Kidney Disease

Implications for the Management of Cardiovascular Disease

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Memorial Cardiac and Vascular Institute

Renal Disease in the PCI Population

- **CRI was present in ~ 25% of the patients[1], and among patients undergoing primary PCI for acute MI, ~ 20% of the population had baseline CRI.[2]**

- **Mild elevations of serum creatinine after contrast exposure (> 1.5 mg/dL) are associated with the development of cardiovascular events.[3]**

[1] *Chew DP* et al, *Am J Cardiol*. 2003;92:919-923
[2] Stone GW et al, *N Engl J Med* 2002;346:957-966
[3] *Hall WD. Am J Med Sci, 1999;317:176–182.*

How to Assess Renal Function?

- **SCr alone is not a reliable indicator of renal function.**
- **Glomerular filtration rate (GFR) is the best measure of overall kidney function.**
- **The normal level of GFR varies according to age, gender, and body size. Normal GFR in young adults is ~ 120 to 130 ml/min per $1.73m^2$ and declines with age.**

How to Assess Renal Function?

Abbreviated Modification of Diet in Renal Disease equation (MDRD) :

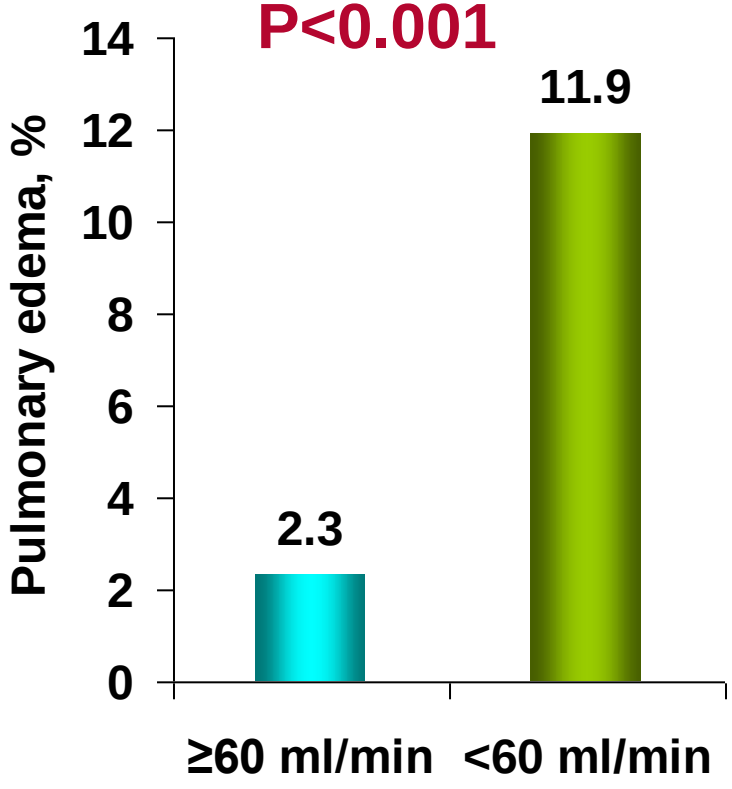
eGFR, ml/min/1.73 m^2= 186 x (Serum Creatinine [mg/dL]) - 1.154 x (Age-0.203x (0.742 if female) x (1.210 if African American)

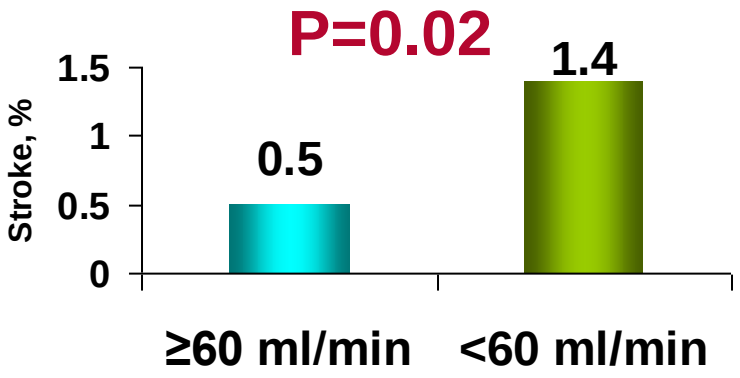
Cockcroft-Gault equation:

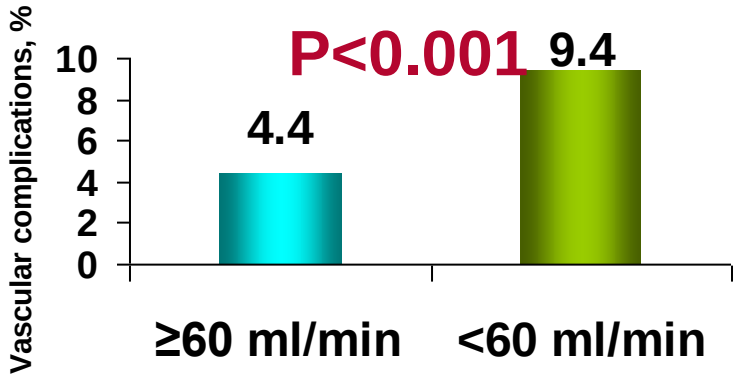
$$\text{Creatinine Clearance, ml/min} = \frac{(140 - \text{age}) \times \text{Body Weight [kg]}^*}{[\text{Serum Creatinine mg/dL}] \times 72}$$

*** Multiple by 0.8 in female**

In-hospital Complications post PCI in Relation to Renal Function

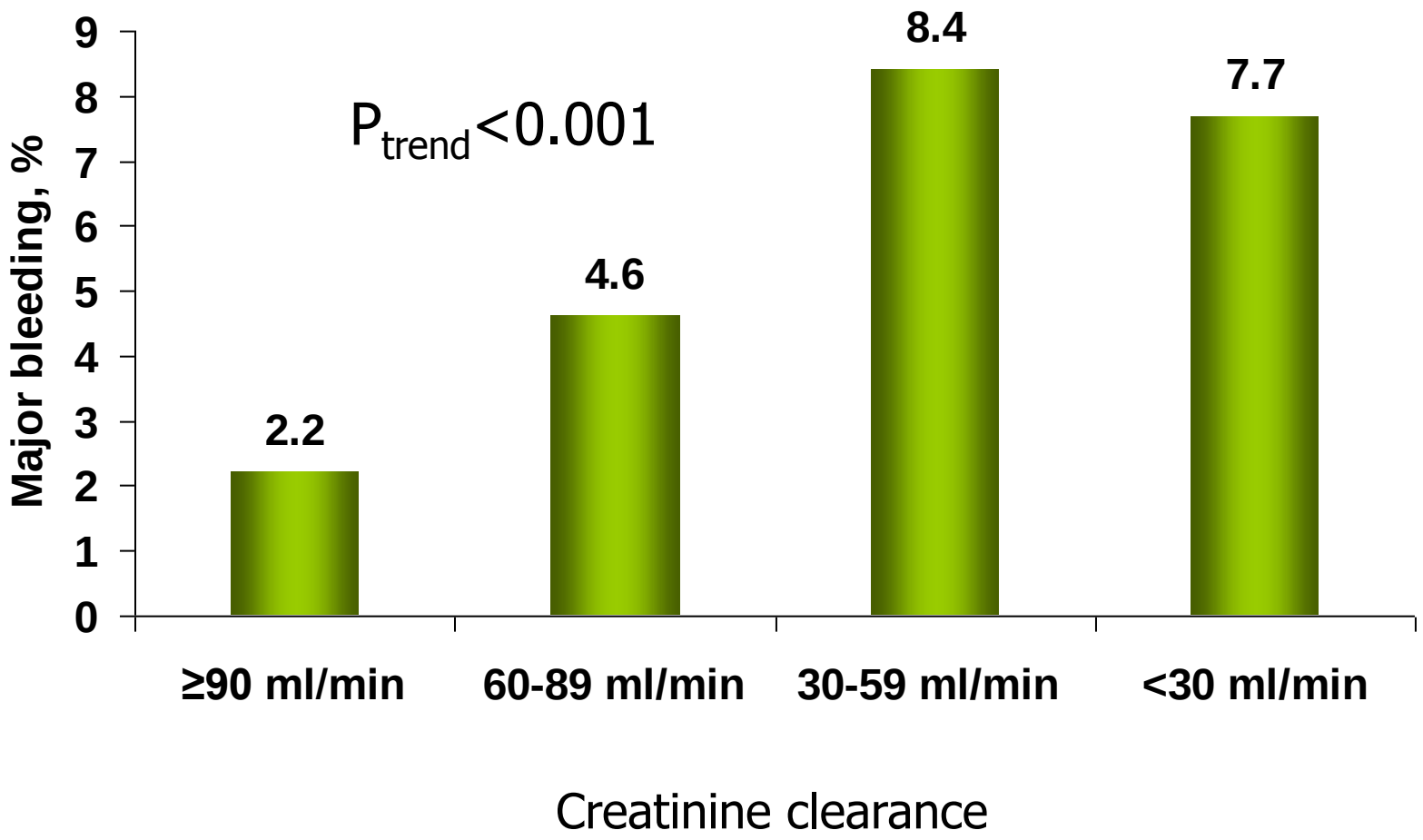






Gruberg L et al, *Catheter Cardiovasc Interv.* 2002;55:66-72

Major Bleeding in Relation to Renal Function: Meta-Analysis of 3 Randomized Trials



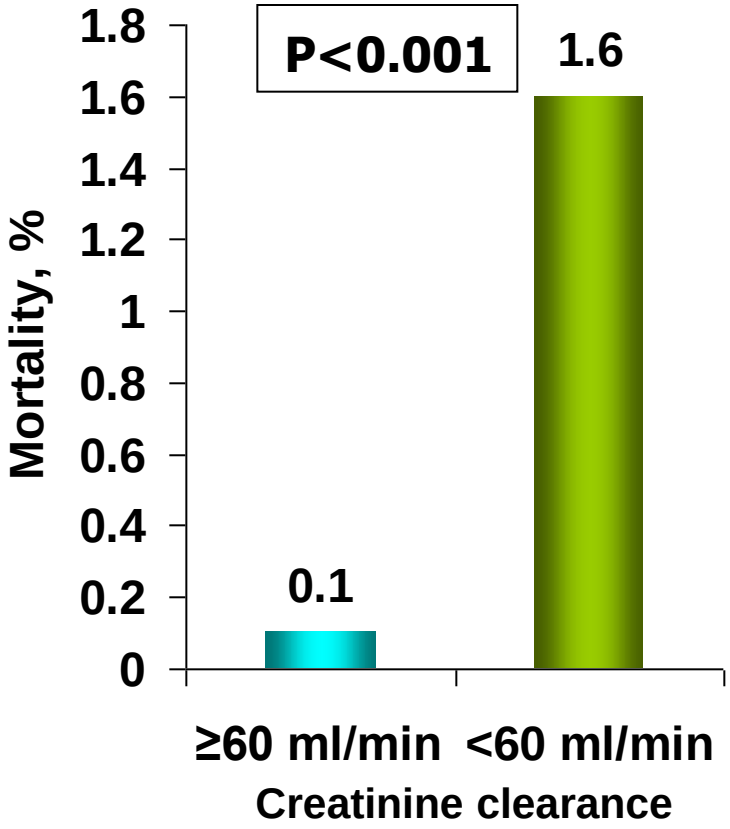
Chew DP et al, *Am J Cardiol.* 2003;92:919-923

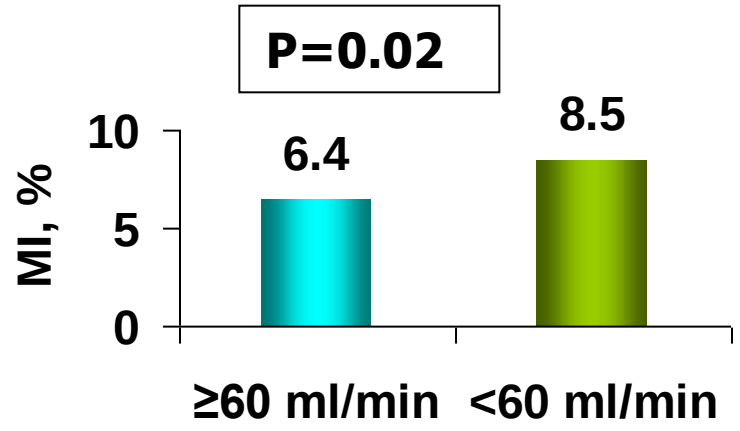
Antithrombotic Therapy in Patients with CRI

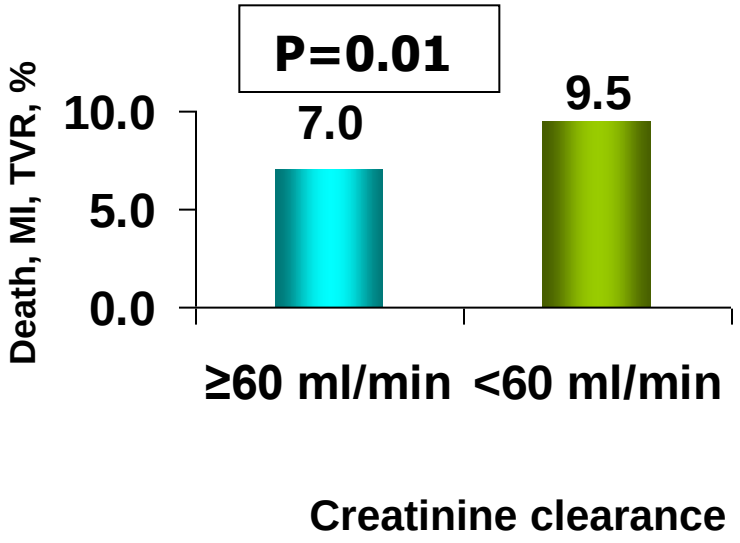
- **Dose adjustment is necessary in patients treated with:**
  - **Bivalirudin**
  - **Eptifibatide**
  - **LMWH**

30-day Outcomes Post-PCI in Relation to Renal Function

REPLACE 2 Trial



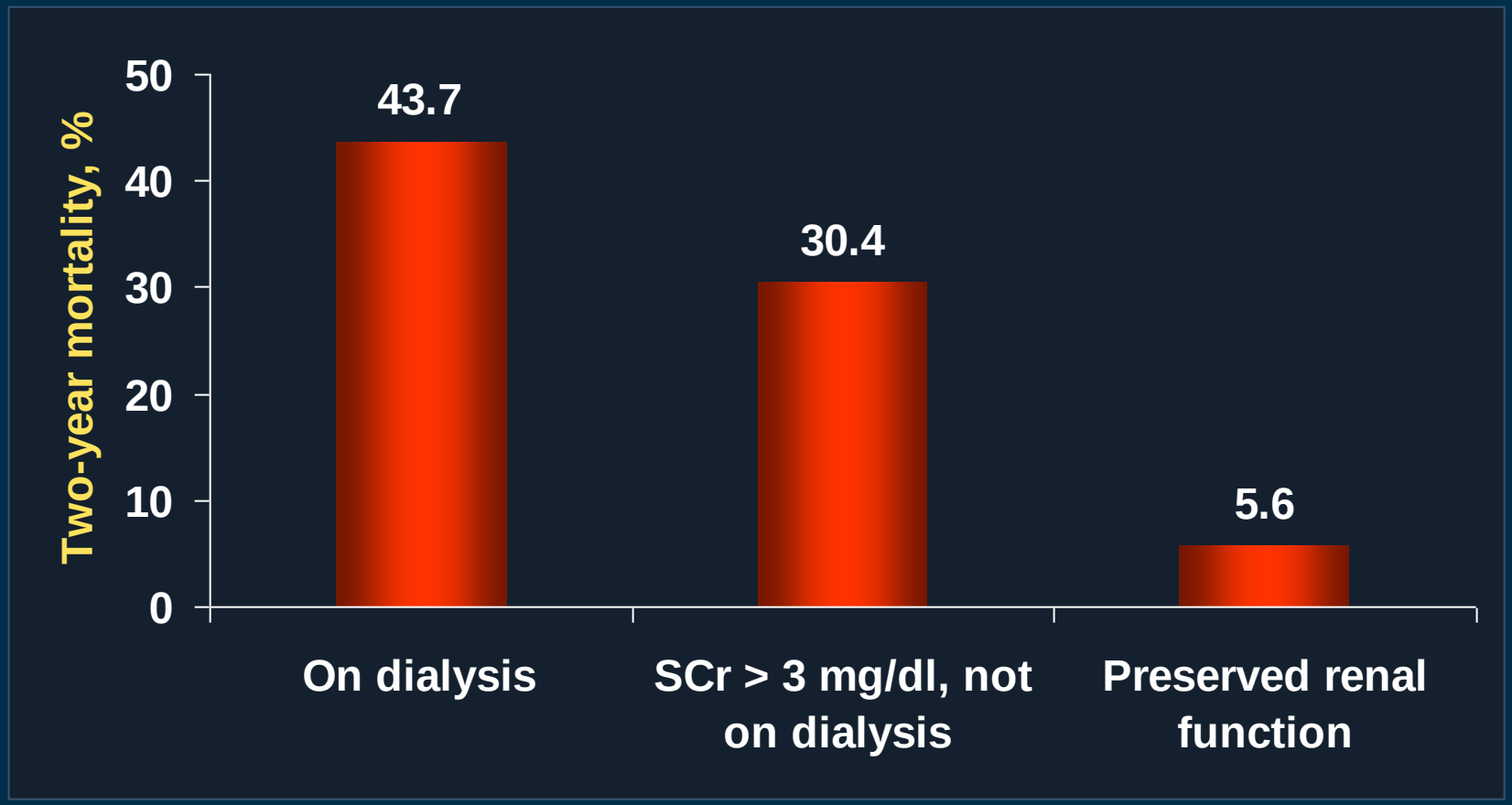




Chew DP et al, *Am J Cardiol.* 2005;95:581-585

Two-year Mortality Post PCI in Relation to Renal Function

2650 consecutive patients from Mayo Clinic



Contrast-Induced Nephropathy

- **With the increasing use of contrast media, CIN has become the 3rd cause of hospital acquired acute renal failure***
- **CIN occurs in ~1% of cases in the general population, though may be as high as 50% in patients with CRI**
- **Depending upon the definition used, CIN may occur in ~3-10% of all cases**

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

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: Pathogenesis

Hemodynamic changes

- Reduction renal blood flow
- Deceleration of red blood cell velocity
- Decrease in oxygen tension

Direct toxicity to renal epithelium

- Prominent vacuolisation
- Appearance of intracytoplasmic granular structure
- Occasional cell necrosis
- Enhanced production of oxygen free radicals

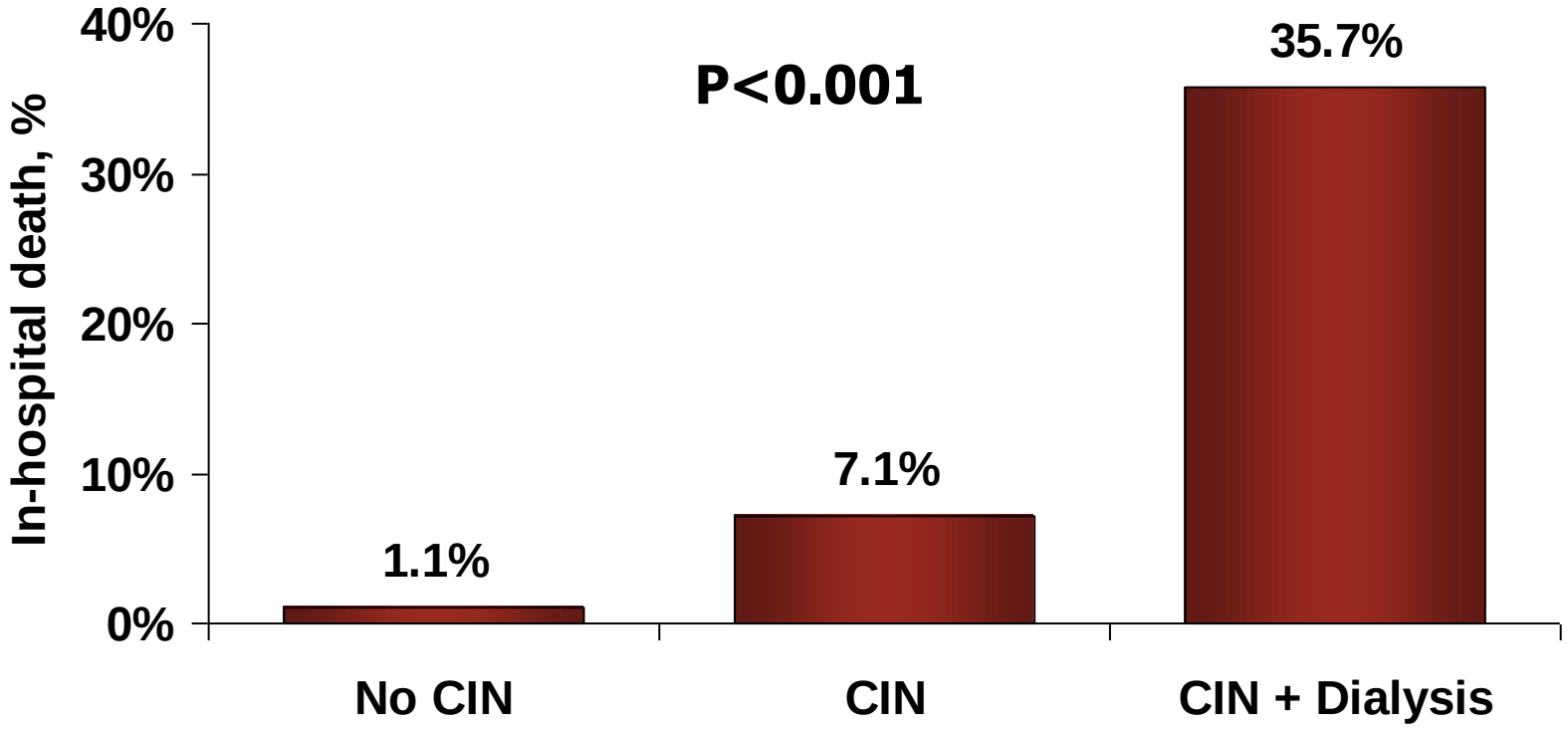
Apoptosis

- DNA fragmentation
- Increase in activity of caspases

Change in concentration of vasoactive substances

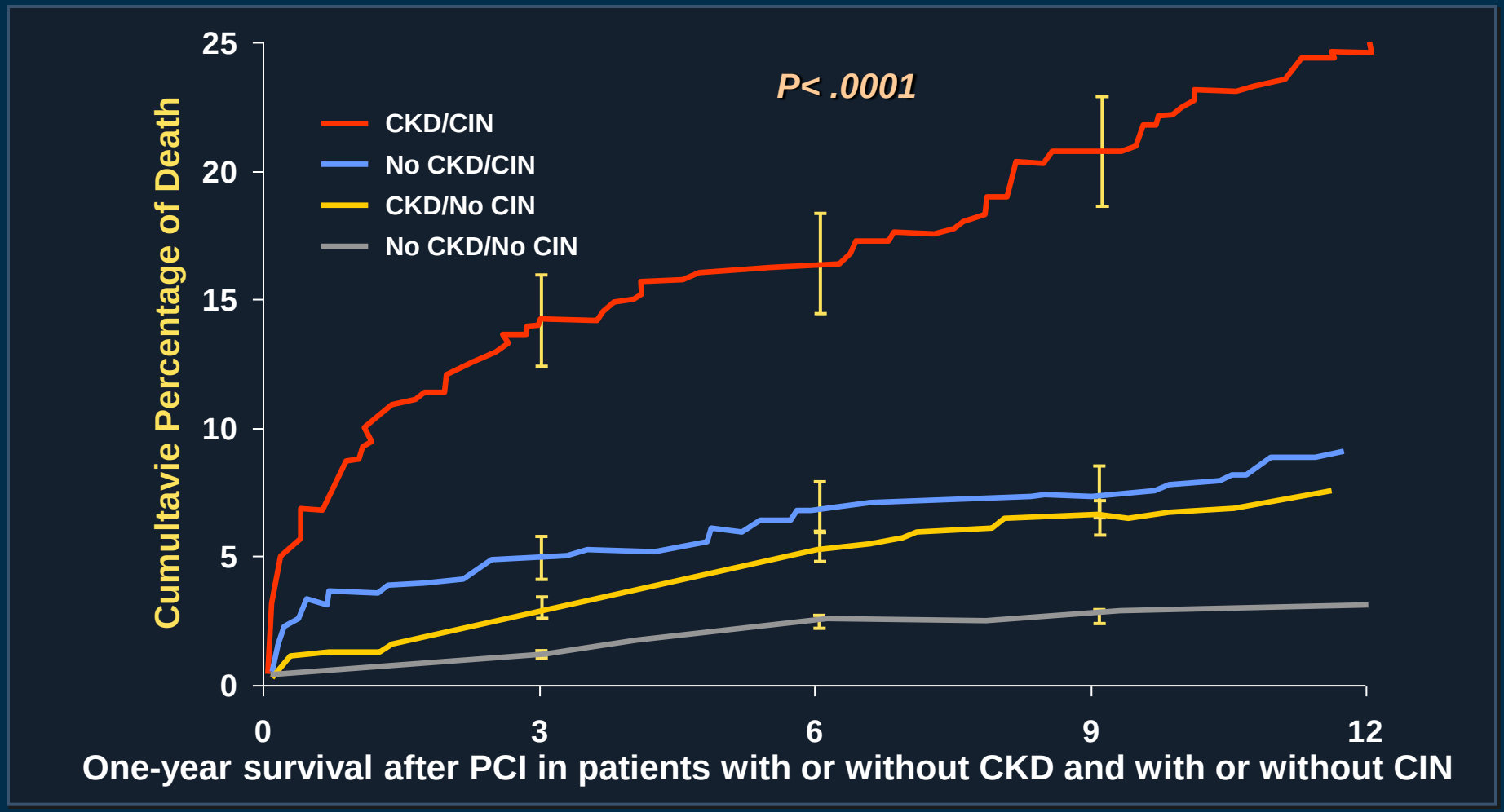
- An increased serum level of endothelin
- Decrease in PGE2
- Decrease in NO production
- Increase in adenosine

Contrast-Induced Nephropathy: In-hospital Mortality



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

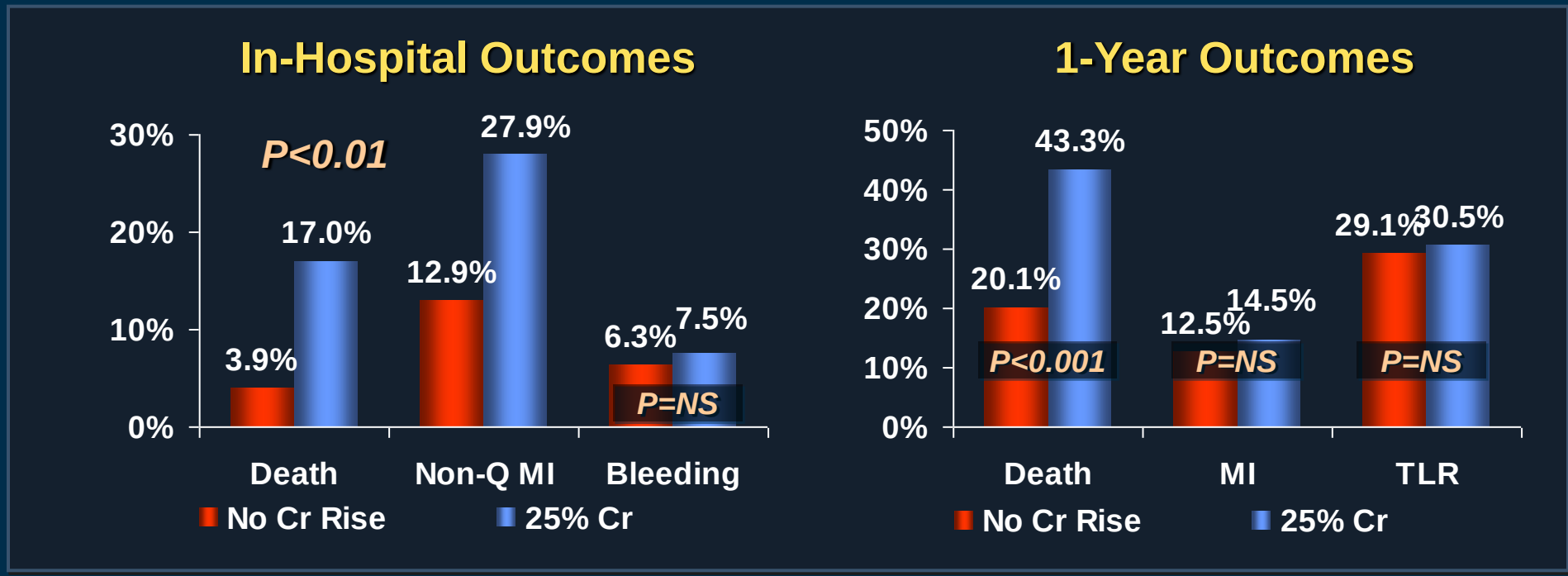
CIN after PCI in relation to Chronic Kidney Disease



Dangas et al, *Am J Cardiol* 2005; 95:13-19.

PTCA in Chronic Renal Failure

- 440 patients with baseline creatinine ≥ 1.8mg/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

Contrast-Induced Nephropathy: Resource Utilization

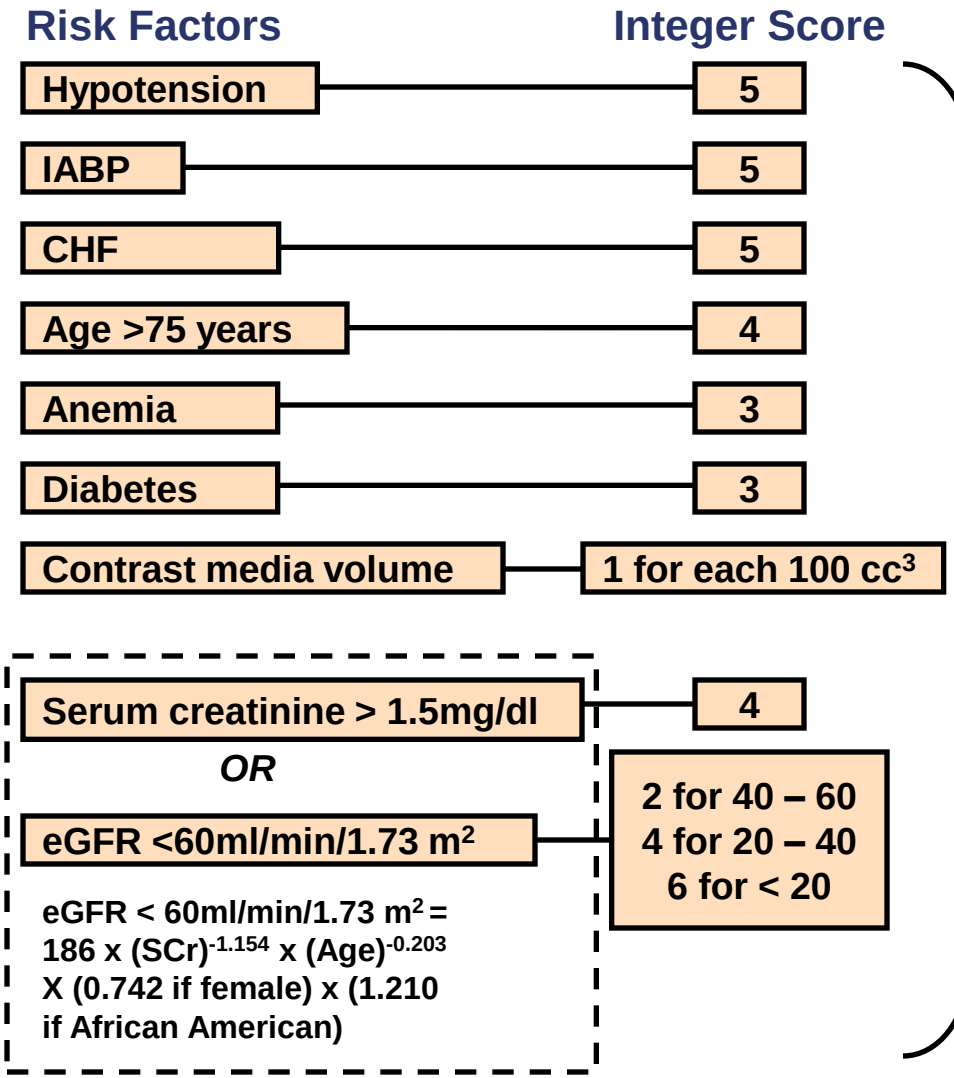
Endpoint (%)	Patients		P-value
	With CIN	Without CIN	
Hospital length of stay (days)	9.6±7.2	3.2±6.4	<0.001
ICU length of stay (days)	2.3±4.4	0.6±1.8	<0.0001
Need for hemodialysis (%)	12	0	<0.0001

Iakovou I et al, *J Am Coll Cardiol.* 2002;39:2A

Risk Factors for the Development of Contrast-Induced Nephropathy

Fixed (non-modifiable) risk factors	Modifiable risk factors
Pre-existing renal failure	Volume and type of contrast medium
Diabetes mellitus	Multiple contrast injections within 72 hours
Advanced congestive heart failure	Hemodynamic instability
Reduced left ventricular ejection fraction	Dehydration
Acute myocardial infarction	Anemia/Blood loss
Cardiogenic shock	Intra-aortic balloon pump
Renal transplant	Low serum albumin level (<35 g/L)
	Angiotensin converting enzyme inhibitors
	Diuretics
	Nephrotoxic drugs (nonsteroidal anti-inflammatory agents, antibiotics, cyclosporine, etc.)

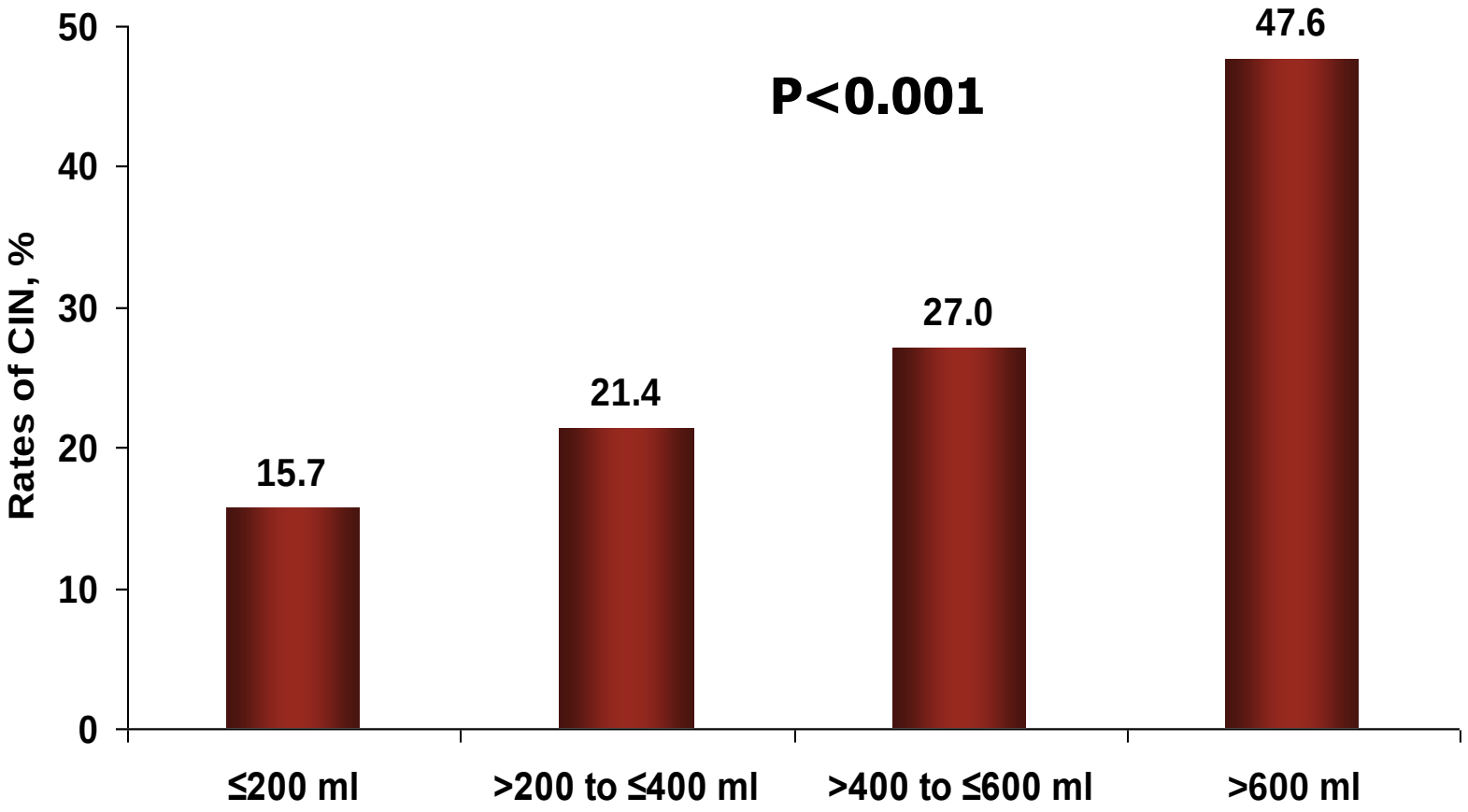
Risk Stratification of Patients Undergoing Contrast Exposure



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%

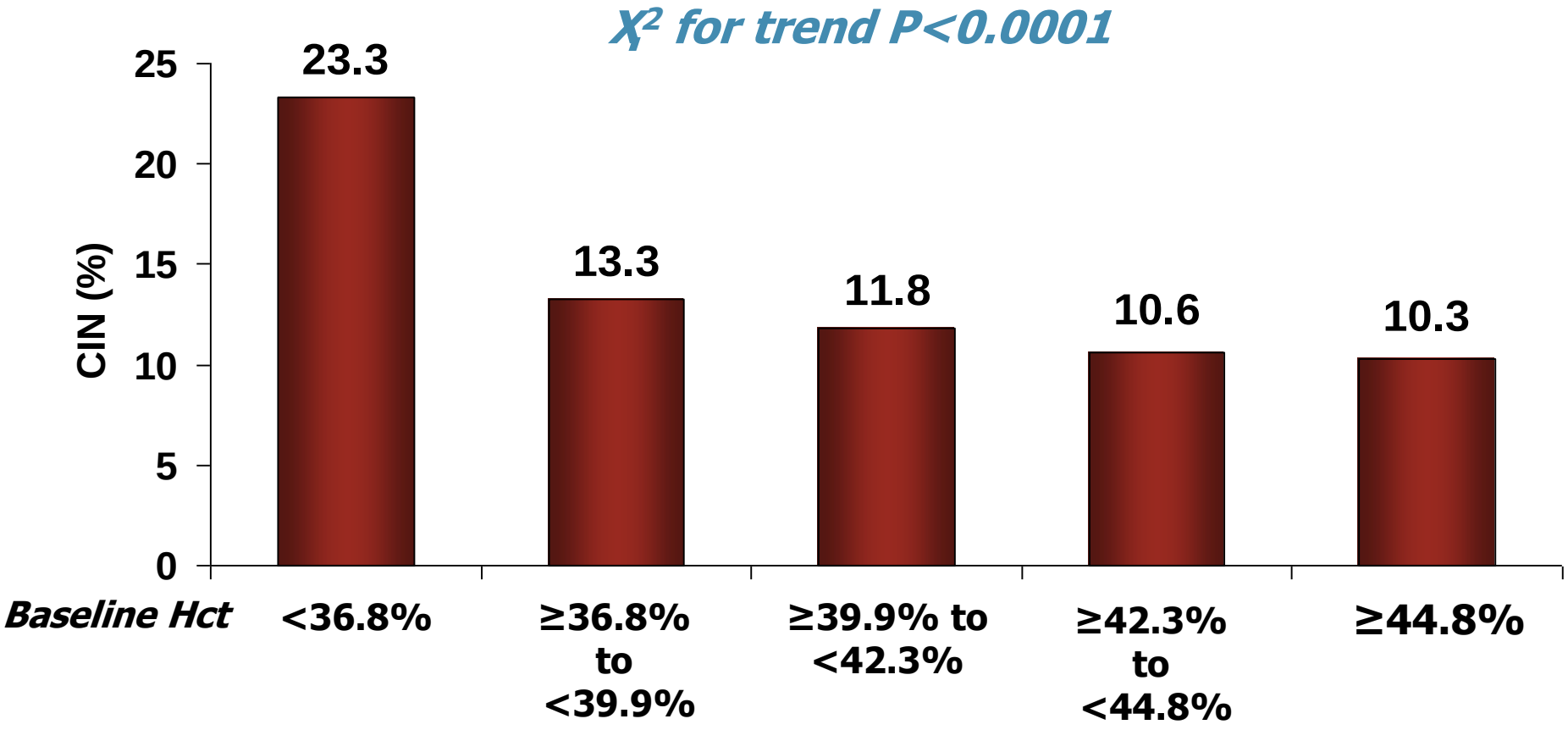
Mehran R et al. *JACC* 2004;44:1393-1399.

Rates of CIN as a Function of Contrast Medium Volume in Diabetic Cohort



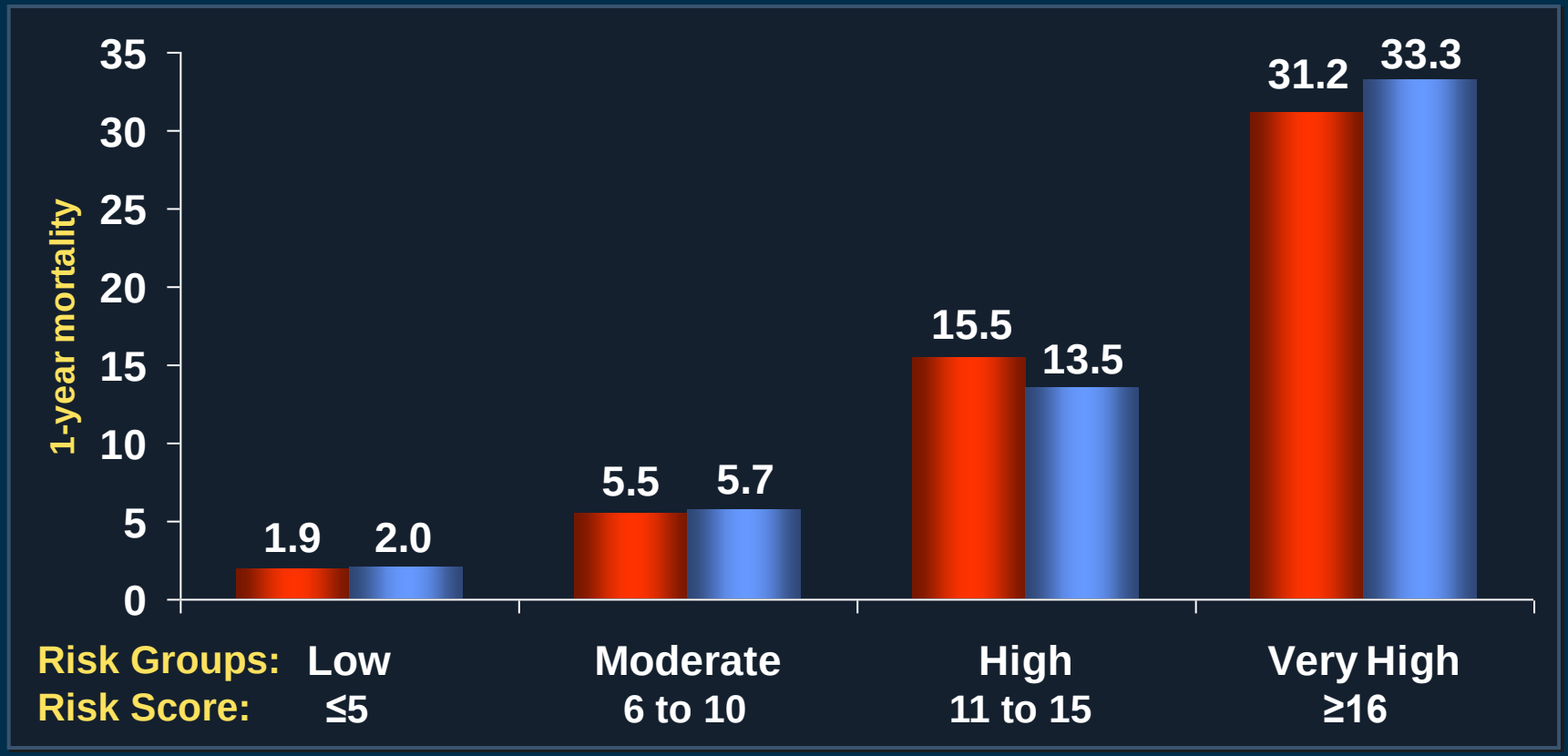
Nikolsky E et al. *AJC* 2004;94:300-305.

Risk of Contrast-induced Nephropathy in Relation to Baseline Hematocrit



Nikolsky E et al. *Kidney Int*. 2005;67:706-713.

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.

Case Example

- 76 y.o. female with diabetes, Hgb 11.5 g/dl and eGFR 36 ml/min
- CIN risk score is 15 if contrast medium volume is 100 ml
  - CIN risk is 26%
  - Dialysis risk is 1%
- CIN risk score is >16 if contrast medium volume is 200 ml
  - CIN risk is 57%
  - Dialysis risk is 12%

Strategies

Prevention of Contrast Induced Nephropathy

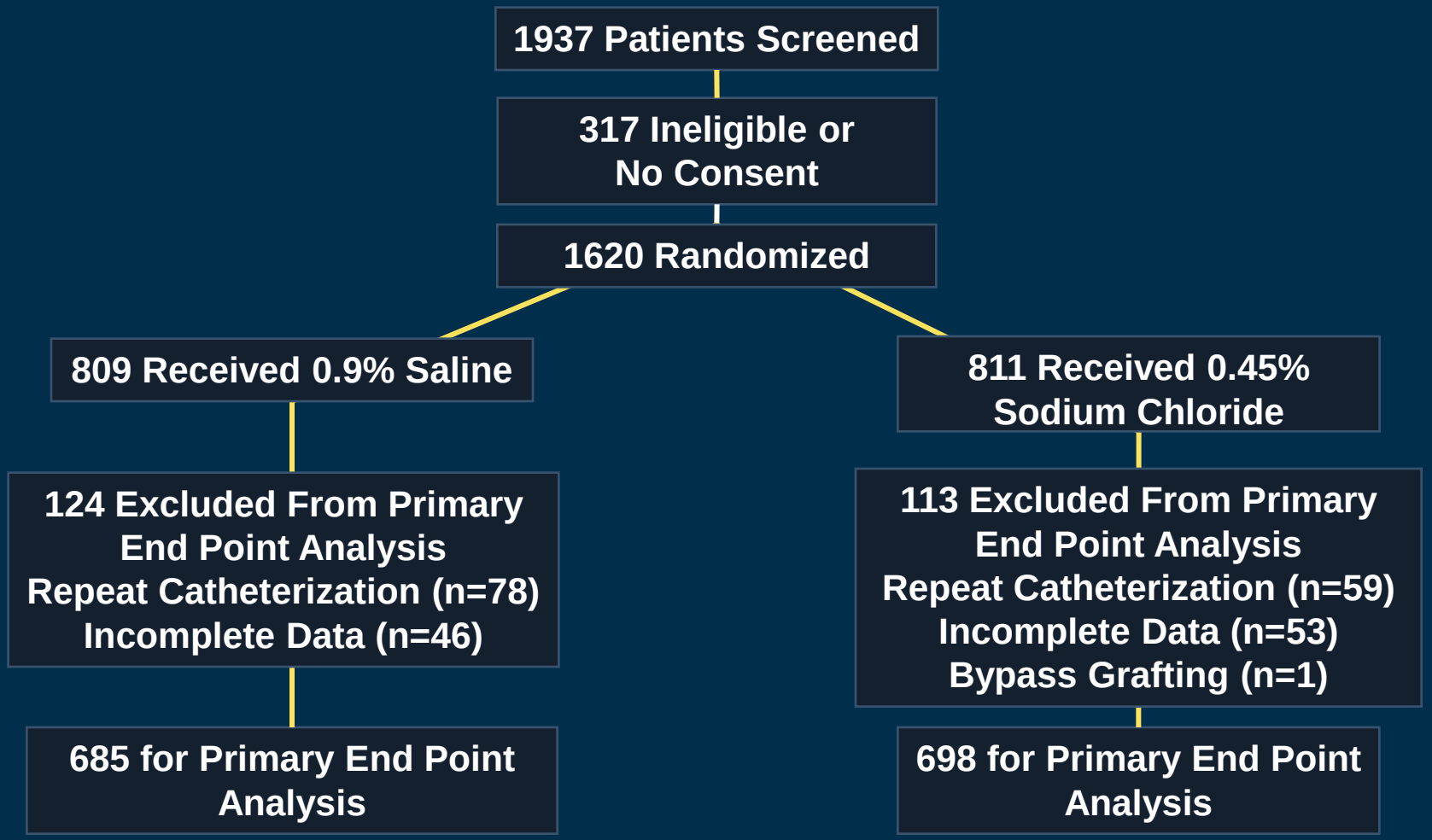
Brar , SS

Treatment Modalities Assessed in Randomized Trials on Prevention of CIN

Treatment	Effect
Hydration	+
Hemofiltration	+
Sodium bicarbonate	+/–
N-acetyl-l-cysteine (Mucomyst)	+/–
Dopamine	+/–
Fenoldopam	+/–
Theophylline	+/–
Calcium channel blockers	+/–
Hemodialysis	+/–
Atrial natriuretic peptide	+/–
Statins	+/–

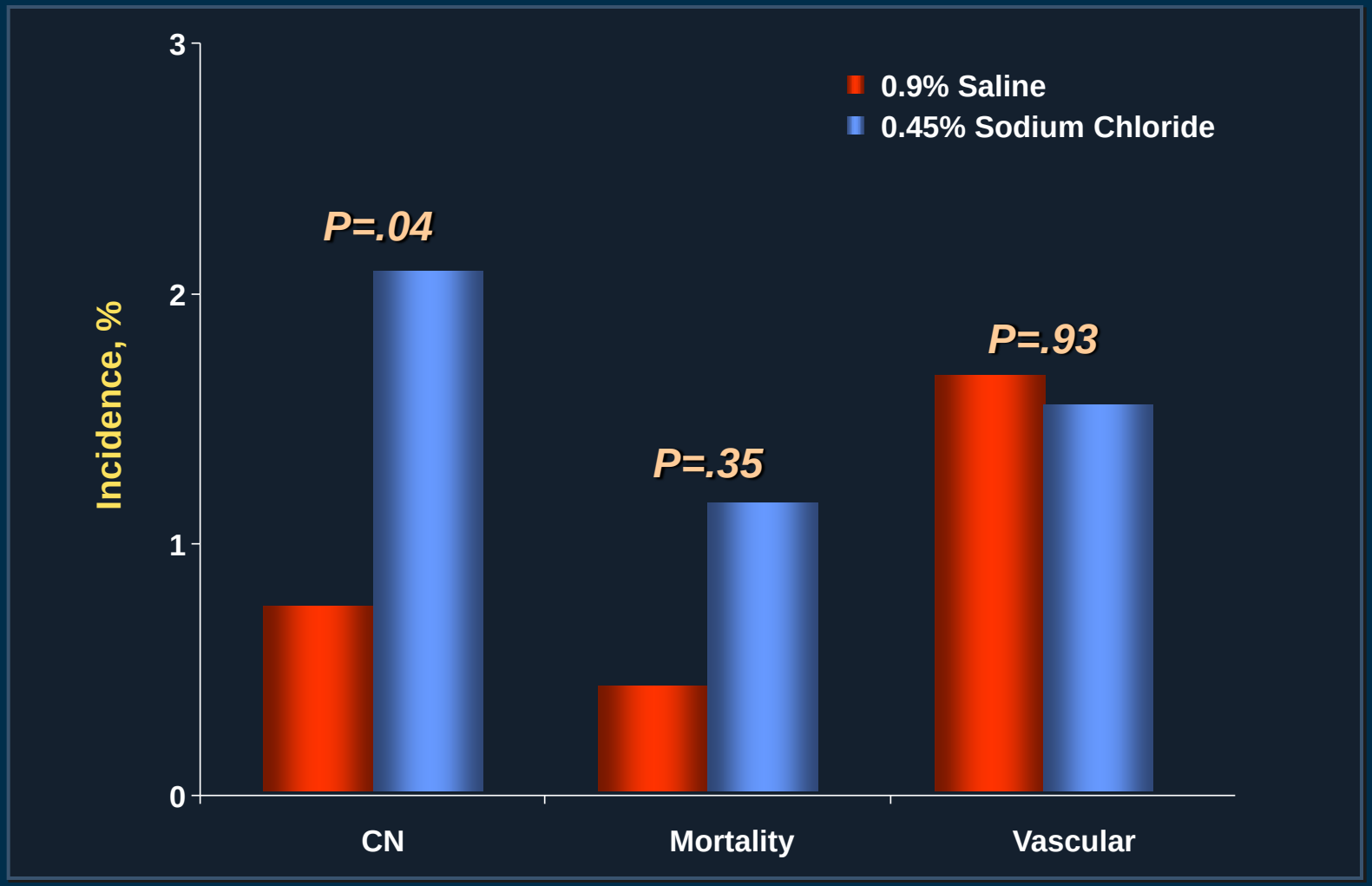
+ positive effect; – no effect; +/– conflicting data

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

RenalGuard™

RenalGuard™ for CI-AKI prevention is designed to:

- Create and maintain high urine output
- Prevent contrast agents from clogging tubules
- Limit toxin exposure in kidneys
- Automated matched fluid replacement in real-time to reduce side effects associated with over- or under-hydration

REMEDIAL II

RE nal Insufficiency Following Contrast MEDIA Administration II TriaL

RenalGuard system in high risk patients for contrast induced acute kidney injury

Carlo Briguori, MD, PhD

Laboratoy of Interventional Cardiology

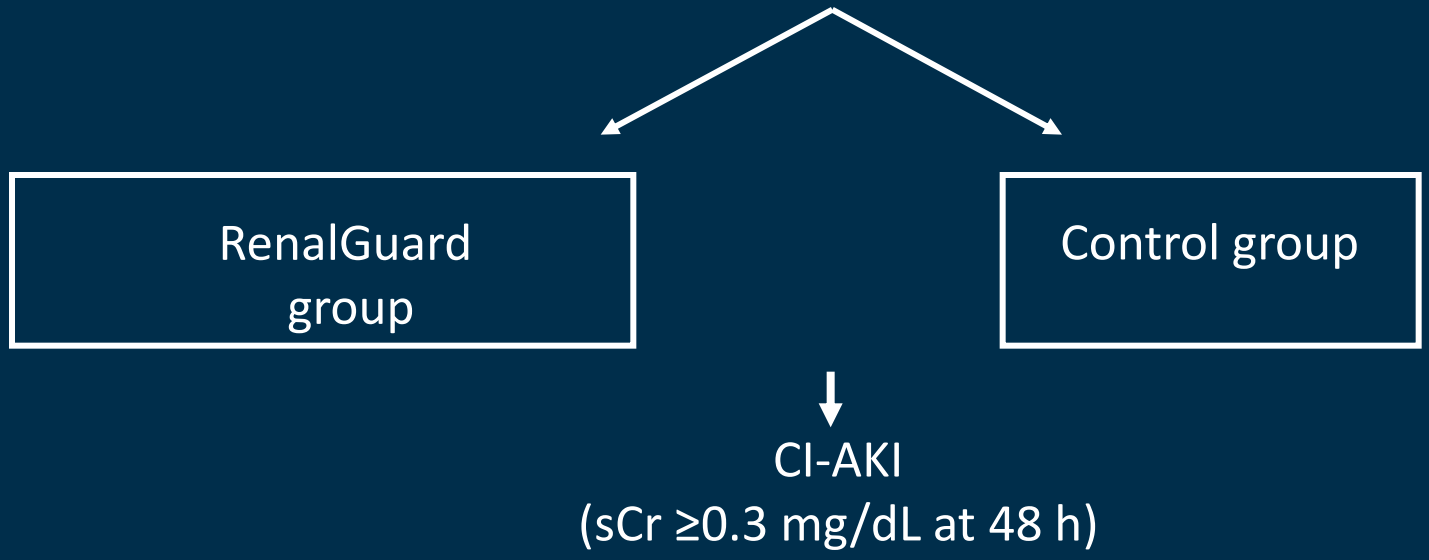
Clinica Mediterranea, Naples – Italy

ACC 2011

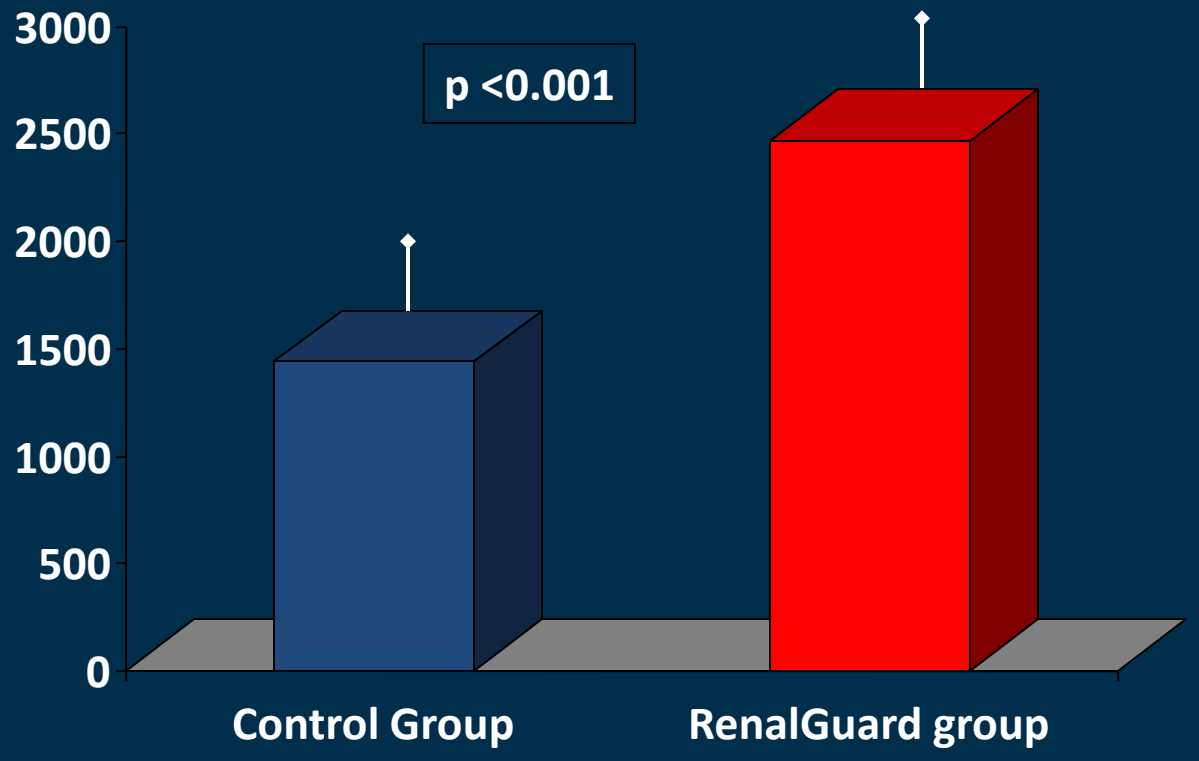
REMEDIAL II

- DESIGN: Prospective, randomized, double-arm, multicenters clinical study

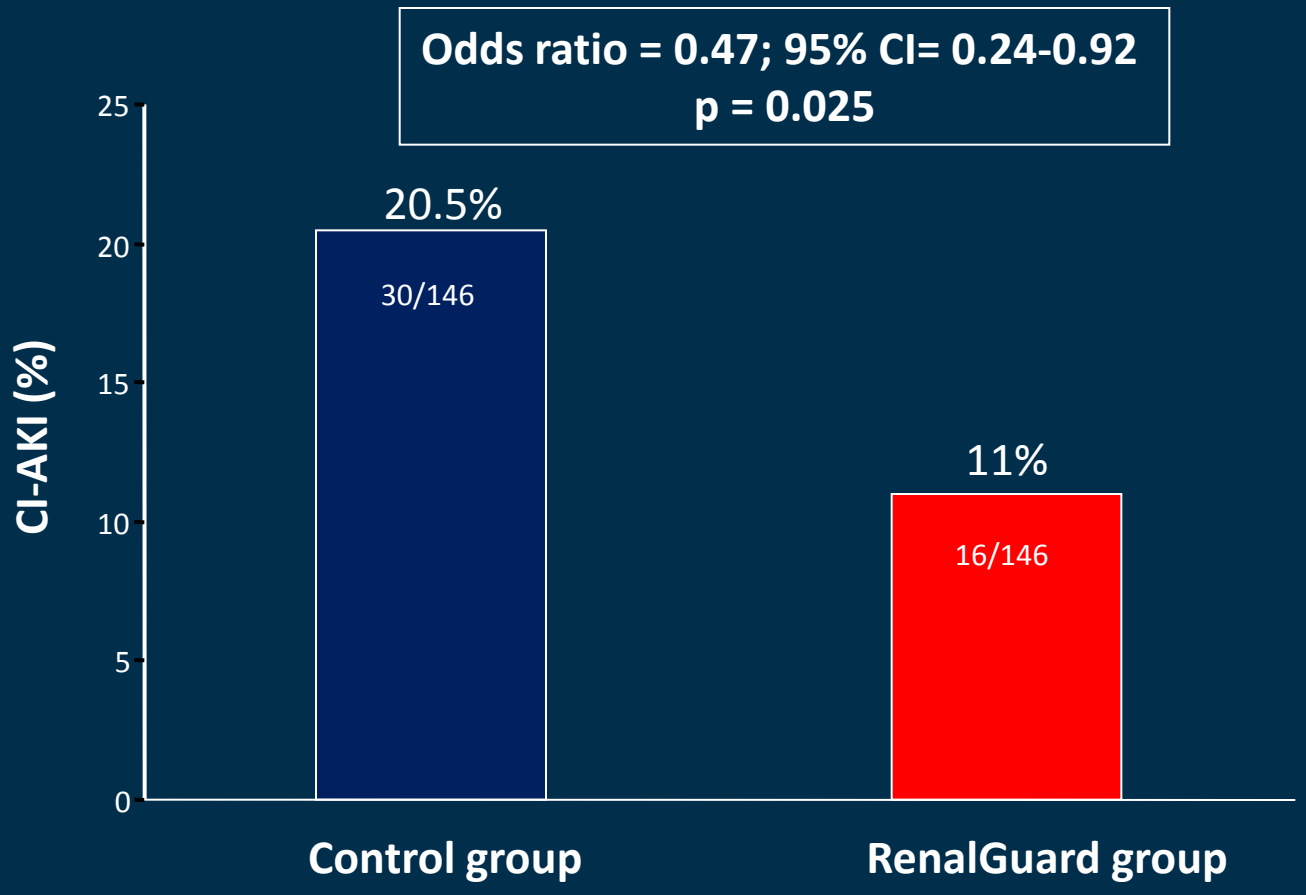
Elective contrast media administration in patients at high risk for CI-AKI
(risk score ≥11 and/or eGFR≤30 ml/min/1.73 m^2)



Urine Volume at 24 hours



Primary endpoint



The Prevention of CIN by Hemofiltration

Design

- **DESIGN: Prospective, open-labeled, randomized trial**
- **OBJECTIVE: to investigate the role of hemofiltration, as compared with isotonic-saline hydration, in preventing CIN in patients with renal failure**

A total of 114 consecutive patients with CRI (SCr >2 mg/dl [176.8 micromol/l]) undergoing elective coronary interventions at Centro Cardiologico Monzino in Milan from 2000 to 2001

Randomization

Hemofiltration 1000 ml/hr without weight loss in ICU 4 to 8 hours before intervention and for 18 to 24 hours post intervention

N=58

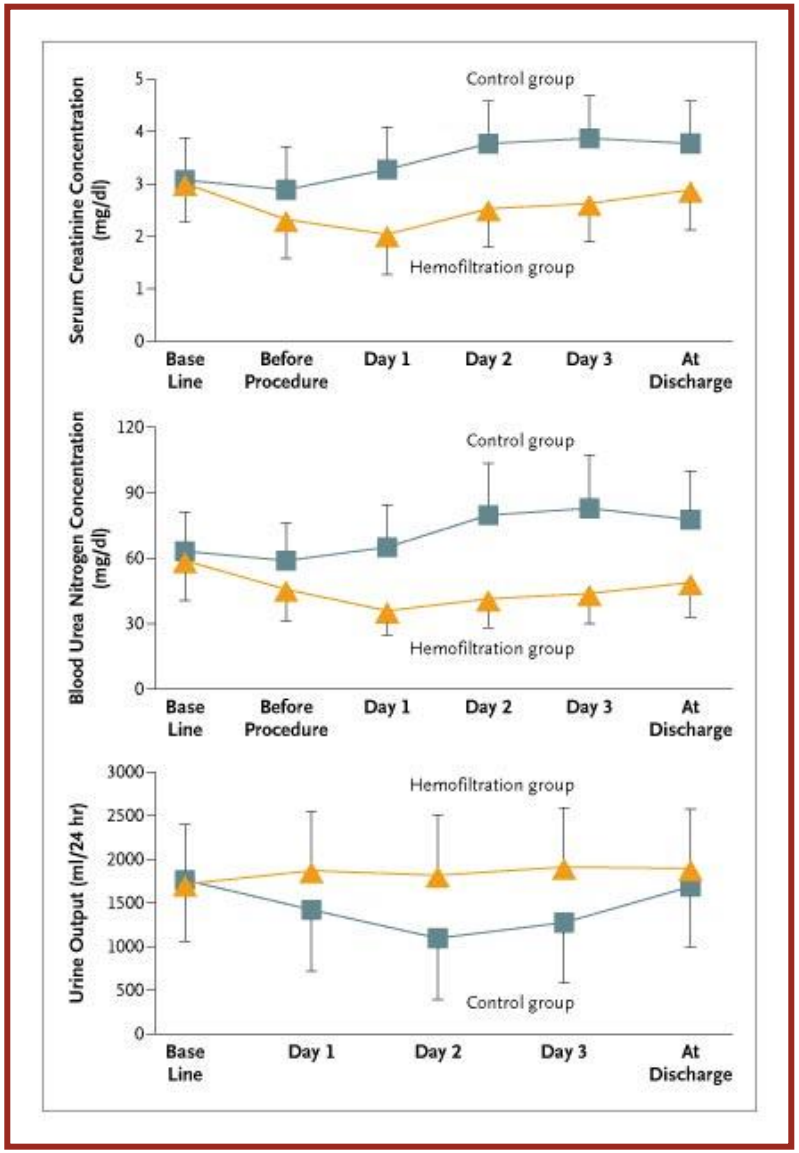
Isotonic-saline hydration 1 ml/kg /hr given in a step-down unit 4 to 8 hours before intervention and for 18 to 24 hours post intervention

N=56

***Primary endpoint:* Change in SCr and in-hospital mortality**

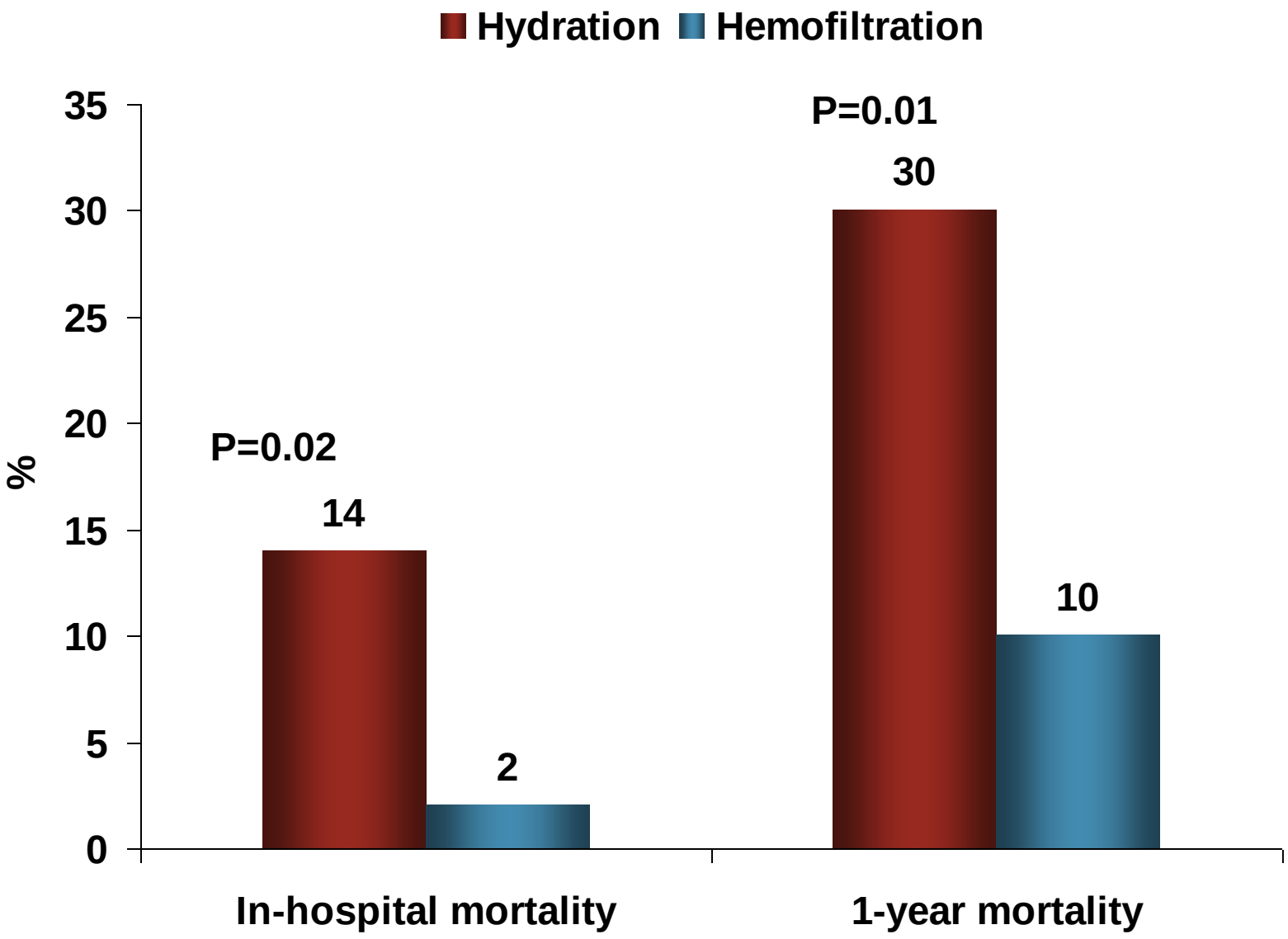
Marenzi G et al, *N Engl J Med.* 2003;349:1333-1340

The Prevention of CIN by Hemofiltration



Marenzi G et al, *N Engl J Med.* 2003;349:1333-1340

The Prevention of CIN by Hemofiltration



Marenzi G et al, *N Engl J Med.* 2003;349:1333-1340

The Prevention of CIN by Prophylactic Hemodialysis

Design

- **DESIGN: Prospective, open-labeled, randomized trial**
- **OBJECTIVE: to investigate the role of prophylactic hemodialysis, as compared with isotonic-saline hydration, in preventing CIN in patients with renal failure**

A total of 82 patients with CRI (SCr > 3.5 mg/dl) undergoing elective coronary interventions at Kaohsiung Veterans General Hospital in Taiwan from 2001 to 2006

Randomization

Normal saline IV 1 ml/kg/h for 6 h before and 12 h after contrast medium exposure and hemodialysis asap post procedure N=42

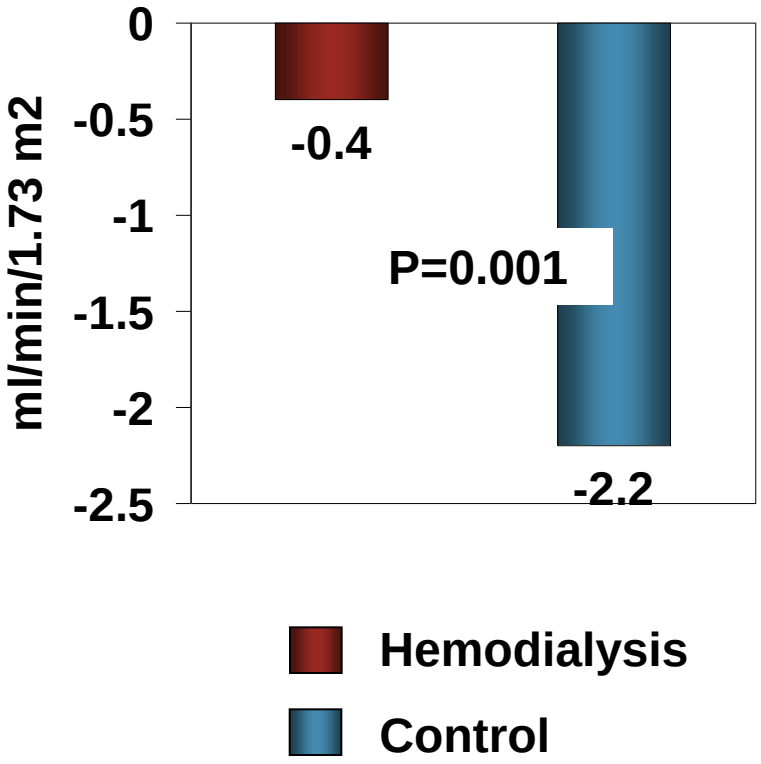
Normal saline IV 1 ml/kg/h for 6 h before and 12 h after contrast medium exposure N=40

Primary endpoint: **the change in CrCl between baseline and the 4th day.**

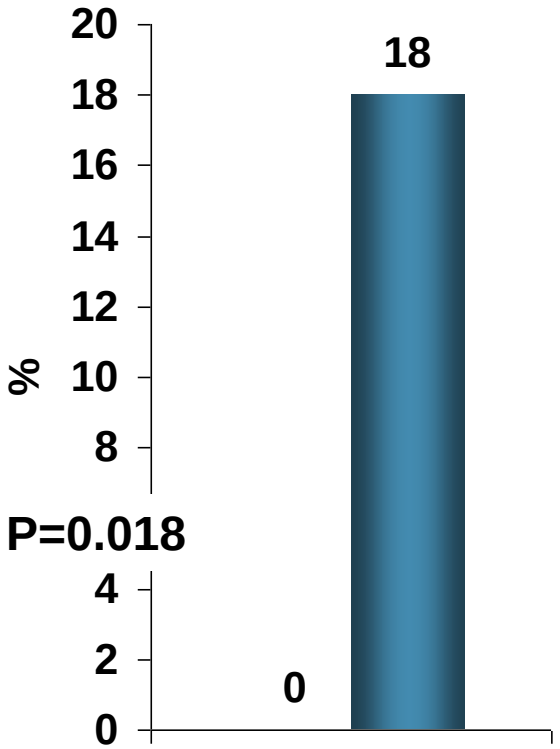
Lee PT et al, *JACC* 2007; 50:1015-1020

The Prevention of CIN by Prophylactic Hemodialysis

Change in CrCl between day 0 and 4:

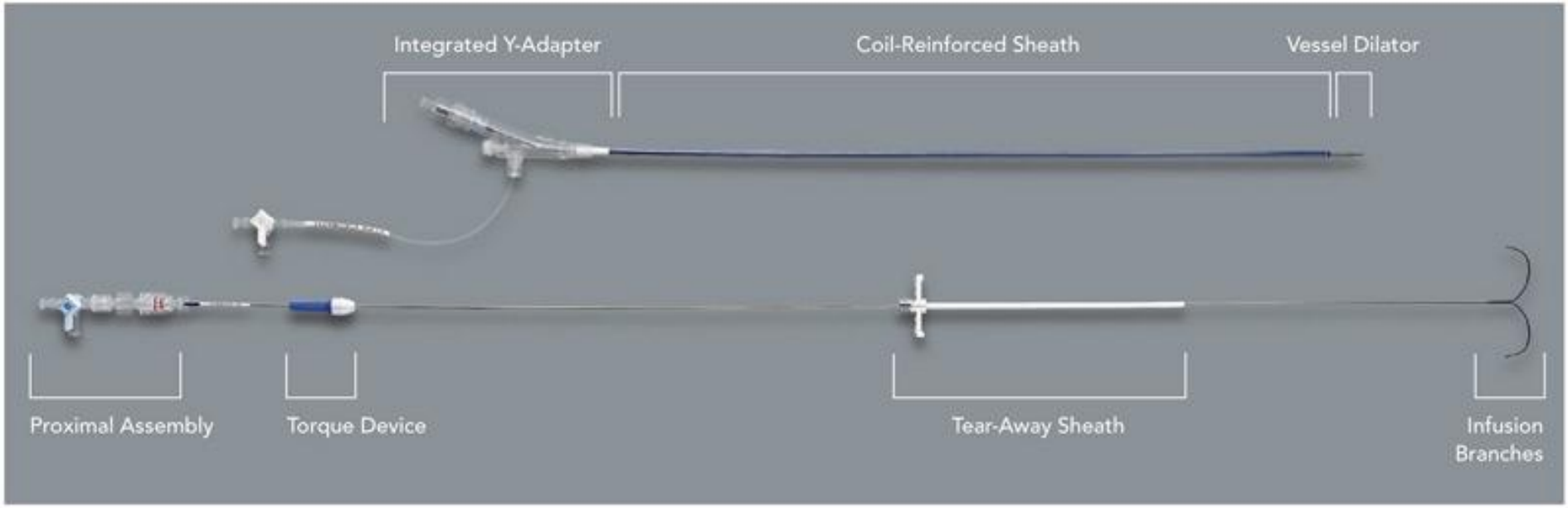


Need in long-term dialysis:



Lee PT et al, *JACC* 2007; 50:1015-1020

Targeted Renal Therapy

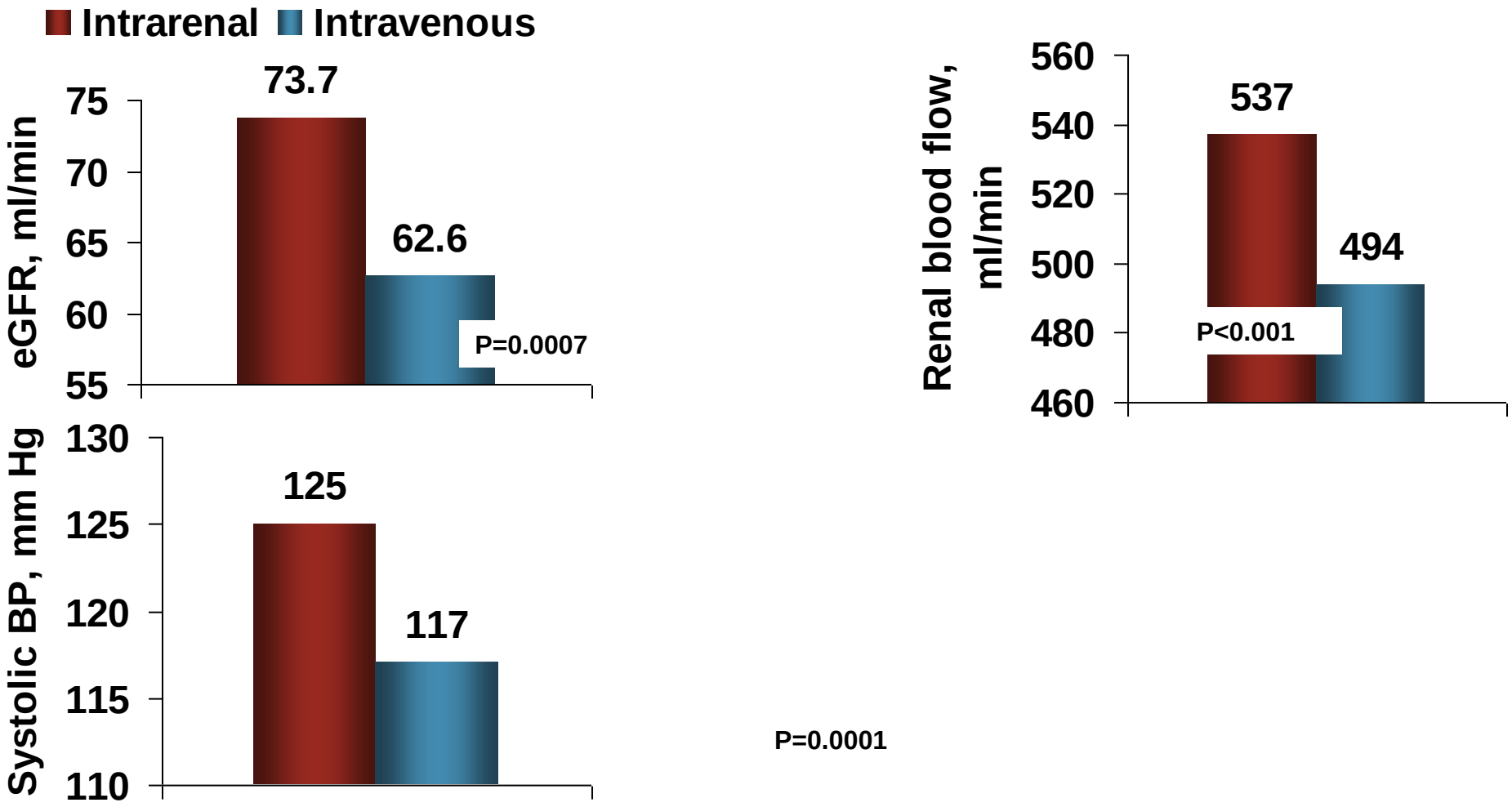


Benephit™ Infusion System (FlowMedica, Inc., Fremont, CA)

- **A bifurcated infusion catheter that is easily inserted into both renal arteries**
- **Allows simultaneous infusion of medication into both arteries**
- **Allows first-pass metabolism by the kidney**
- **Smaller doses of medication can be given to patients while higher local concentrations in the kidneys are achieved**

Differential Effects Between IV and Targeted Renal Delivery of Fenoldopam

A total of 33 pts who underwent coronary angiography were randomized in a 1:2 ratio to control or fenoldopam (initially IV, then crossed over to IR).



Teirstein PS et al, *Am J Cardiol.* 2006;97:1076-1081.

Benephit System Renal Infusion Therapy (Be-RITe) Multicenter Registry

Design

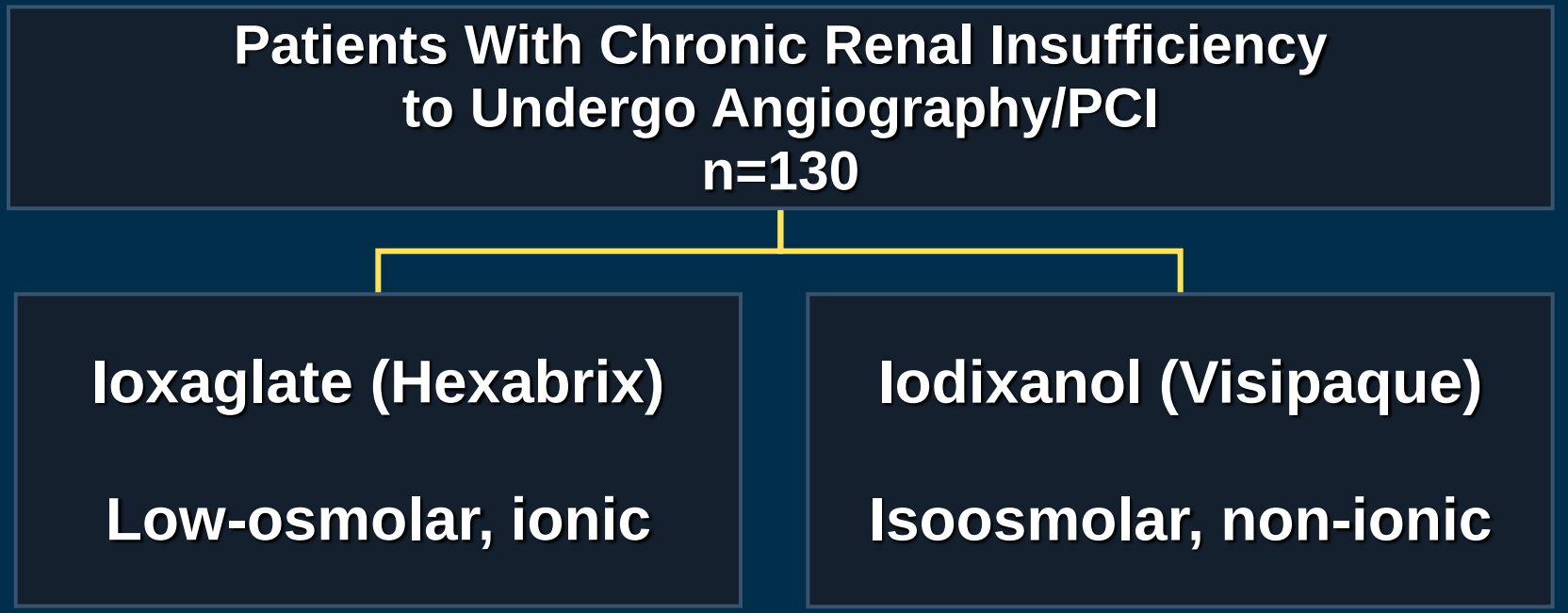
- **DESIGN: Prospective, real-world registry**
- **OBJECTIVE: to evaluate safety and efficacy of targeted renal therapy in preventing CIN**

A total of 366 patients (diabetics 61%, mean CrCl 37.1 ml/min, mean SCr 2.1 mg/dl) enrolled at 16 sites worldwide

- **Local delivery of fenoldopam, sodium bicarbonate, alprostadil and nesiritide**
- **Mean time of bilateral renal arteries access 2 min**
- **Rates of CIN 9.4% compared with 30.6% expected rates**

Wiechmann BN. 32nd Scientific meeting of the SIR, 2007

The ICON Trial: Protocol



Primary Endpoint: Peak increase in the serum creatinine concentration between day 0 (when contrast medium was administered) and day 3

Mehran et al. JACC Int 2009

ICON Trial: Increase of Serum Creatinine from Baseline (Secondary Study End Point)

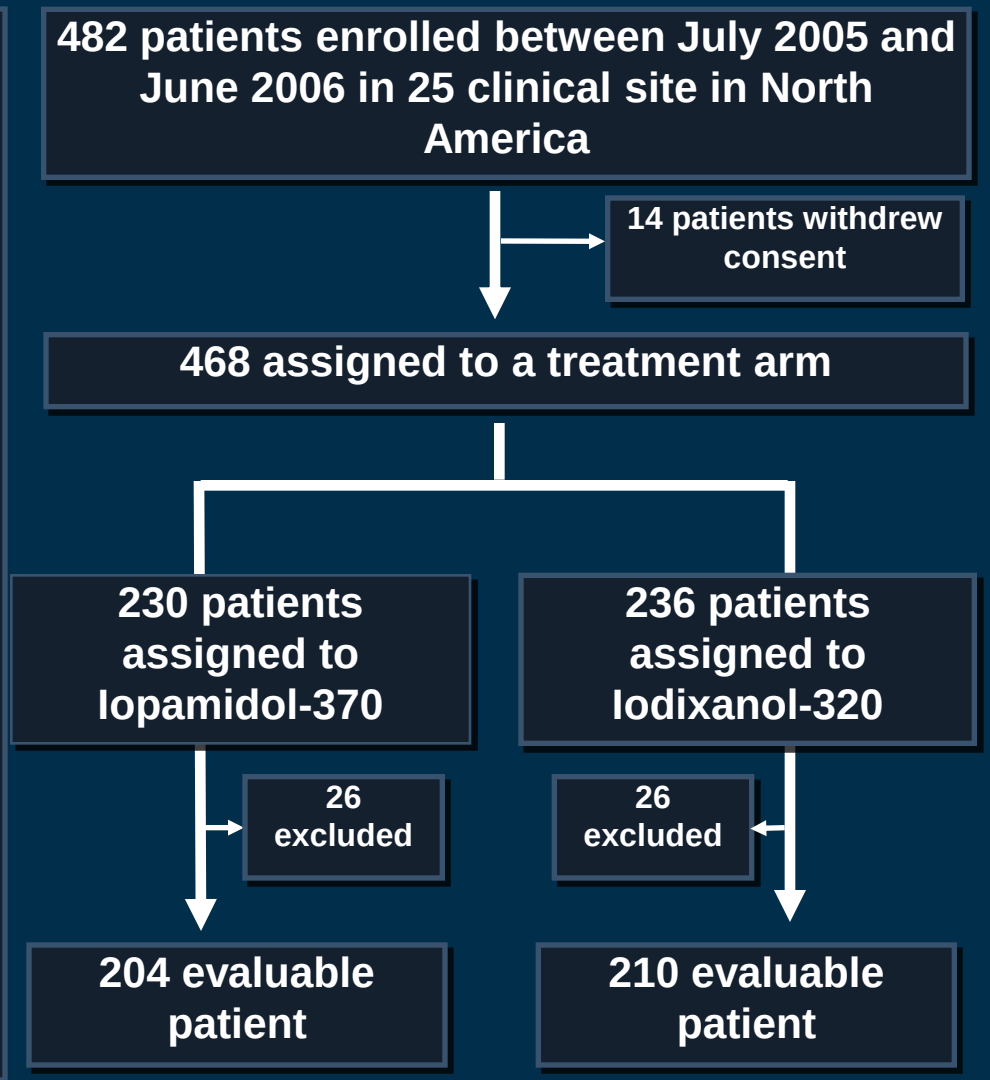
	Ioxaglate N=74	Iodixanol N=71	p
≥ 0.5 mg/dL	18.2 %	16.2 %	0.82
≥ 1 mg/dL	4.5 %	1.5 %	0.36
≥ 25%	24.2 %	16.2 %	0.29
≥ 25% or ≥ 0.5 mg/dL	24.2 %	16.2 %	0.29

Mehran et al. JACC Int 2009

CARE

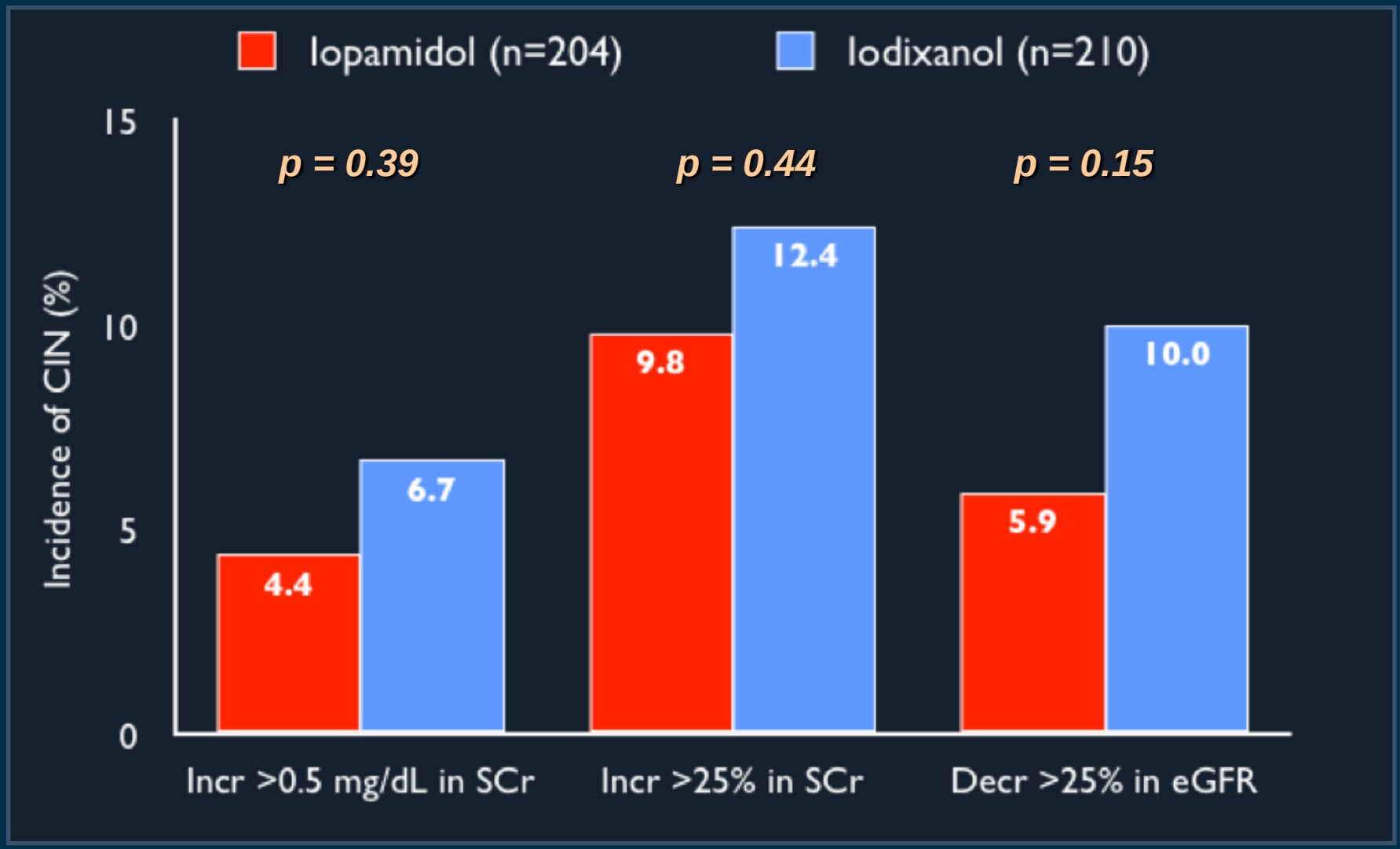
Design

- **DESIGN:** Prospective, randomized, double-blind, parallel-group, multi-center clinical evaluation iopamidol-370 and iodixanol-320
- **OBJECTIVE:** To compare the incidence of CIN between iopamidol-370 and iodixanol-320
- **PRIMARY ENDPOINT:** Increase in SCr ≥ 0.5 mg/dL from baseline to 45 to 120 hours after administration

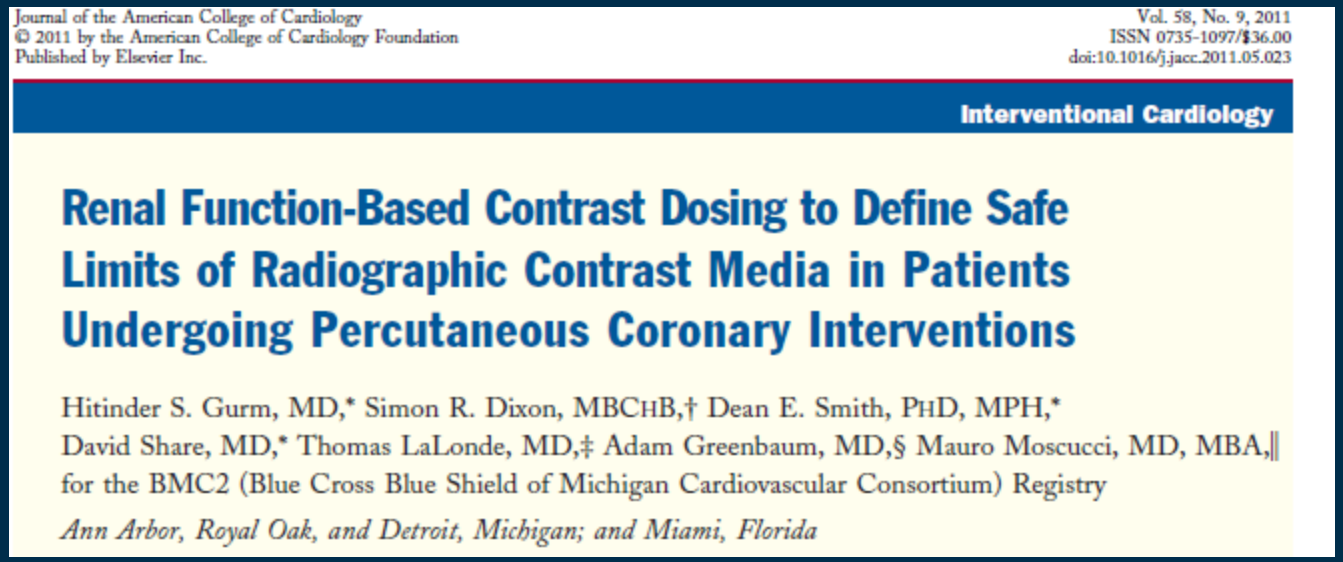


Solomon, RJ et. al., Circulation 115, 3189 (2007)

CARE



Solomon, RJ et. al., Circulation 115, 3189 (2007)



Journal of the American College of Cardiology
© 2011 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 58, No. 9, 2011
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.05.023

Interventional Cardiology

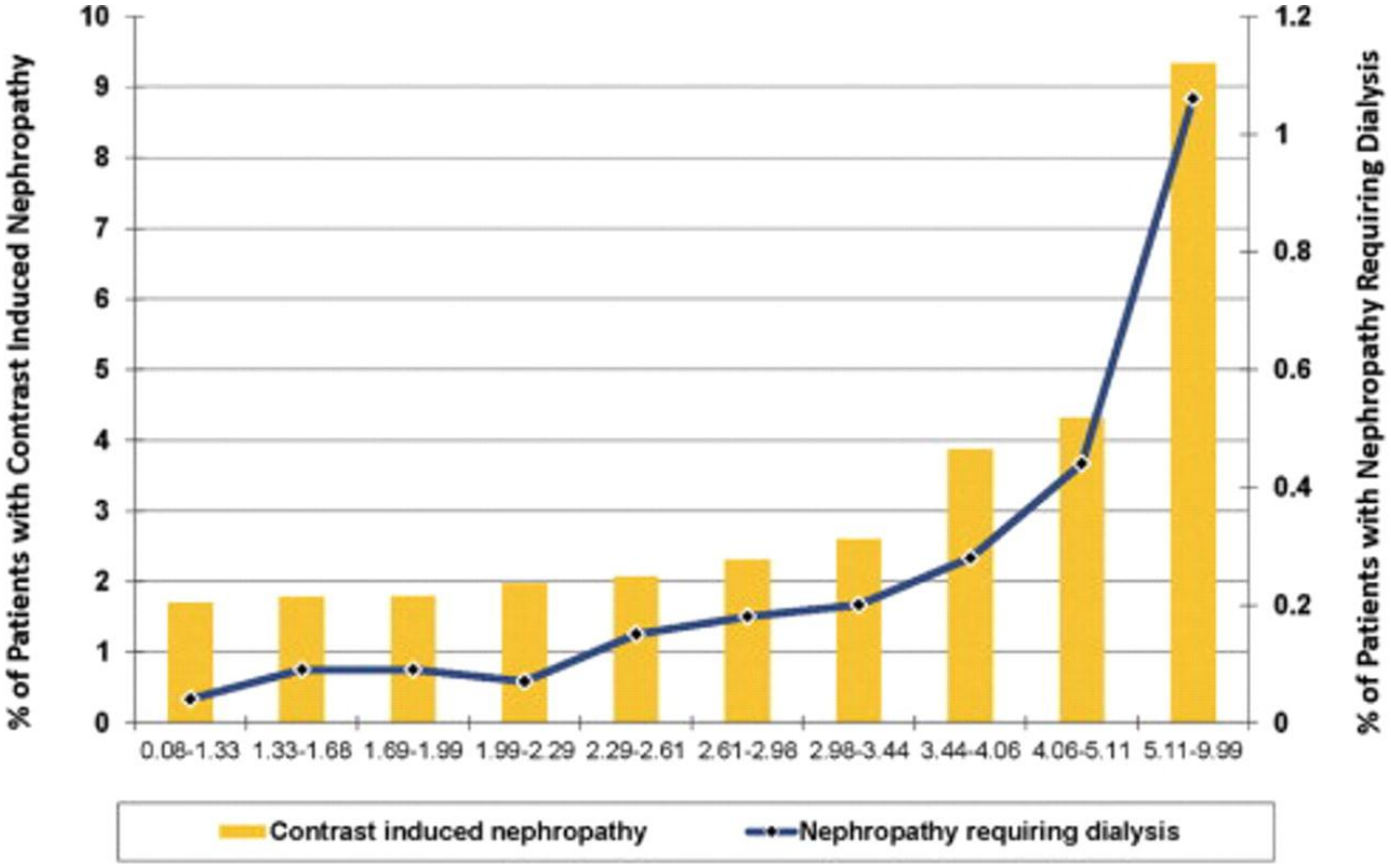
Renal Function-Based Contrast Dosing to Define Safe Limits of Radiographic Contrast Media in Patients Undergoing Percutaneous Coronary Interventions

Hitinder S. Gurm, MD,* Simon R. Dixon, MBChB,† Dean E. Smith, PhD, MPH,* David Share, MD,* Thomas LaLonde, MD,‡ Adam Greenbaum, MD,§ Mauro Moscucci, MD, MBA,‖ for the BMC2 (Blue Cross Blue Shield of Michigan Cardiovascular Consortium) Registry

Ann Arbor, Royal Oak, and Detroit, Michigan; and Miami, Florida

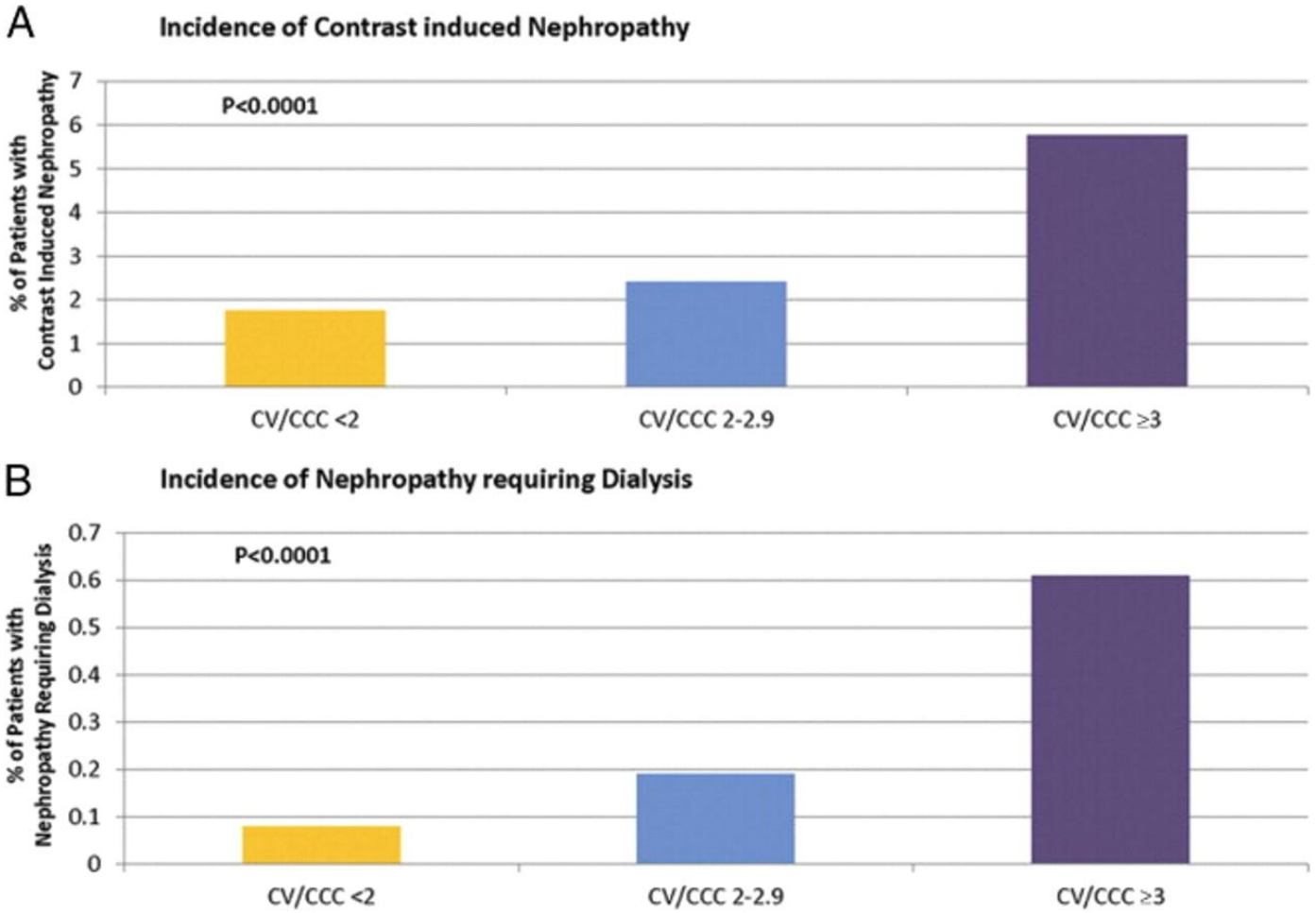
- MACD = 5 x weight (kg)/baseline SCr
  - Not based on *renal function*
- CV/CCC
  - Based on renal function

The Incidence of Contrast-Induced Nephropathy and Nephropathy Requiring Dialysis by Deciles of CV/CCC



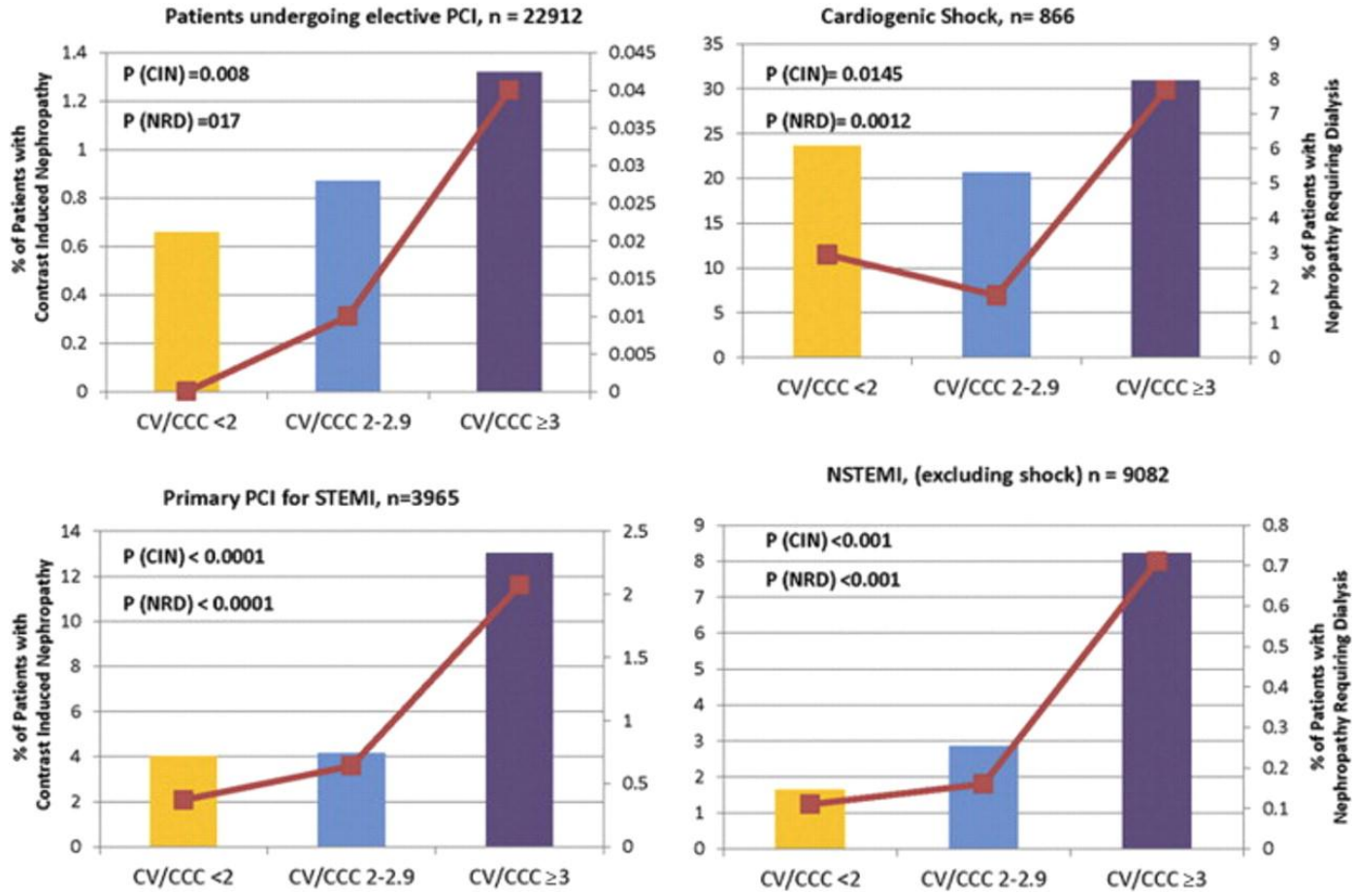
Gurm, H. S. et al. J Am Coll Cardiol 2011;58:907-914

Incidence of CIN and NRD



Gurm, H. S. et al. J Am Coll Cardiol 2011;58:907-914

Incidence of CIN and NRD by Categories of CV/CCC in Various Subgroups



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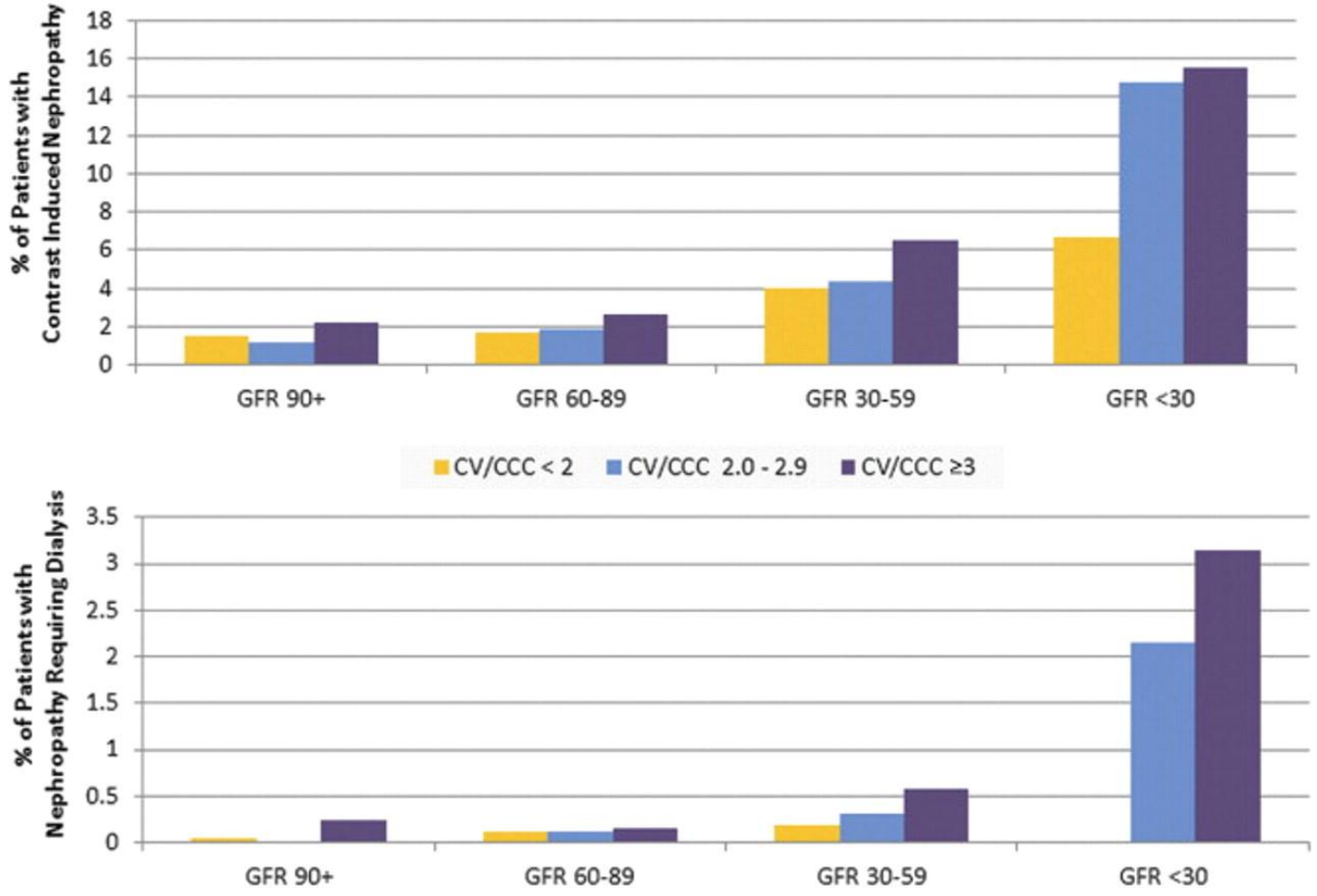
Incidence of CIN and NRD by Categories of CV/CCC Across Different Categories of Baseline GFR



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Conclusions (1)

- **Chronic renal insufficiency is a frequent co-morbidity in patients undergoing PCI and is one of the strongest predictors of morbidity and mortality post PCI**
- **CIN is the third most common cause of hospital-acquired ARF and is associated with increased morbidity and mortality, and higher resource utilization**

Conclusions (2)

- **Several factors predispose patients to CIN and should be assessed prior to angiographic procedures**
- **Hydration before and after contrast exposure is still the most reliable way to preserve renal function and to prevent CIN**
- **NAC and sodium bicarbonate provide questionable benefit**

Conclusions (3)

- **The volume of CM should be as low as possible. CV/CCC <2.0**
- **Significant blood loss and hypotension should be avoided.**
- **Drugs that adversely effect renal function should be withheld peri-procedurally.**
- **Controversy persists regarding the benefit of one specific CM over another for its potential to cause less nephrotoxicity.**