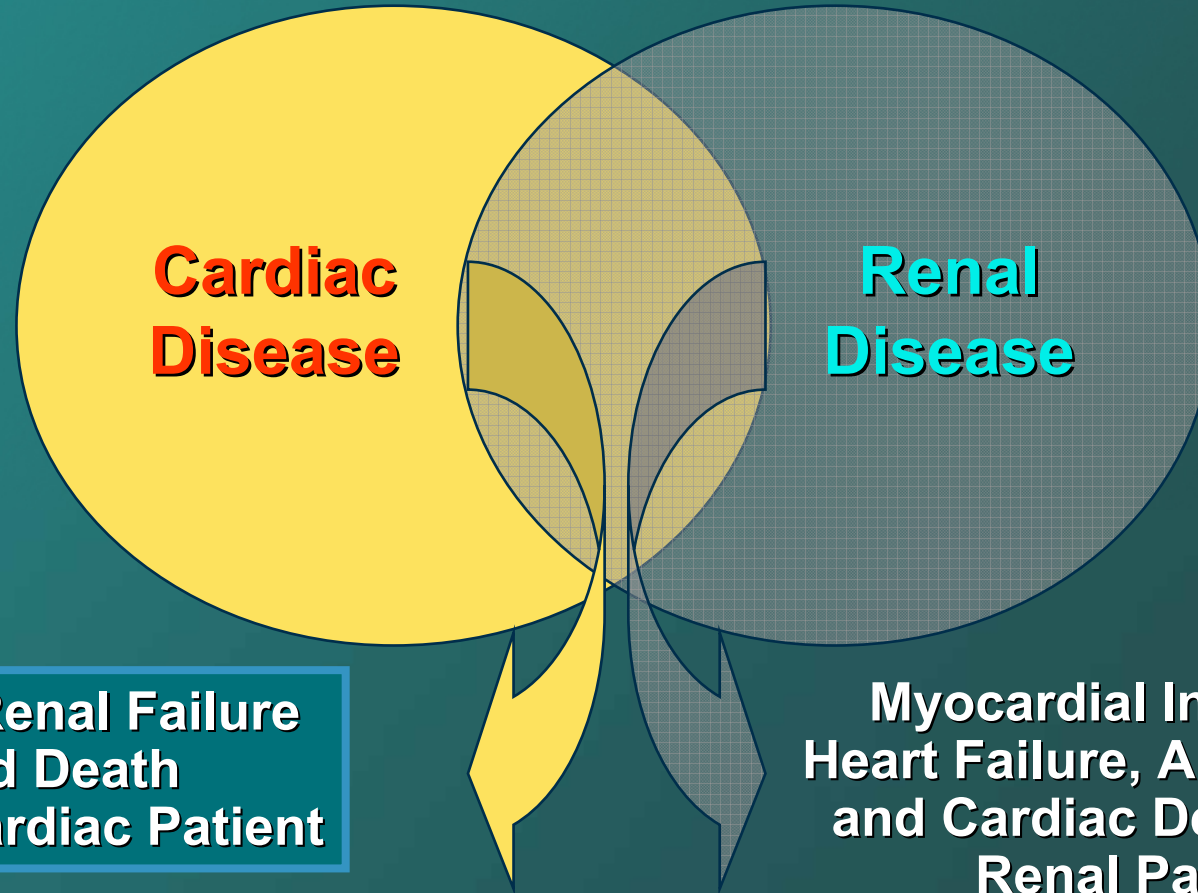
# **Radiocontrast Nephropathy: Still the Achilles Heel of Interventional Cardiology**

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Associate Professor of Medicine***

***Columbia University Medical Center  
Cardiovascular Research Foundation***



# Cardiorenal Risk



**Acute Renal Failure  
and Death  
in the Cardiac Patient**

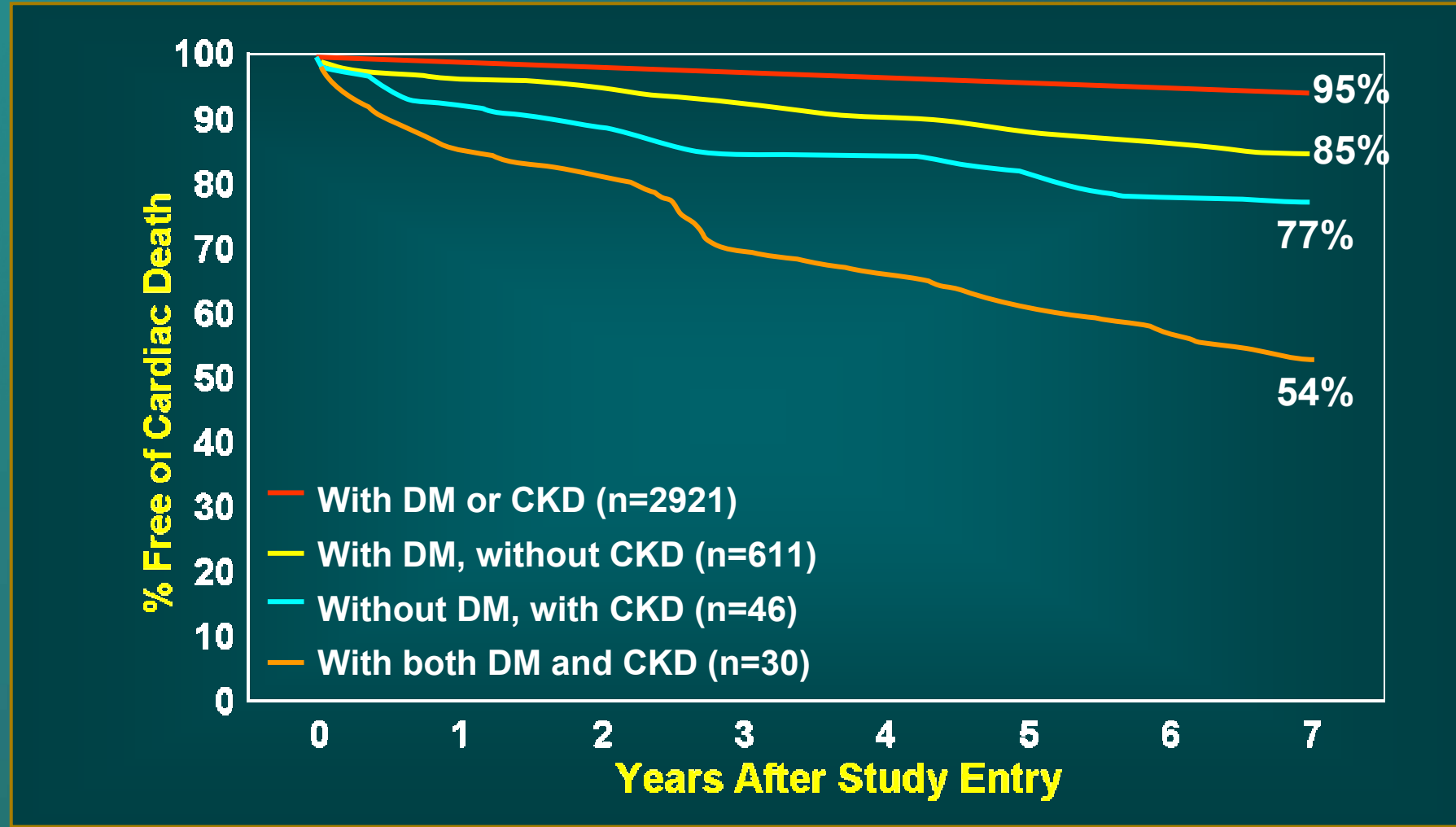
**Myocardial Infarction,  
Heart Failure, Arrhythmias,  
and Cardiac Death in the  
Renal Patient**

# Predictors of All-Cause Mortality to 7 Years BARI Trial + Registry

	<b>RR</b>	<b>95% CI</b>	<b>P</b>
<b>CKD (baseline Cr &gt; 1.5 mg/dl)</b>	<b>2.31</b>	<b>1.63-3.28</b>	<b>&lt;0.001</b>
Sex, female vs. male	0.91	0.75-1.10	0.32
Race, black vs. non-black	1.40	1.04-1.89	0.028
Age, y	1.05	1.04-1.06	<0.001
<b>Diabetes mellitus</b>			
Oral hypoglycemics	1.63	1.29-2.06	<0.001
Insulin	1.80	1.26-2.58	<0.001
PTCS vs. CABG	1.04	0.87-1.25	0.67
Interaction between PTCA and insulin-treated diabetics	1.73	1.11-2.69	0.02
<b>Smoking history</b>			
Prior tobacco use	1.30	1.06-1.59	0.01
Tobacco use at baseline	1.82	1.42-2.33	<0.001

Szczzech L. et al., *Circulation* 2002; 105:2253-8.

# Freedom from Cardiac Death for Patients with CKD\* and Diabetes (DM) BARI Trial + Registry



\* CKD defined as baseline Cr > 1.5 mg/dl

Szczech L. et al., *Circulation* 2002; 105:2253-8.



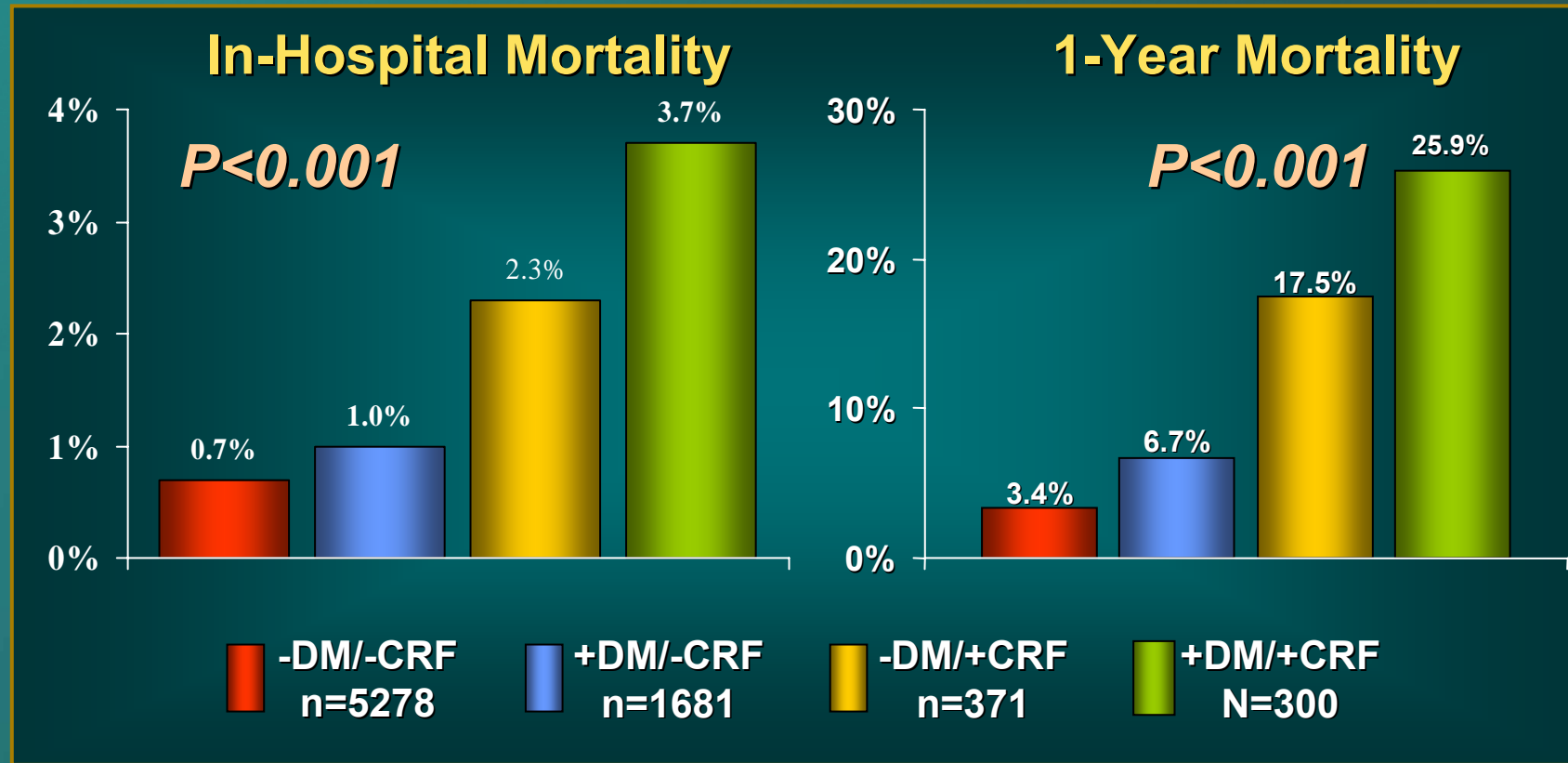
# Outcomes of acute coronary syndrome in a large Canadian cohort: impact of chronic renal insufficiency, cardiac interventions, and anemia:

- observational cohort of 5,549 adult patients who survived to discharge with a discharge diagnosis of ACS
- Advanced and moderate CRI independently predicted death (hazard ratio, 1.06; 95% confidence interval [CI], 1.01 to 1.12; and hazard ratio, 1.23; 95% CI, 1.18 to 1.29)

- **Keough-Ryan, TM et al. *Am J Kidney Dis.* 2005 Nov;46(5):845-55**

# Post PCI Prognosis in Pts with DM/CRF

7,445 consecutive pts followed for one year after PCI.



Mehran et al. J Am Coll Cardiol 2000; 35:1 878

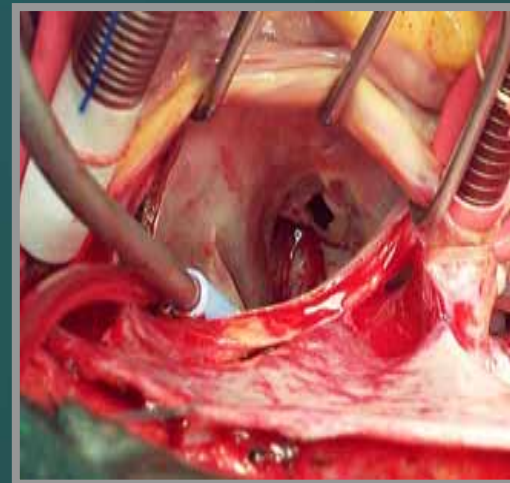


# Major Causes of Acute Renal Failure In Cardiac Patients

1) Radiocontrast Nephropathy (RCN)



2) Acute Renal Failure after Cardiopulmonary Bypass Procedures



# Contrast-Induced Nephropathy

## Definition

- New onset or exacerbation of renal dysfunction after contrast administration in the absence of other causes:

increase by > 25%

*or*

absolute ↑ of > 0.5 mg/dL

from baseline  
serum creatinine

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





# Contrast-Induced Nephropathy: Incidence

- 3rd most common cause of hospital acquired renal failure
- Occurs in less than **1%** of general population
- Occurs in "only" **5.5%** of patients with renal insufficiency
- But, occurs in **50%** of patients with both renal insufficiency and diabetes mellitus

Parfrey PS, et al, *NEJM* 1989; 320:143-149

# Contrast-induced Nephropathy: Incidence, Risk Factors

**1,826 consecutive pts undergoing PCI:**

**ARF w/o dialysis = 144.6/1,000 or 14.5%**

**ARF with dialysis = 7.7/1,000 or 0.7%**

<b>Predictors of ARF +D</b>	<b>OR</b>	<b>CI</b>	<b>P</b>
<b>Cr Clearance</b>	<b>0.83</b>	<b>0.77-0.89</b>	<b>&lt;0.001</b>
<b>Diabetes</b>	<b>5.47</b>	<b>1.41-21.32</b>	<b>0.01</b>
<b>CONTRAST dose</b>	<b>1.008</b>	<b>1.002-1.013</b>	<b>0.01</b>

McCullough et al. *Am J Med* 1997; 103-375



# Risk Factors for CIN

## Patient-related Risk Factors

- Renal insufficiency
- Diabetes mellitus with renal insufficiency
- Age
- Volume depletion
- Hypotension
- Low cardiac output
- Class IV CHF
- Other nephrotoxins
- Renal transplant
- Hypoalbuminemia (<35 g/l)

## Procedure-related Risk Factors

- Multiple contrast media injection within 72 hrs
- Intra-arterial injection site
- High volume of contrast media
- High osmolality of contrast media



# Scheme to define CIN risk 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 <sup>3</sup>

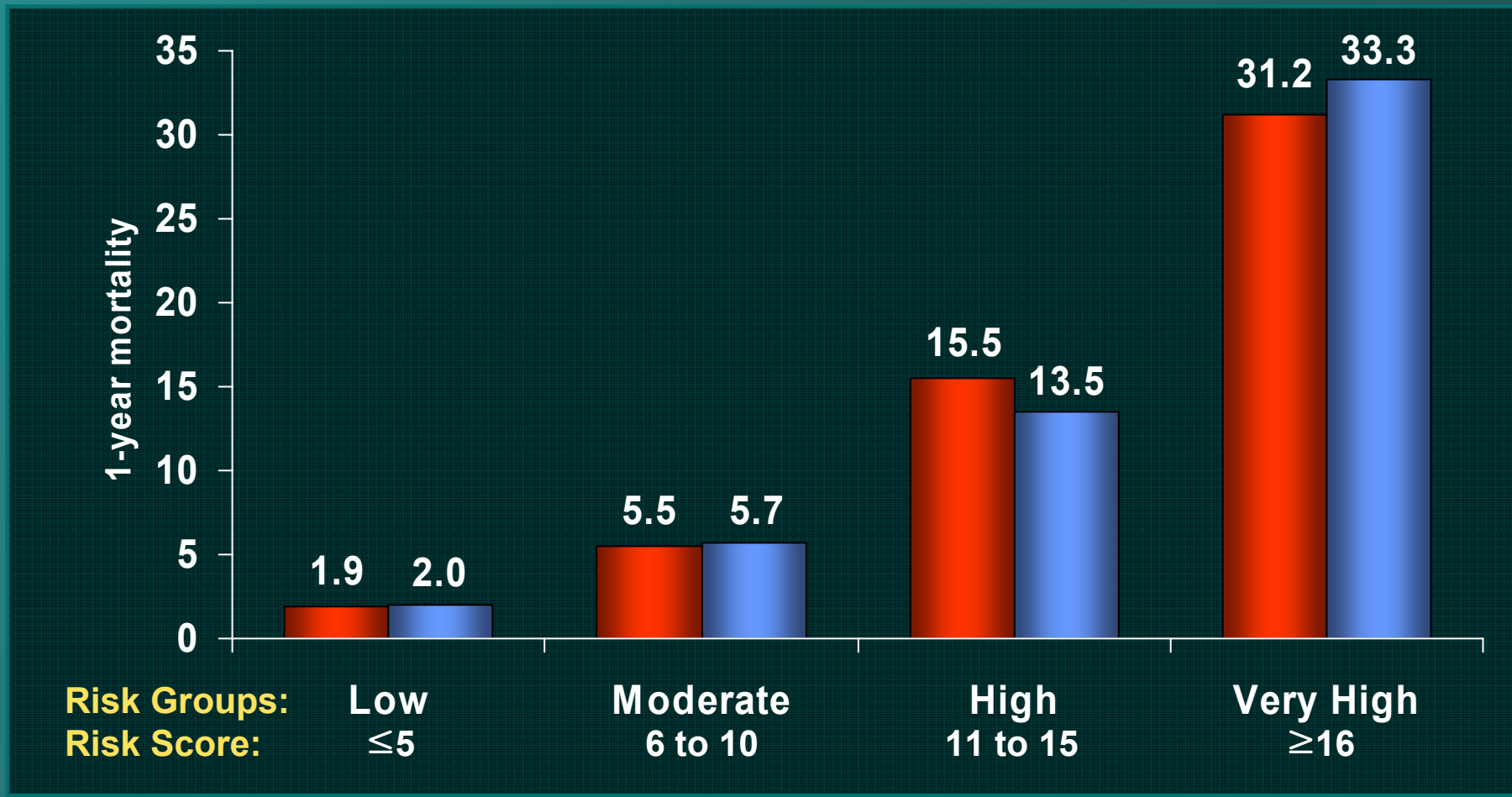
Serum creatine > 1.5mg/dl	4
OR	
eGFR < 60ml/min/1.73 m <sup>2</sup>	2 for 40 – 60 4 for 20 – 40 6 for < 20
$eGFR < 60ml/min/1.73 m^2 = 186 \times (SCr)^{-1.154} \times (Age)^{-0.203}$ $\times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$	

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%

Mehran et al. *JACC* 2004;44:1393-1399.

# CIN Risk Score & 1-year mortality

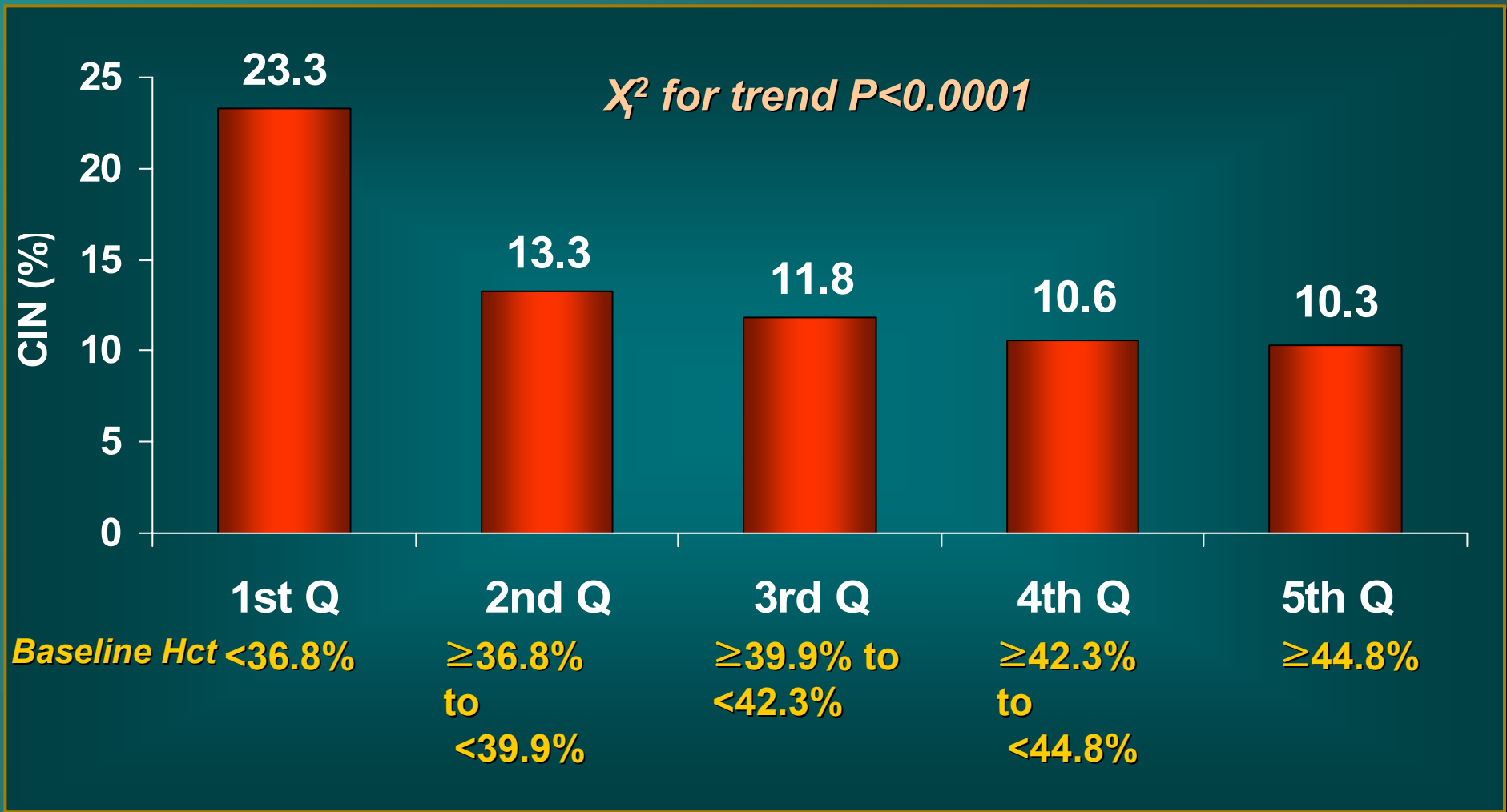


*Prognostic significance of the proposed risk score for CIN extended to prediction of 1-year mortality. (Red bars = development dataset; blue bars = validation dataset.)*

Mehran et al. *JACC* 2004;44:1393-1399.



# Risk of Contrast-induced Nephropathy in Relation to Baseline Hematocrit



Nikolsky, Mehran, et al. KI 2005

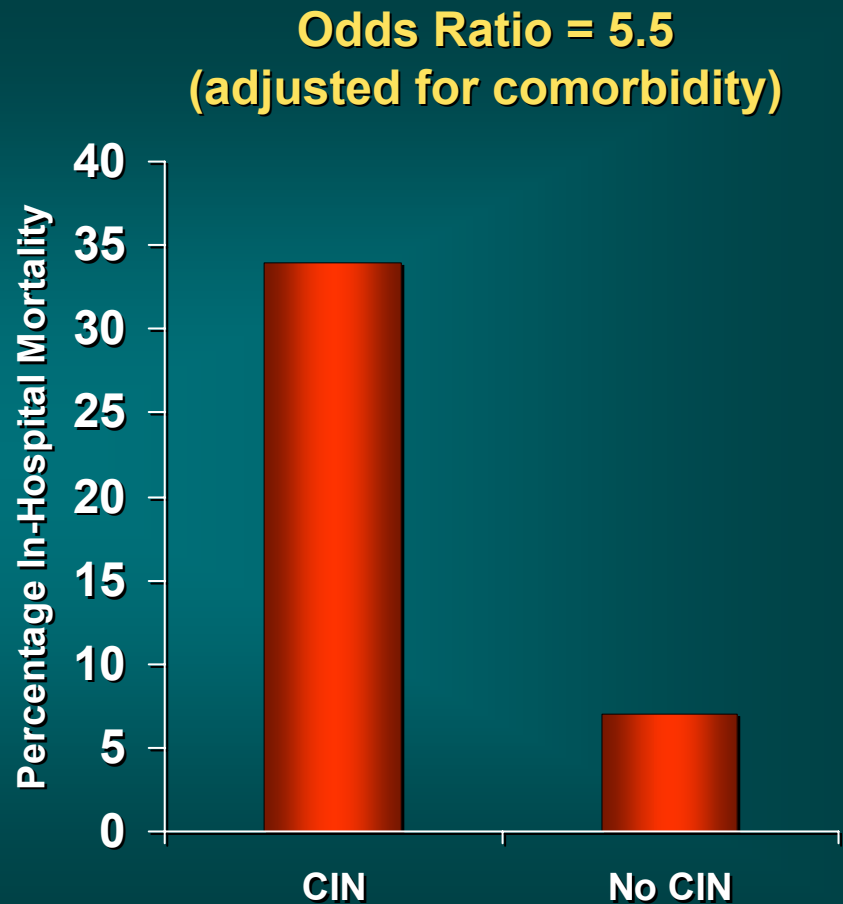


# Prognostic Impact of CKD and Contrast Induced Nephropathy



# Contrast-Induced Nephropathy Predicts Mortality

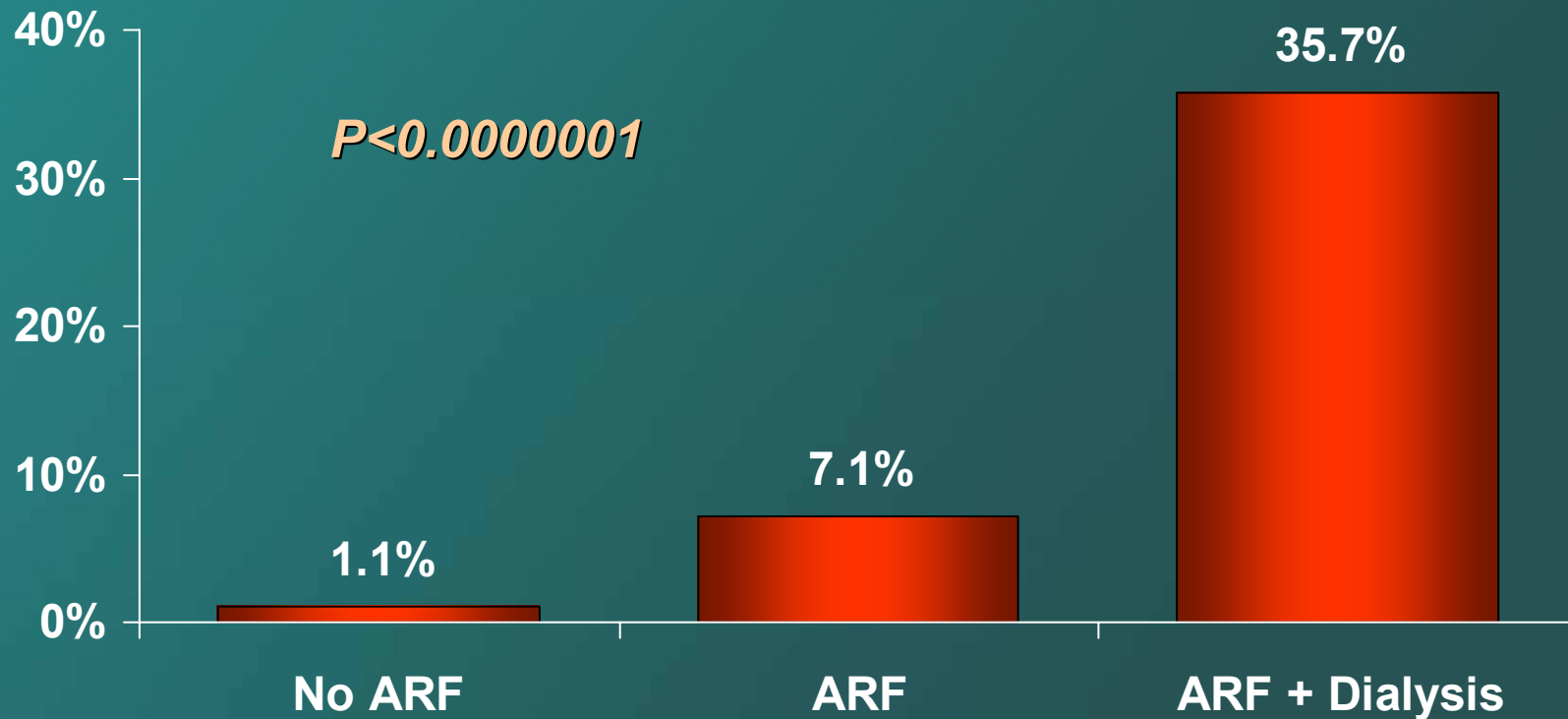
- Retrospective case control study of 16,248 hospitalized inpatients who received contrast procedures
- Cases with RCN (n = 183) matched with controls (n = 174):
  - APACHE II
  - Baseline serum creatinine
- RCN defined as > 25% increase in serum cr



Levy EM, Viscoli CM, Horwitz RI. *JAMA* 1996;275(19):1489-94.

# Contrast-Induced Nephropathy: In-hospital Mortality

**% In-hospital Death**

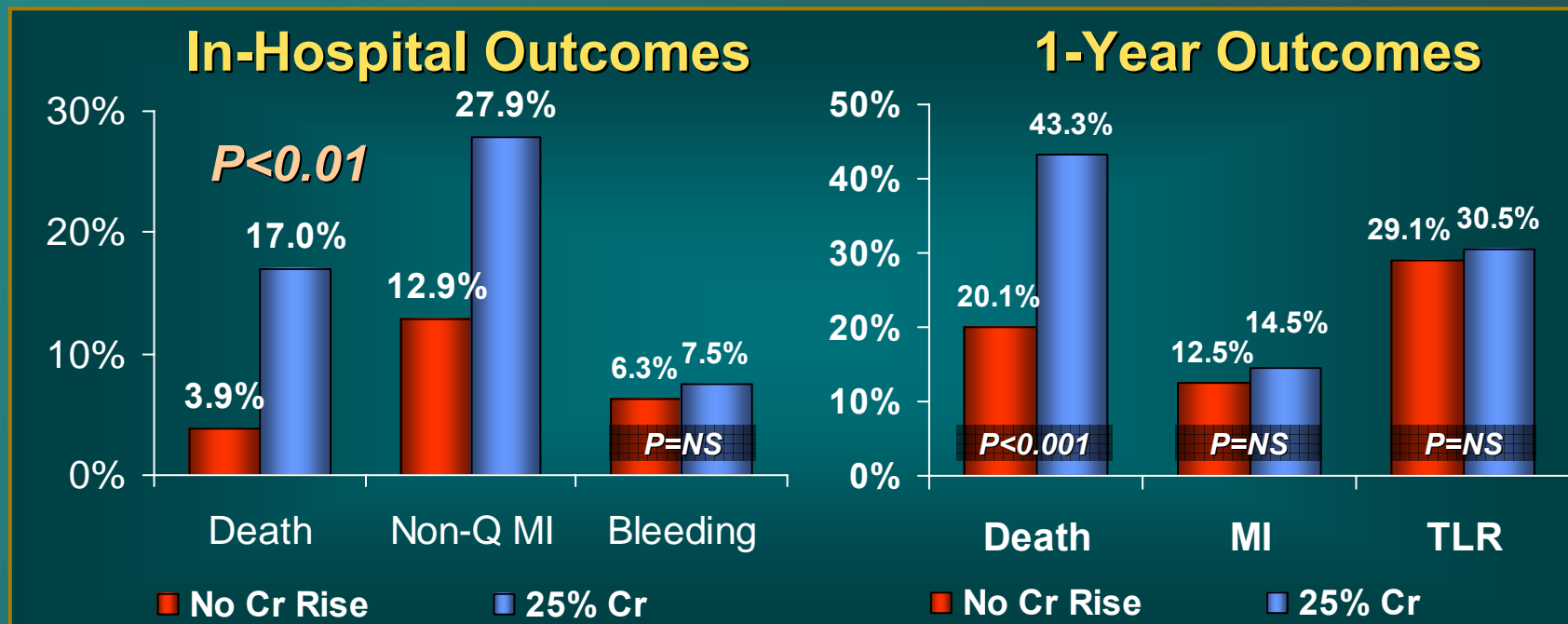


McCullough et al. *Am J Med* 1997; 103-375



# PTCA in Chronic Renal Failure

- 440 patients with baseline creatinine  $\geq 1.8$ mg/dl
- 158 pts had 25% rise in serum creatinine and 282 pts had no rise
- Procedure success  $>97\%$  in both groups

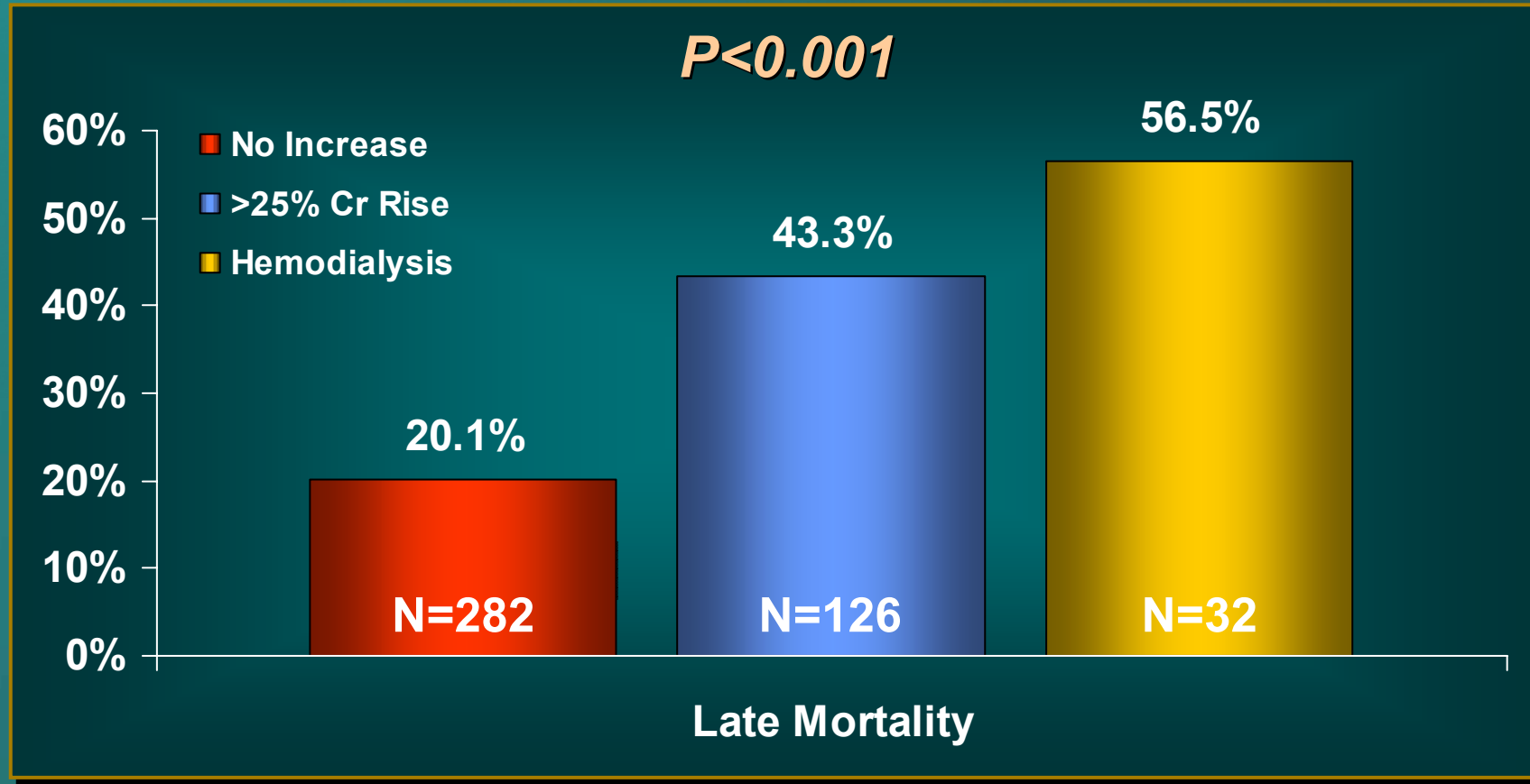


**Independent predictors of late death:  
Creatinine rise (OR 3.86,  $p < 0.001$ ) and Age (OR 1.05,  $p = 0.03$ )**

Gruberg et al. Circ 1999



# Late Mortality After PCI



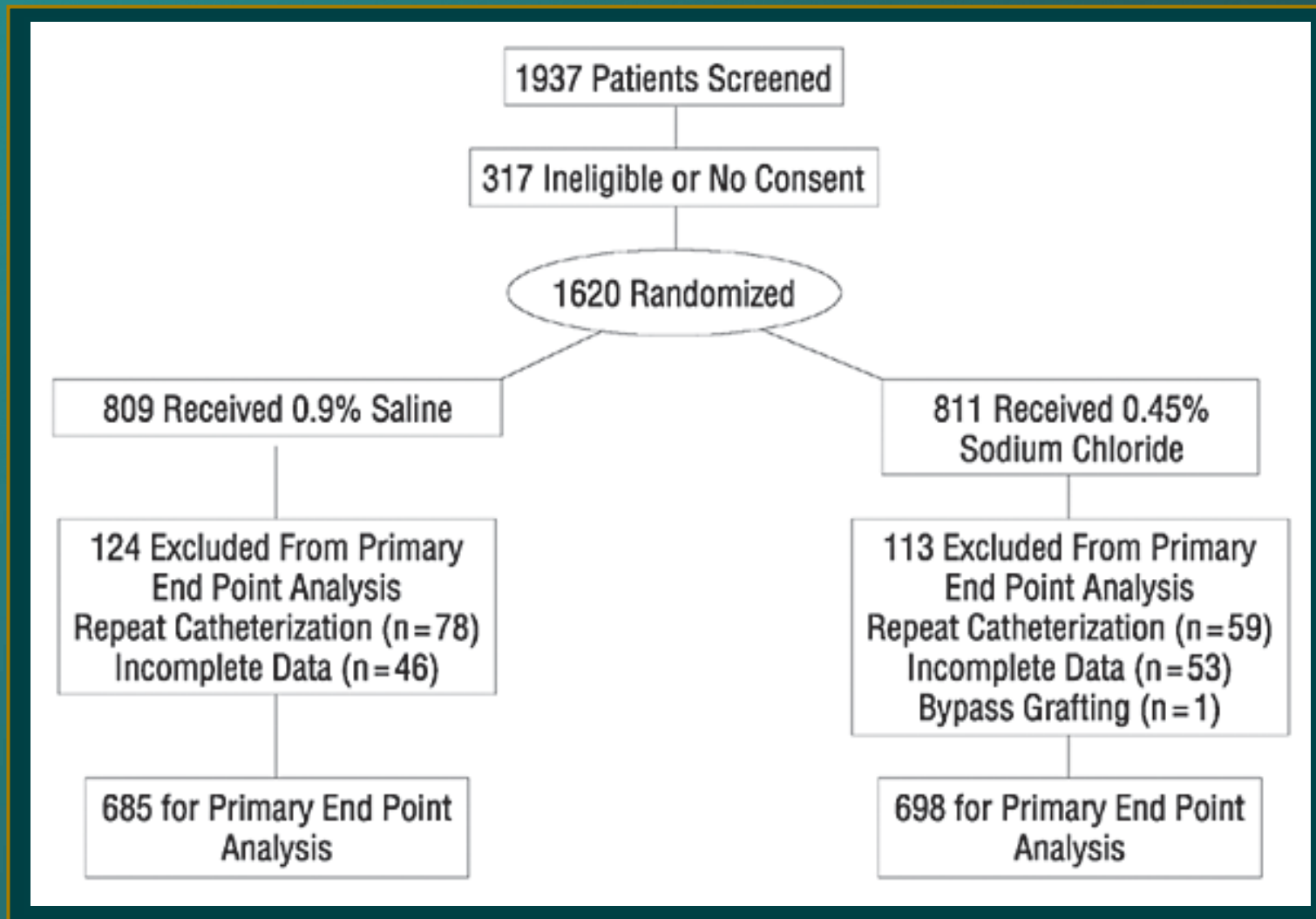
# Preventive Trials



# Hydration



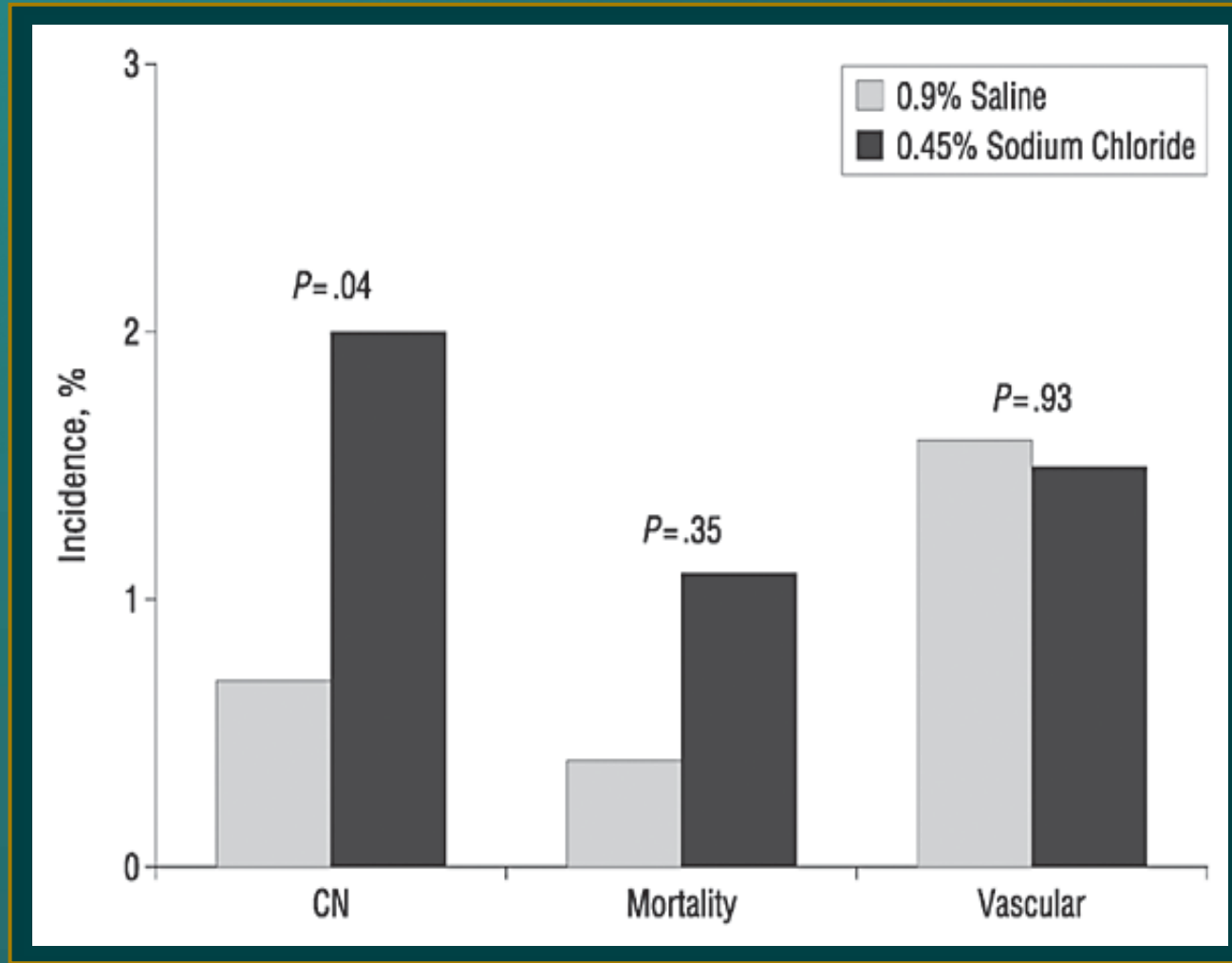
# Optimal Hydration Regimen



Mueller et al *Arch Intern Med* 2002

# Optimal Hydration

## 0.9 NS vs 0.45 NS



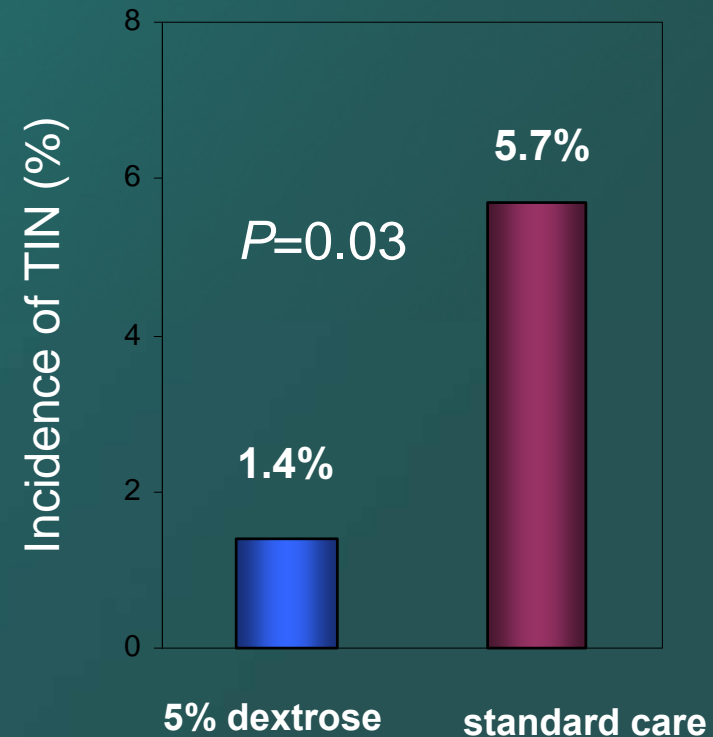
Mueller et al *Arch Intern Med* 2002





# Effect of a rapid intra-arterial infusion of dextrose 5% prior coronary angiography on frequency of CIN in high-risk patients

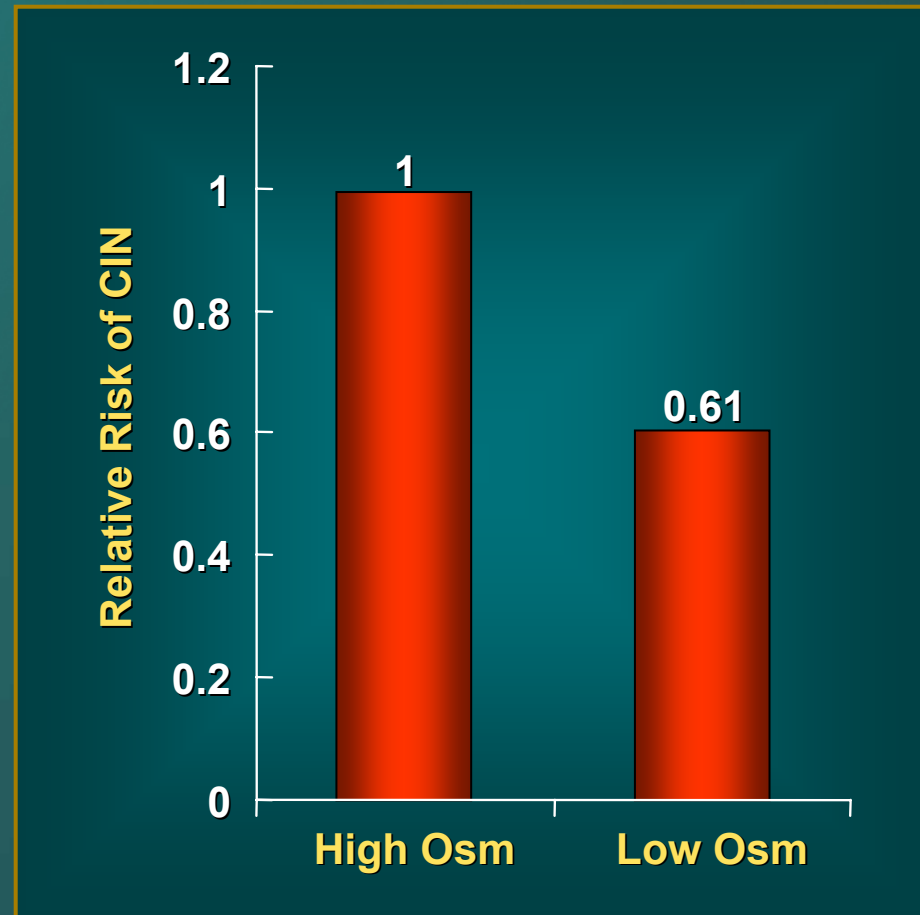
- retrospective analysis
- 976 pts. with creatinine clearance  $\leq 60$  ml/min
- 144 pts. received 1 L of 5% dextrose through femoral artery sheath  $> 5$  min before angiography
- CIN defined as an increase of serum creatinine  $\geq 0.5$  mg/dl 24 to 72 hrs. after procedure



Clavijo et al. *Am J Cardiol* 2006;97:981-983.

# Meta-analysis: High vs. Low Osm Contrast Media

- 39 Trials - 5146 patients
- CIN  $\geq$  0.5 mg/dl
- CIN in 7% of all patients
- CIN in 30% of CRI patients
- For CRI, NNT=8 (treat 8 to prevent 1 CIN case)
- Low osmolal group included ioxaglate (Hexabrix); iodixanol (Visipaque) not studied



Barrett and Carlisle *J Am Soc Nephrol* 92;

# Specific DA-1 Agonism: Fenoldopam

*A New Renal and Systemic Vasodilator*



# The **CONTRAST** Trial

## Algorithm

**300 patients**

at increased risk for contrast nephropathy undergoing PCI



**Hydrate**

**Randomize**



**Fenoldopam**

**Matching placebo**

1° prior to and 12° after cath

**Primary endpoint**

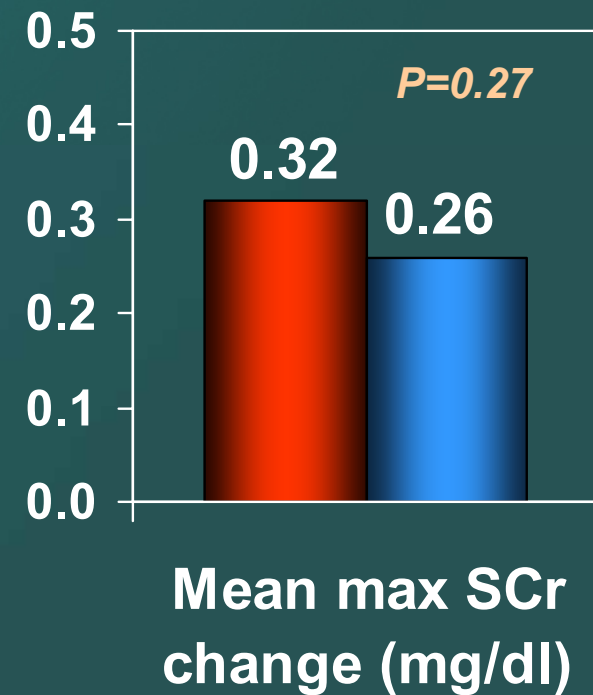
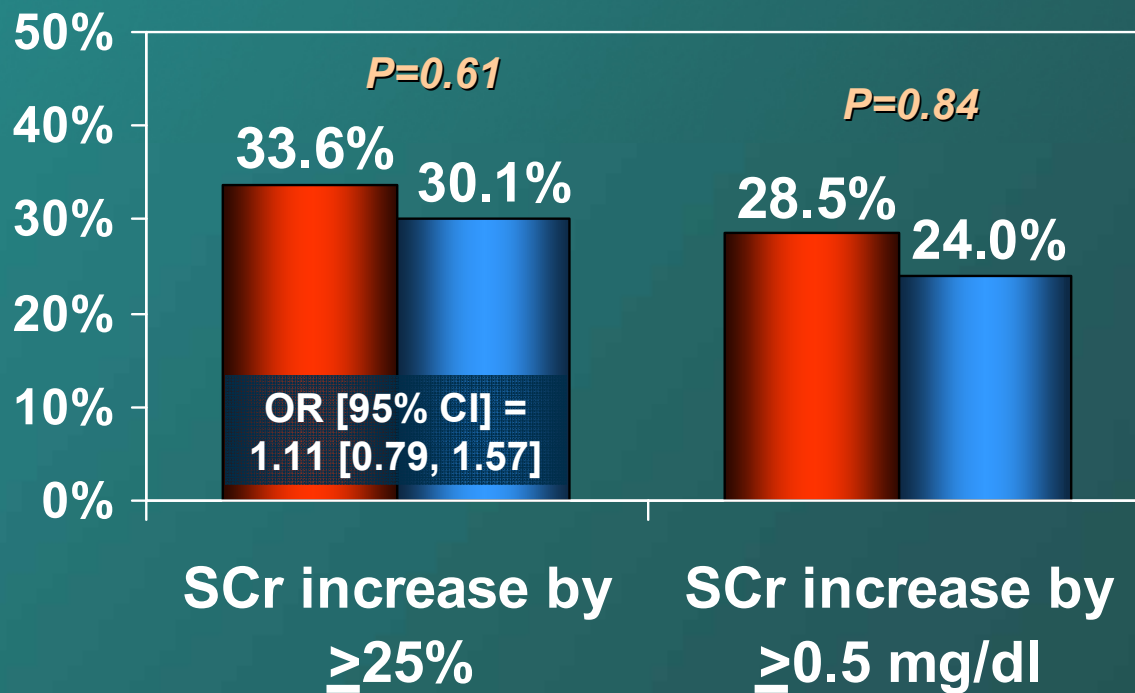
**Worsening renal insufficiency within 12-96 hours**



# CONTRAST STUDY: CIN

SCr at both baseline and during the 96<sup>h</sup> post drug administration period were available and analyzed at the central lab in 283 of 315 randomized patients (90%).

■ Fenoldopam (n=137) ■ Placebo (n=146)

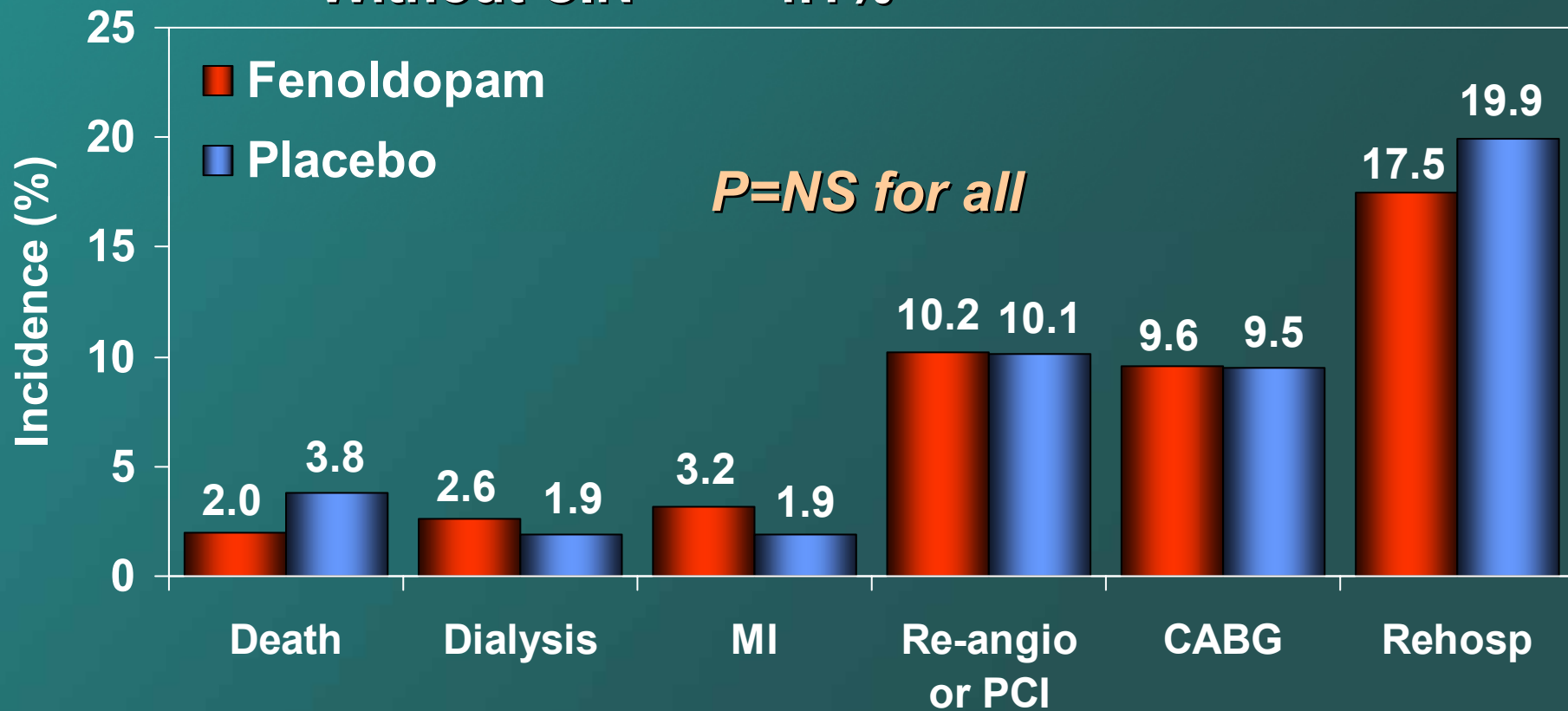


Stone GW, et al. ACC-2003

# CONTRAST: 30-Day Adverse Events

30-day incidence of death, MI or dialysis:

- With CIN 12.2%
  - Without CIN 4.1%
- p=0.02*



Stone GW, et al. ACC-2003

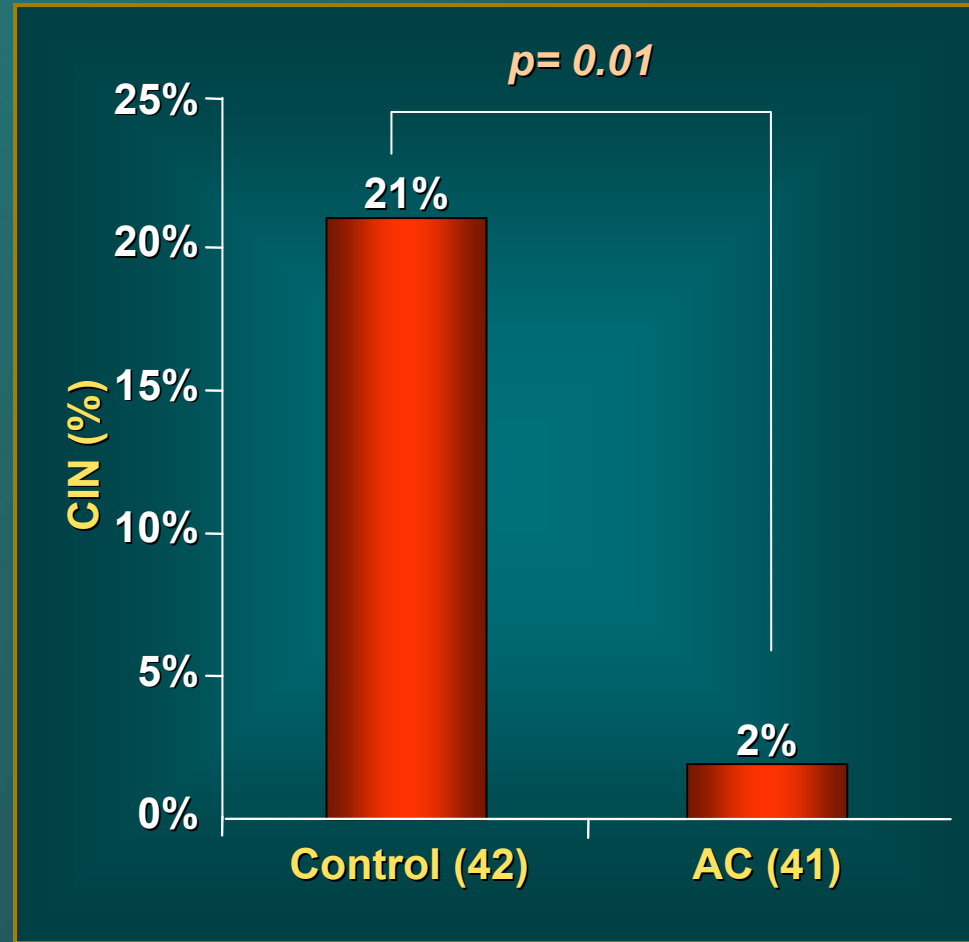


# N-ACETYLCYSTEINE (NAC)



# CIN: Effect of n-Acetylcysteine

- Prospective, randomized
- 83 high risk patients
  - CrCl < 50 ml/min
  - Diabetes 33%
- IV CONTRAST for CT (75 ml of Low Osmolar CM)
- n-AC 600 bid x 2 days pre-
- CIN definition: creatinine increase of 0.5 mg/dl
- Hydration with 0.45% @ 1 ml/kg/h x 24 h



Tepel *NEJM* 2000



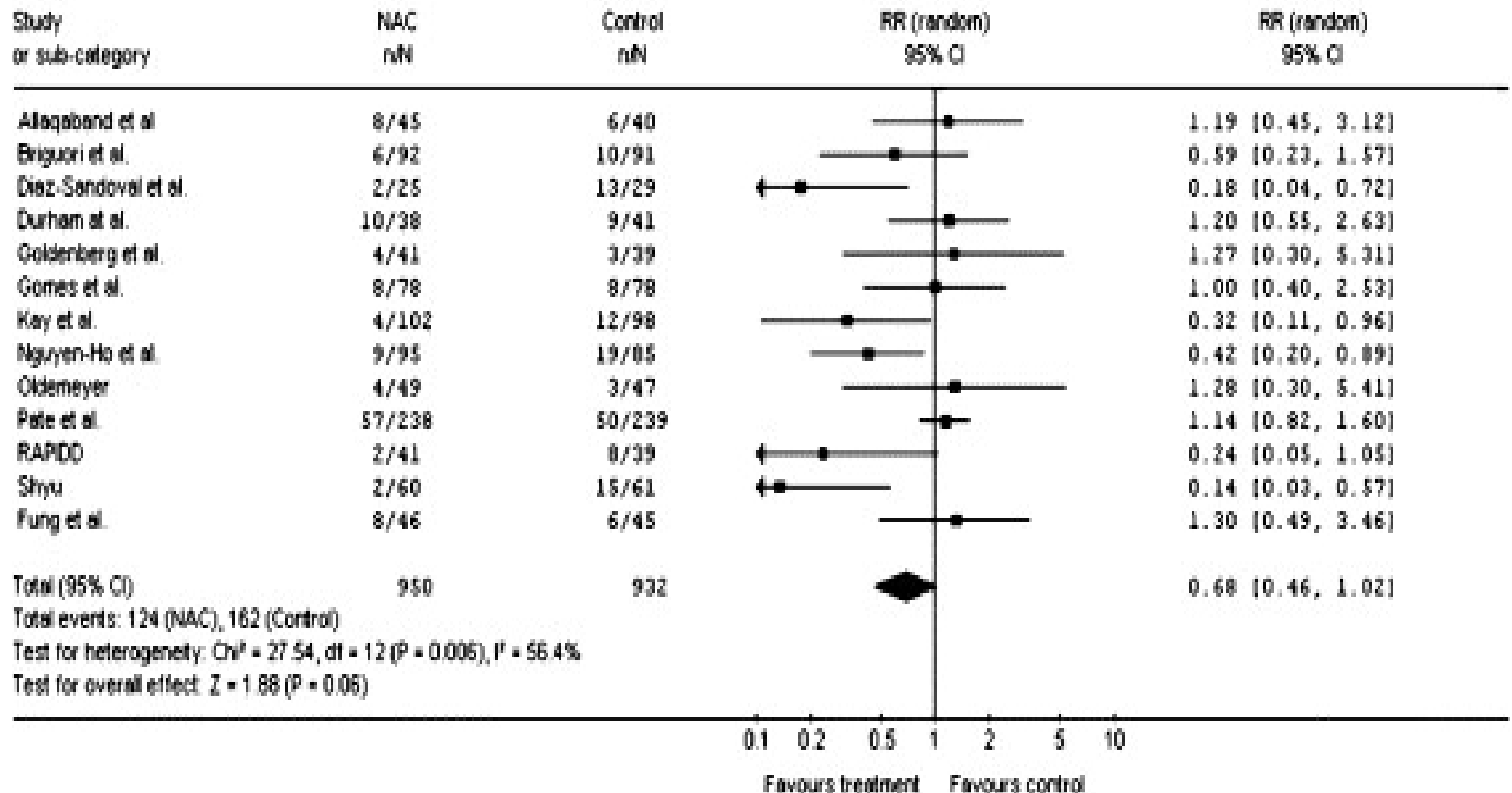
## **N- acetylcysteine (NAC) and contrast-induced nephropathy: a meta-analysis of 13 randomized placebo controlled trials**

- 1892 pts. undergoing coronary angiography
- All hydrated w/ IV fluids and low-osm nonionic CM
- impaired renal function ( $> 1.2$  mg/dL)
- treated with NAC oral or intravenously
- CIN defined as increase in creatinine  $\geq 0.5$  mg/dL or  $\geq 25\%$  from baseline to 48 hrs.
  
- 4 of 13 trials reported statistically significant reduction in CIN after NAC
- overall nonsignificant 32% reduction in the risk for CIN after NAC (combined RR 0.68, 95% CI 0.46-1.01)

Zagler et al. *Am Heart J* 2006;151:140-145.

# Relative risk for developing CIN after NAC

Review: Acetylcysteine and CIN  
 Comparison: 01 NAC on CIN  
 Outcome: 01 CIN



# **The NEPHRIC Study**

***Nephrotoxicity in High-risk Patients  
a Double Blind Randomized Multicentre  
Study of Iso-osmolar and Low-osmolar  
Non-ionic Contrast Media***



# NEPHRIC Study: Protocol

Patients with diabetes and serum creatinine 1.5-3.5 mg/dl who underwent coronary or aortofemoral angiography

Iso-osmolar, non-ionic  
Iodixanol [Visipaque]

N=64

Mean Contrast Volume = 163 ml  
PTCA – 17%

Low-osmolar, non-ionic  
Iohexol [Omnipaque]

N=65

Mean Contrast Volume = 162 ml  
PTCA – 25%

- Randomized, double blind, prospective, multicenter
- Primary endpoint: peak increase in serum creatinine concentration @ 3 days after angiography

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





# Primary Endpoint – Peak Increase in Scr from Baseline to Day 3

( $\mu\text{mol/l}$ )  $p=0.002$

	Iodixanol	Iohexol
	<b>n=62</b>	<b>n=64</b>
<b>Mean</b>	11.2 $\pm$ 19.7	41.5 $\pm$ 68.6
<b>Minimum</b>	- 19.0	- 21.0
<b>Max</b>	74.0	331.0



# Effect of nonionic radiocontrast agents on occurrence of CIN in patients with mild-moderate CRI: pooled analysis of the randomized trials

- trials comparing different contrast media or premedication (NAC, theophylline, or fenoldopam) to placebo
- included only patient from control arms, not receiving premedication
- creatinine 1.2 to 3.5 mg/dL and/or creatinine clearance 20 to 60 mL/min
  
- **245 pts. received iopamidol**
- **209 pts. received iodixanol**
- **106 pts. received iohexol**

Sharma et al. *Catheter Cardiovasc Interv* 2005;65:386-393.

# Effect of nonionic radiocontrast agents on occurrence of CIN in patients with mild-moderate CRI: pooled analysis of the randomized trials

- Significantly highest incidence of CIN with iohexol then two other agents

	Incidence of CIN	P value
Iopamidol (Isovue)	13.5%	0.024
Iohexol (Omnipaque)	25.0%	
Iodixanol (Visipaque)	11.0%	0.001

- Difference between iopamidol and iodixanol was not statistically significant ( $P=0.227$ )

Sharma et al. *Catheter Cardiovasc Interv* 2005;65:386-393.

# The **ICON** Trial: Protocol

**Patients With Chronic Renal Insufficiency  
to Undergo PCI With at Least 150cc of Contrast Volume  
n=130**

**Ioxaglate (Hexabrix)**

**Iodixanol (Visipaque)**

- **Randomization stratifies for diabetes mellitus**
- **GPIIb/IIIa inhibitor can be used per the operator**
- **Mandated pre-procedure hydration**

# Prevention of CIN with Sodium Bicarbonate

**Patients With Baseline Serum Creatinine 1 to 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**

**Primary endpoint: increase in serum creatinine  $\geq 25\%$   
within 2 days post-exposure**

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

# Prevention of CIN with Sodium Bicarbonate: Results

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

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

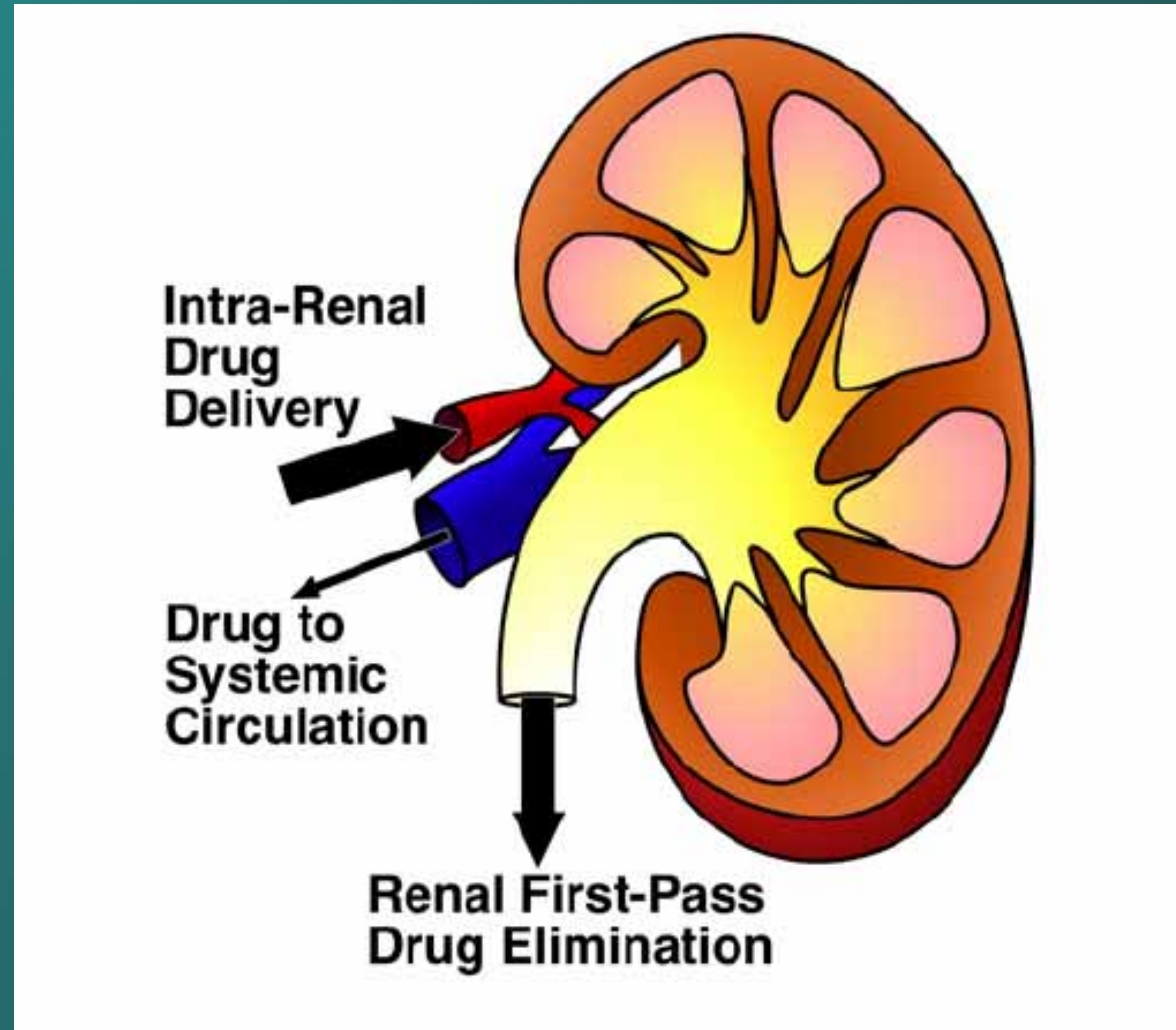


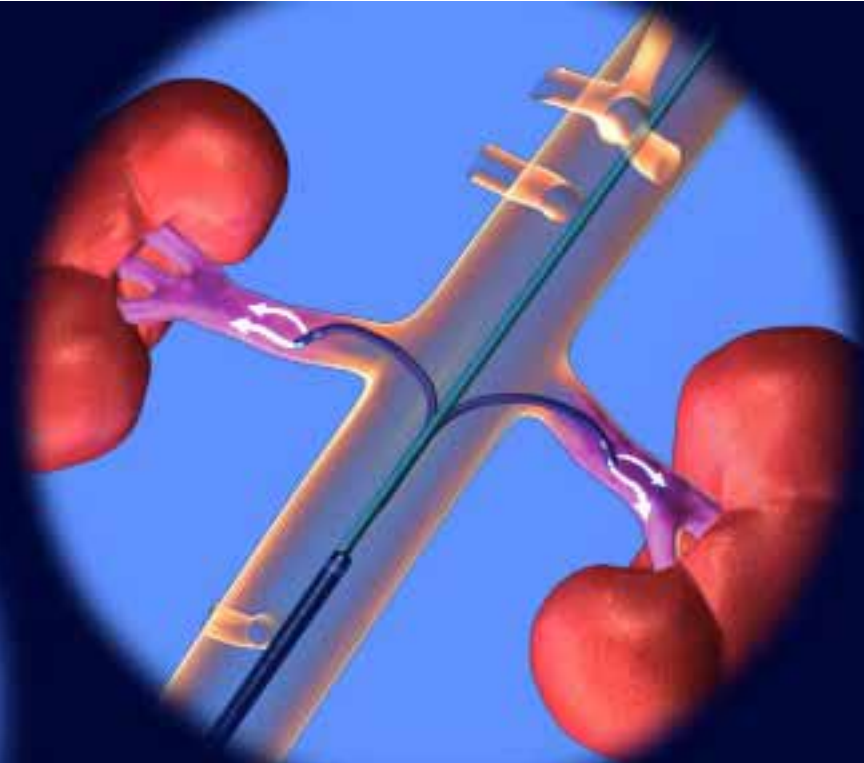


# Intra-Renal Delivery Hypothesis



# Targeted Renal Delivery

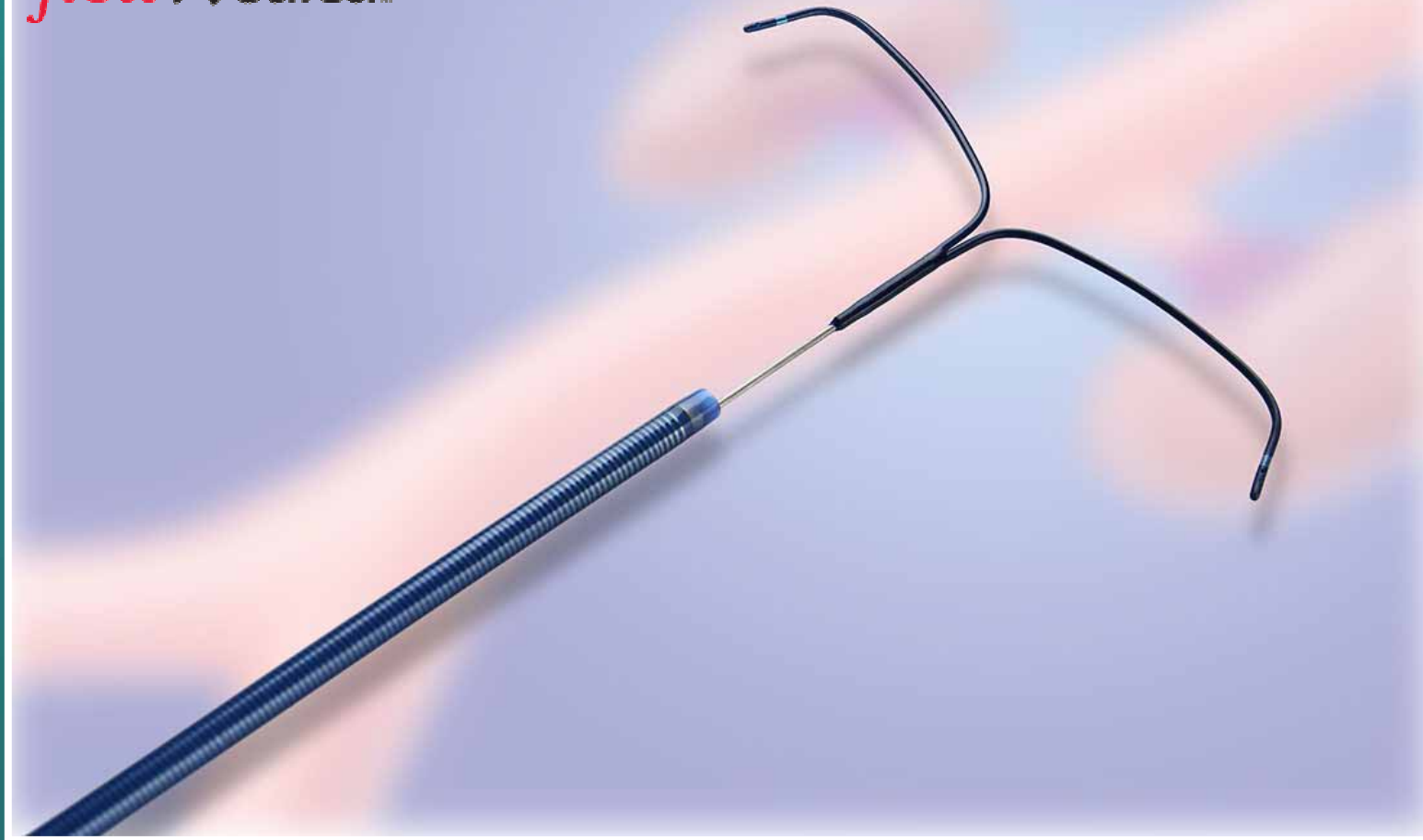




**Benephit™ Infusion System**  
(FlowMedica, Inc., Fremont, CA)

FDA (510K) Cleared January 2004

*flow*Medica™



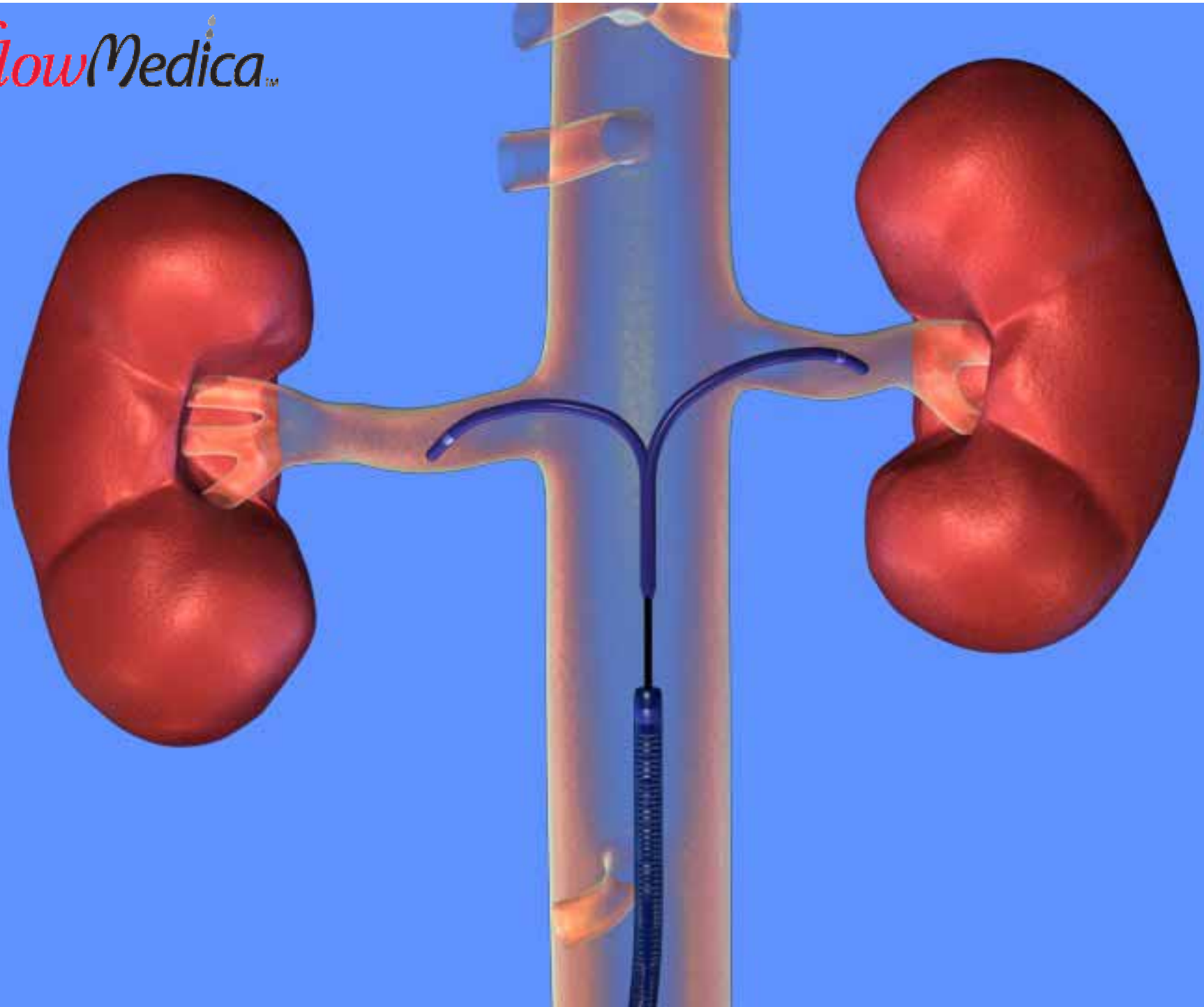
COLUMBIA UNIVERSITY  
MEDICAL CENTER

CARDIOVASCULAR  
RESEARCH FOUNDATION



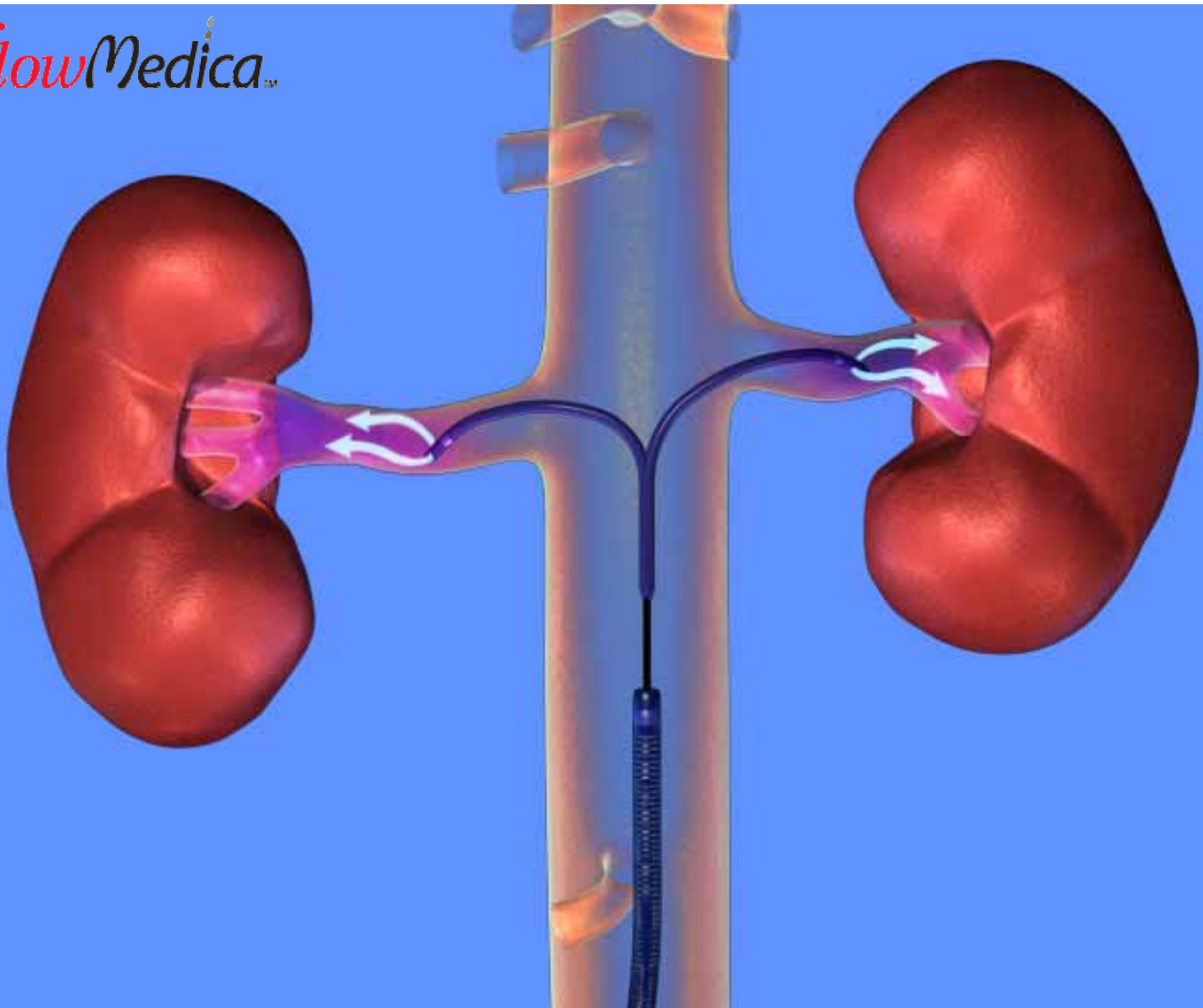


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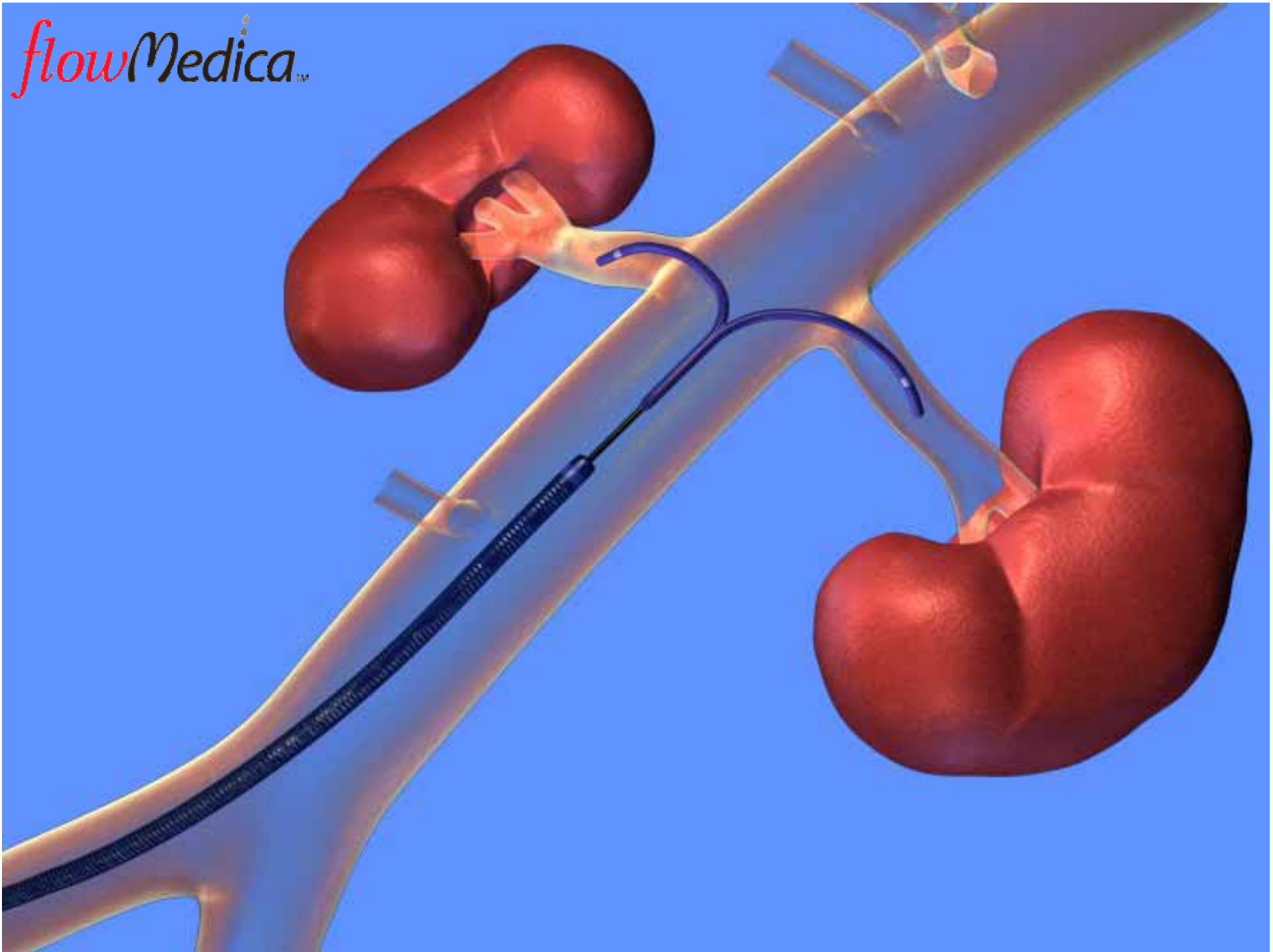




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# Conclusions (1)

- **CKD is common in patients with CAD and CAD is common in patients with CKD**
- **CKD is one of the most important single independent predictors of poor outcome**
- **CIN remains a frequent source of acute renal failure and is associated with increased morbidity and mortality, and higher resource utilization**
- **Baseline renal insufficiency, diabetes, dehydration predispose patients to contrast induced renal failure**
- **Preventive measures pre procedure, as well as careful post procedure management should be routine in all patients**

# Conclusions (2)

- Hydration pre-PCI (12 hours recommended)
- D/C nephrotoxic drugs (NSAIDs, abx etc)
- ? n-acetylcysteine
- No Role for IV Fenoldopam
- Limit contrast agent volume
- Low Osmolar better than High Osmolar
  - Within non-ionic contrast, iso-osmolar better than low osmolar (? Applicable in high-volume PCI)
- Role of Ionicity and Viscosity ?
- Role of sodium bicarbonate to be determined
- Role of local drug delivery for prevention of CIN requires further investigation

