PCI in Chronic Kidney Disease: RECOVER, CARE, LOCM-Related Studies, and Meta-Analysis

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How to Assess Renal Function?

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

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

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

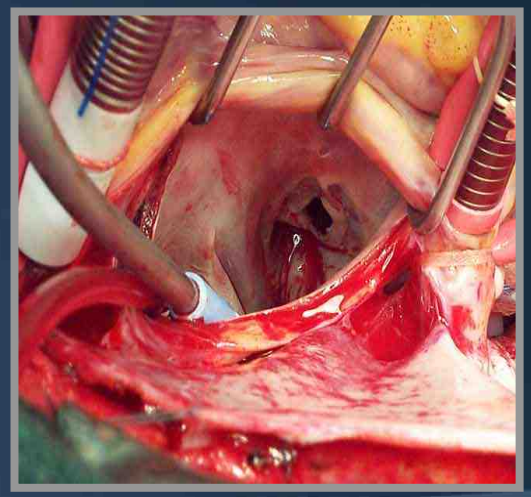
	RR	95% CI	P
CKD (baseline Cr > 1.5 mg/dl)	2.31	1.63-3.28	<0.001
Sex, female vs. male	0.91	0.75-1.10	0.32
Race, black vs. non-black	1.40	1.04-1.89	0.028
Age, y	1.05	1.04-1.06	<0.001
Diabetes mellitus			
Oral hypoglycemics	1.63	1.29-2.06	<0.001
Insulin	1.80	1.26-2.58	<0.001
PTCS vs. CABG	1.04	0.87-1.25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

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

Major Causes of Acute Renal Failure In Cardiac Patients

1) Contrast Induced Nephropathy (CIN)

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

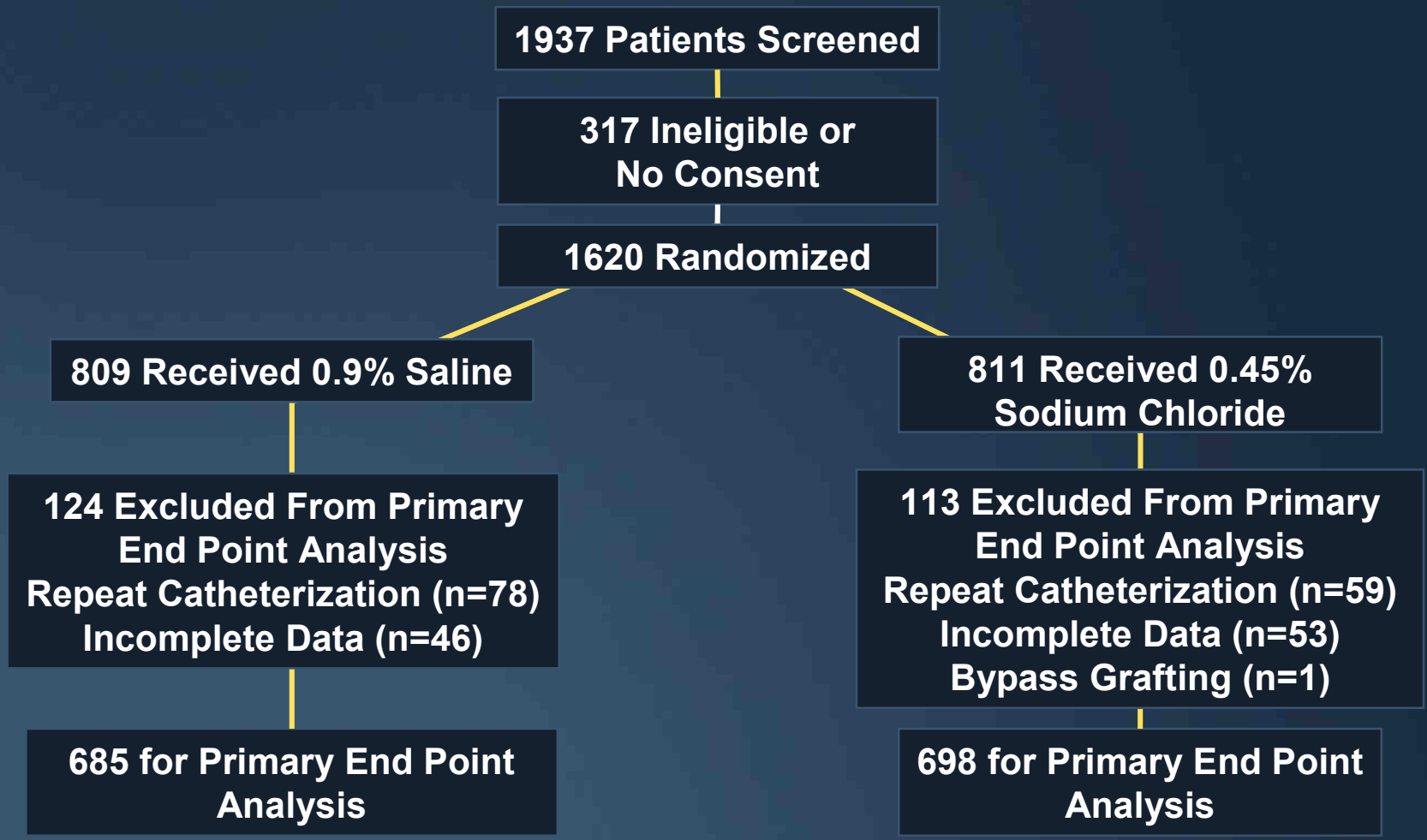
Preventive Trials

Strategies

Prevention of Contrast Induced Nephropathy

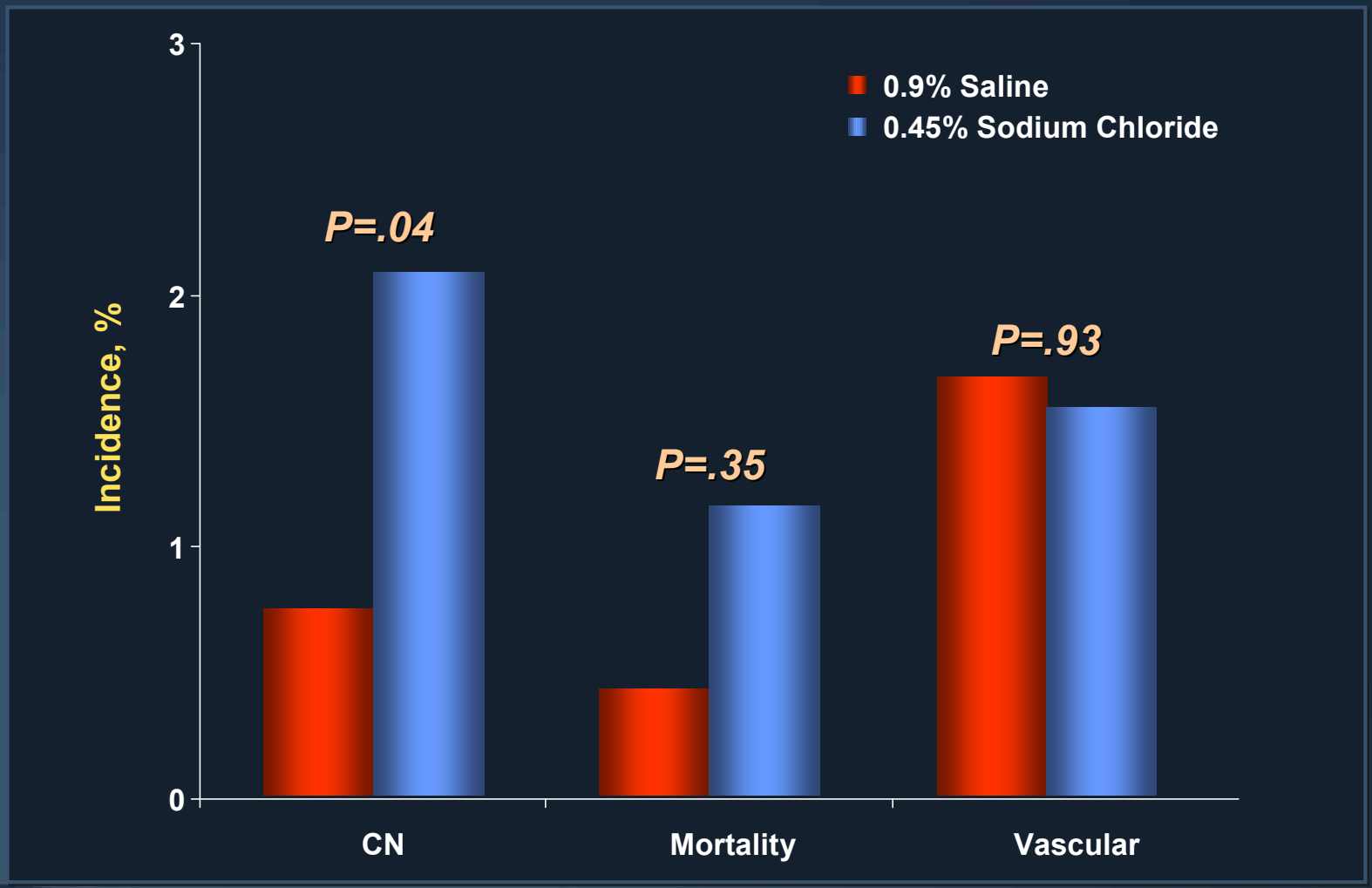
Brar , ss

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

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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

US: Investigational device. Limited by Federal Law to investigational use.

RenalGuard™

Results

Patients who developed CIN	2/21 (9.5%)
Mean SCr change at 48-60 hrs	6.3%
Patients who achieved target urine output	21/23 (91%)
Patients with major complications possibly device or procedure related	2/23 (9%)

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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

Primary endpoint: increase in serum creatinine ≥25% within 2 days post-exposure

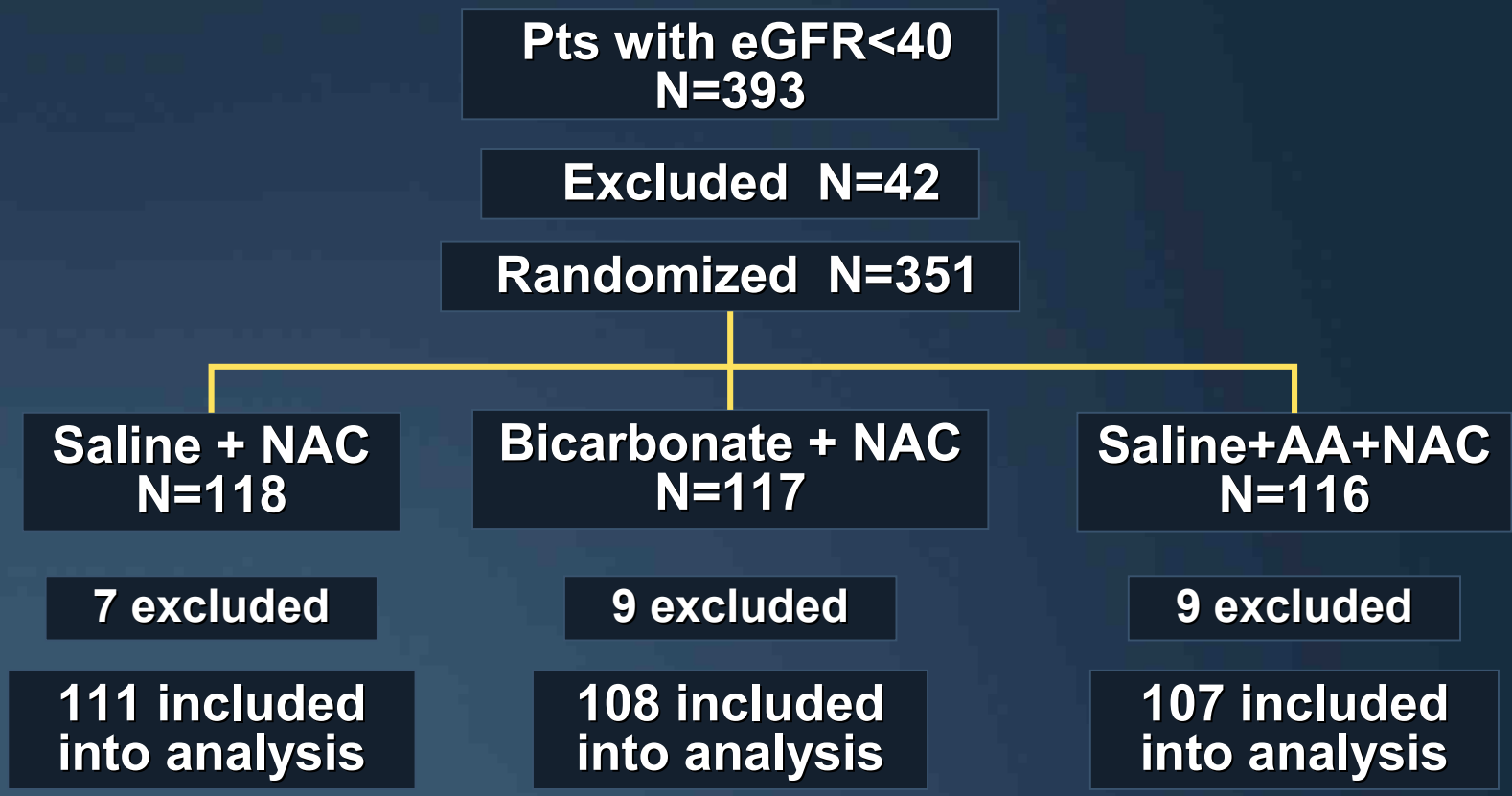
Merten GJ et al. *JAMA*, 2004;291:2328-2334

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 (↑SCr 0.5 mg/dL)	11.9%	1.7%	0.03

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

REMEDIAL Trial



NAC = *N*-acetylcysteine, AA = ascorbic acid

REMEDIAL Trial: Results

	Saline + NAC	Bicarbonate + NAC	Saline + Ascorbic Acid + NAC	P Value
	N=111	N=108	N=107	
Serum creatinine increase by ≥25%	11 (9.9%)	2 (1.9%)*	10 (10.3%)	0.010
Serum creatinine increase by ≥0.5 mg/dL	12 (10.8%)	1 (0.9%)†	12 (11.2%)	0.026
eGFR decrease by ≥25%	10 (9.2%)	1 (0.9%)†	10 (10.3%)	0.018

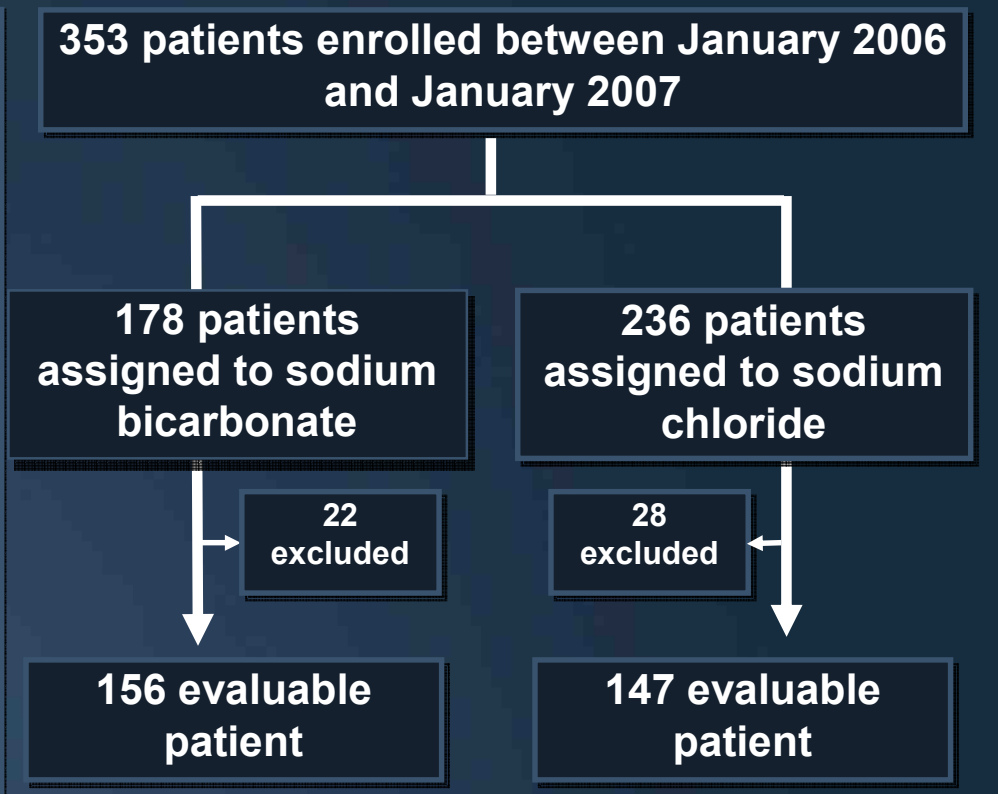
***P=0.019*, †*P<0.01* vs. saline + NAC group**

Briguorio C. et al, *Circulation* 2007

MEENA

Design

- **DESIGN:** Prospective, randomized, parallel-group, single-center clinical evaluation of two hydration strategies for patients undergoing coronary angiography
- **OBJECTIVE:** To compare the incidence of CIN between periprocedural hydration with sodium bicarbonate vs. sodium chloride (0.9%, normal saline)
- **PRIMARY ENDPOINT:** Decrease in estimated GFR by ≥ 25% within 4 days of coronary angiography



Hydration Protocol

- 3 mL/kg for 1 hr before the procedure
- 1.5 mL/kg during and for 4hrs post-procedure

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Brar SS, et al, *JAMA* 2008;300:1038-1046.

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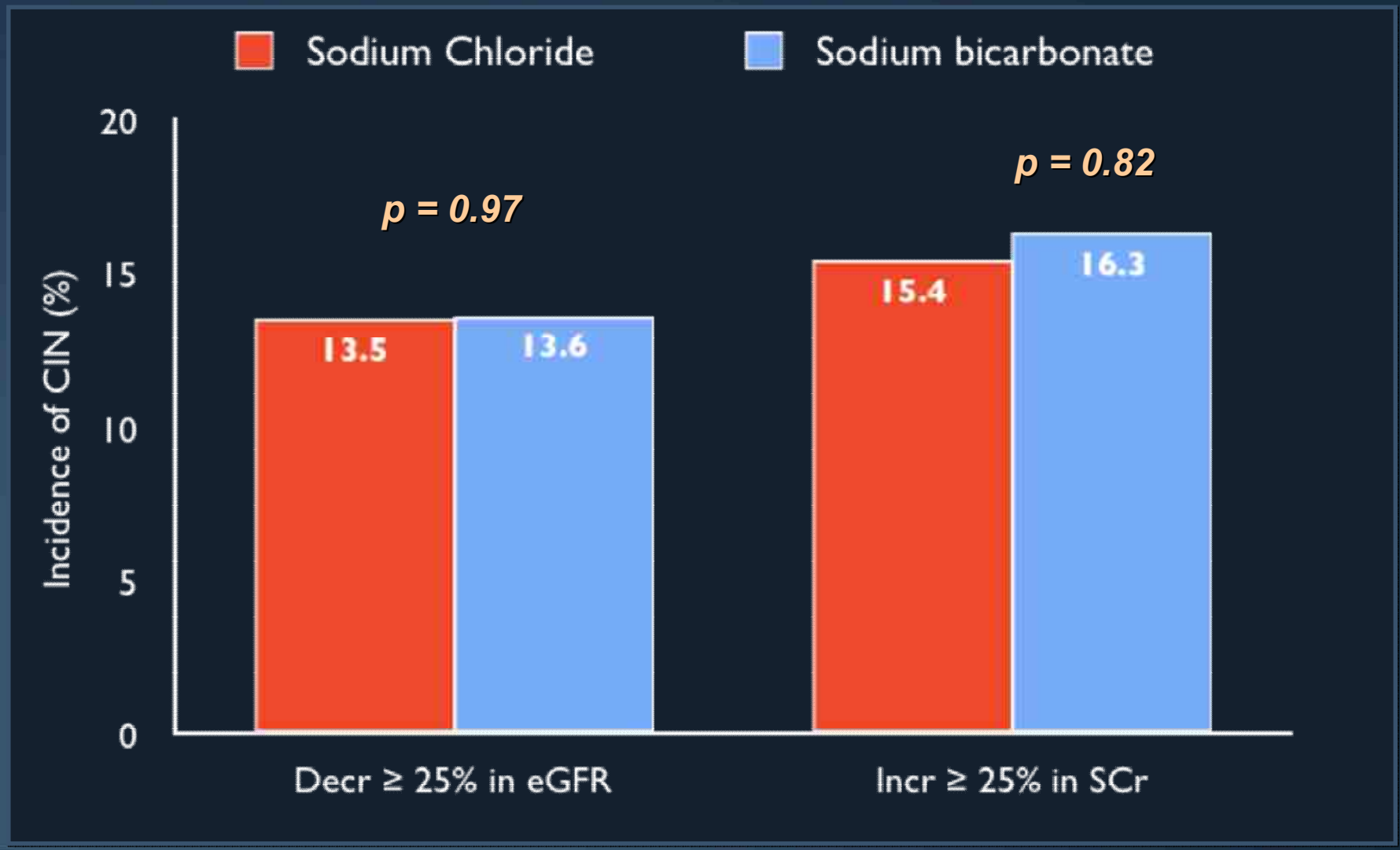

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Brar SS, et al, *JAMA* 2008;300:1038-1046.

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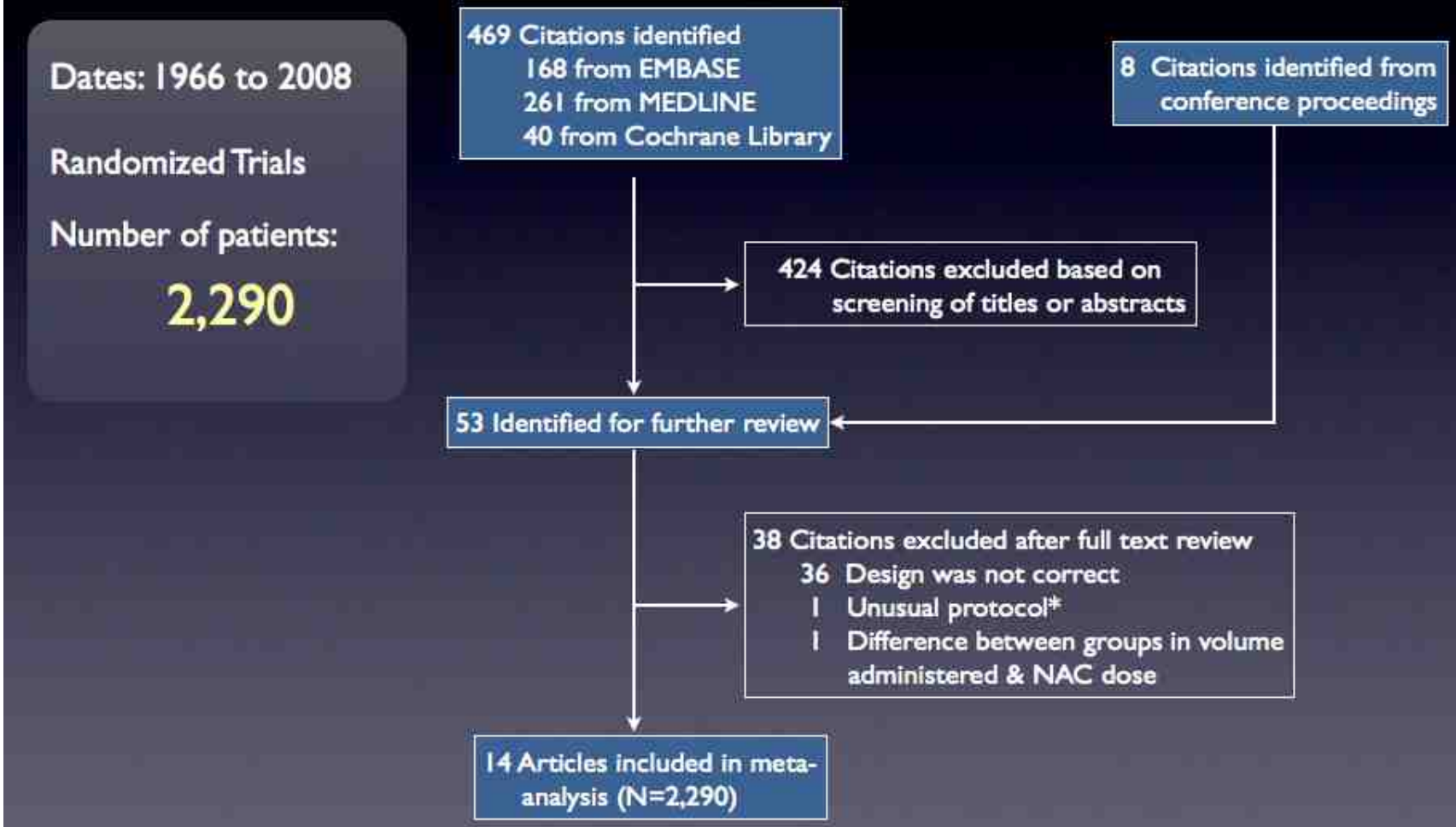
Meta - Analysis

Sodium Bicarbonate for the Prevention of CIN

Brar et al. cJASN 2009

Meta-Analysis

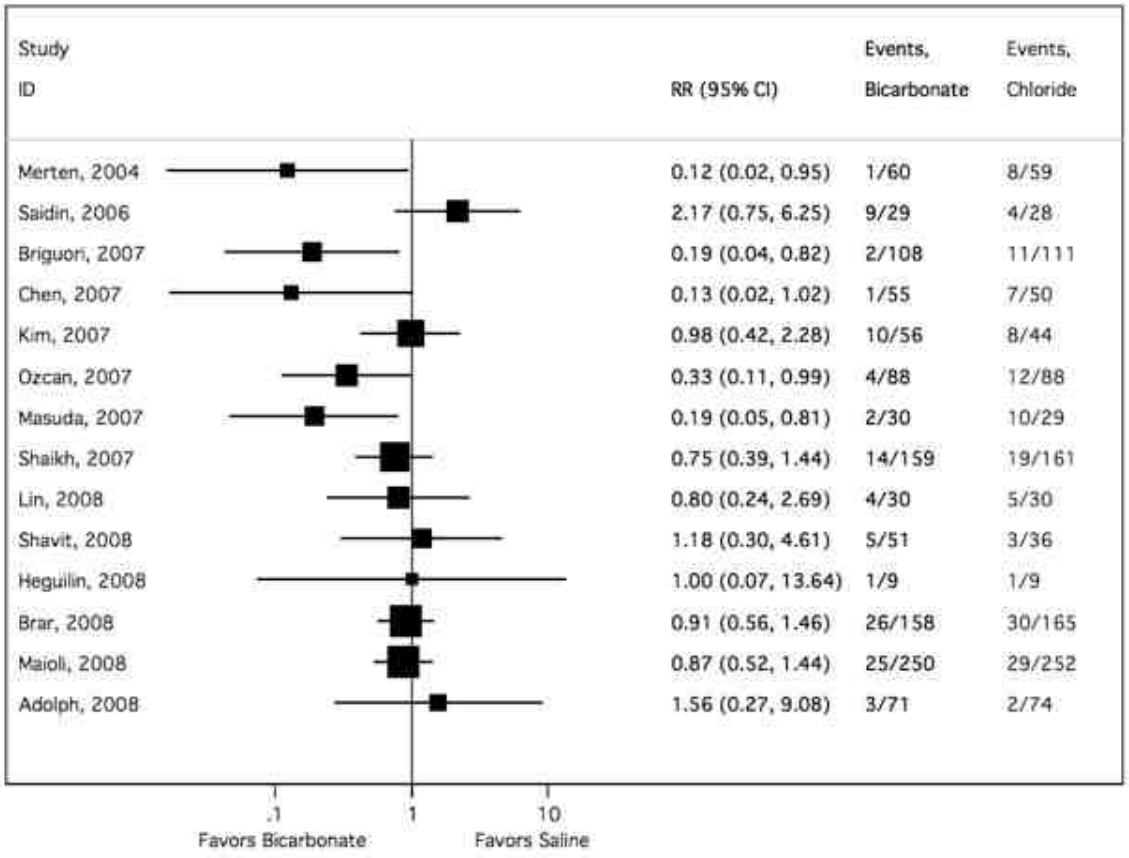
Study Flow



Brar et al. cJASN 2009

Forest Plot

Summary of Published & Unpublished RCTs



Heterogeneity

$P = 0.02$

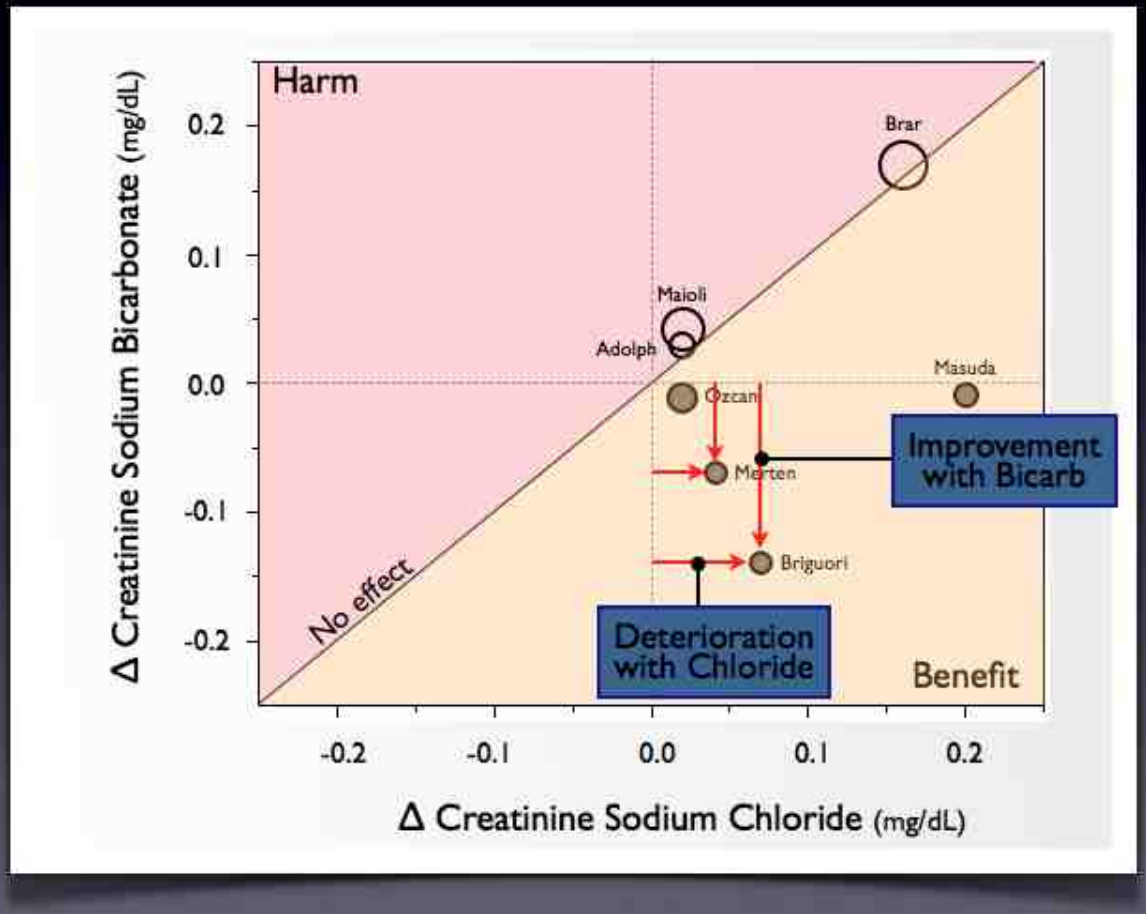
$I^2 = 48\%$

Summary:
A summary statistic is not shown because of the significant heterogeneity that precluded pooling of these results.

Brar et al. cJASN 2009

Change in Renal Function

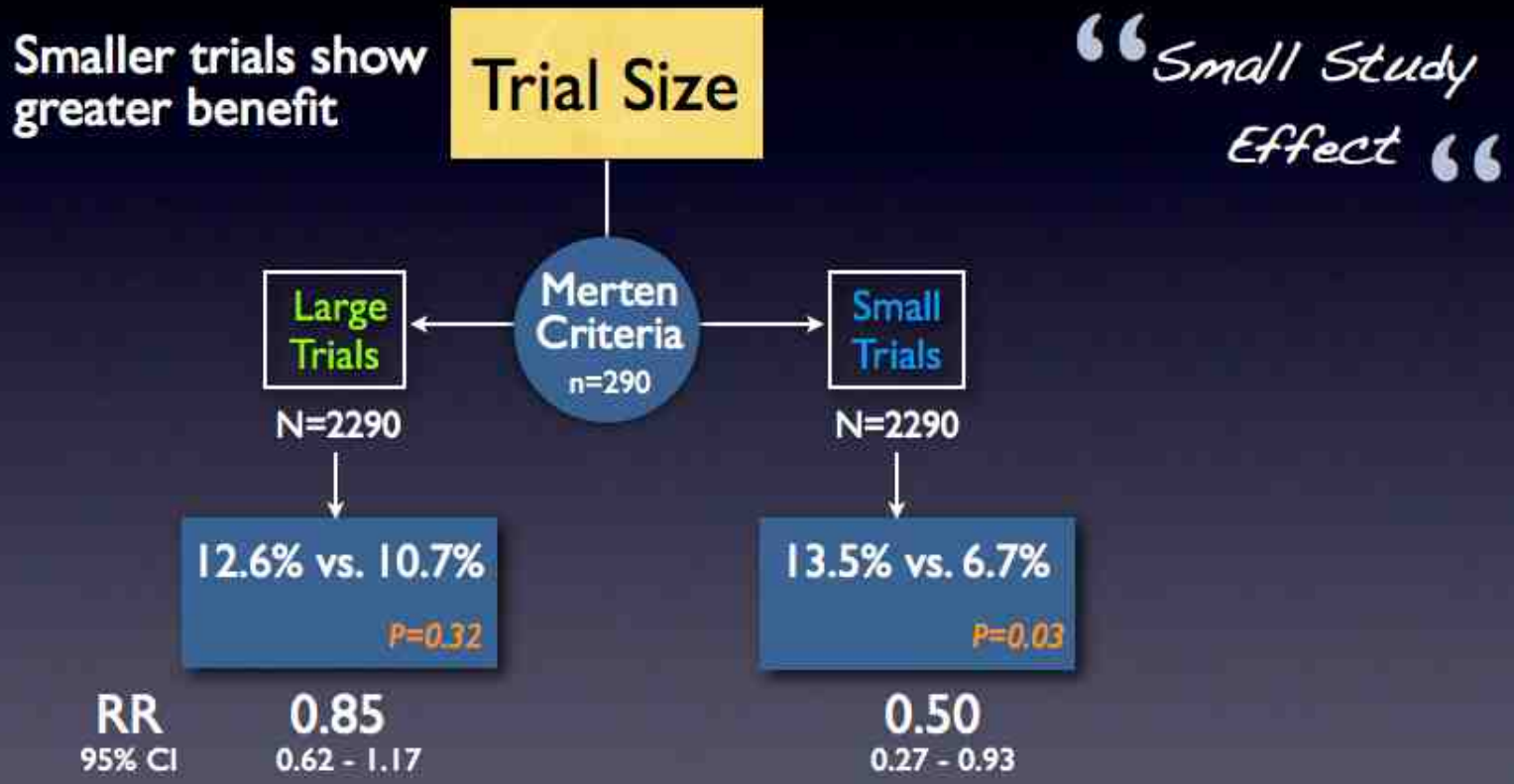
Published Randomized Trials



Brar et al. cJASN 2009

Meta-regression

Understanding Sources of Heterogeneity

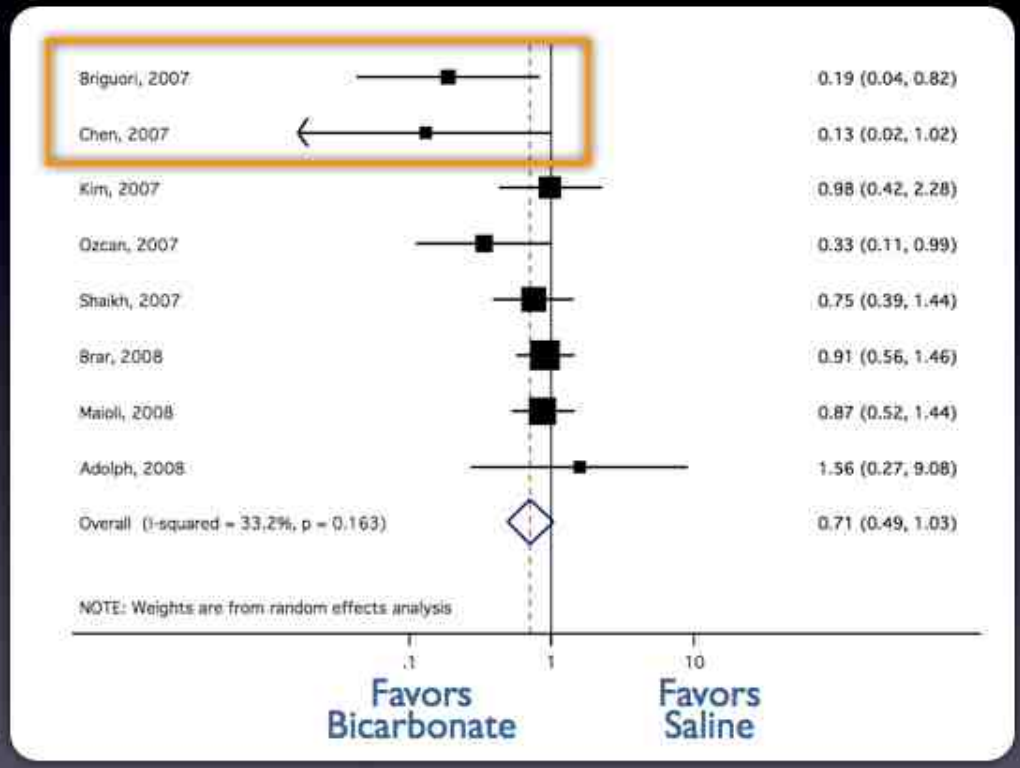


Summary: Positive effect only observed in small trials

Brar et al. cJASN 2009

Forest Plot

High Quality Studies



Quality Criteria

- Similar volume
- > 100 patients
- If NAC used, dose & route similar between groups
- No early termination

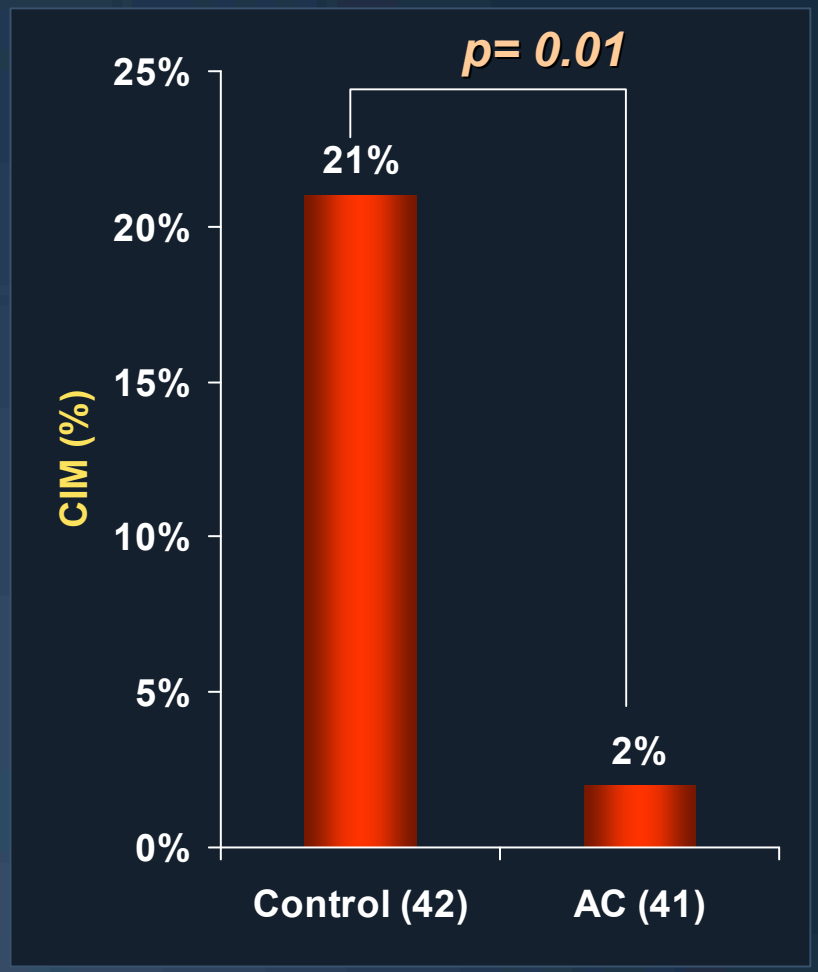
Summary: No overall benefit, but trend driven by studies with extreme treatment effects

Brar et al. cJASN 2009

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

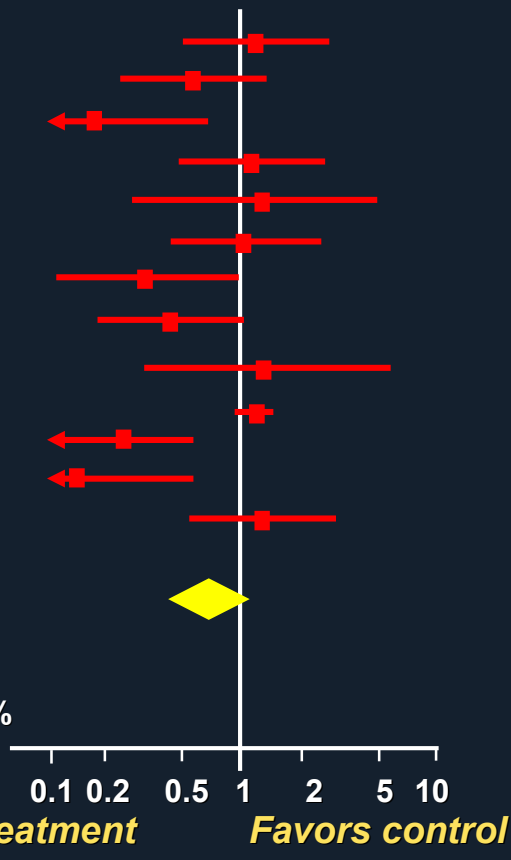


Tepel *NEJM* 2000

Relative Risk for Developing CIN after NAC

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

Study or substury	NAC n/N	Control n/N	RR (Random) 95% CI	Risk Ratio (Random) 95% CI
Allaqaband et al	8/45	6/40		1.19 (0.45, 3.12)
Briguori et al	6/92	10/91		0.59 (0.23, 1.57)
Diaz-Sandoval et al	2/25	13/29		0.18 (0.04, 0.72)
Durham et al	10/38	9/41		1.20 (0.55, 2.63)
Goldenberg et al	4/41	3/39		1.27 (0.30, 5.31)
Gomes et al	8/78	8/78		1.00 (0.40, 2.53)
Kay et al	4/102	12/98		0.32 (0.11, 0.96)
Nguyen-Ho et al	9/95	19/85		0.42 (0.20, 0.89)
Oldemeyer	4/49	3/47		1.28 (0.30, 5.41)
Pate et al	57/238	50/239		1.14 (0.82, 1.60)
RAPIDO	2/41	8/39		0.24 (0.05, 1.05)
Shyu	2/60	15/61		0.14 (0.03, 0.57)
Fung et al	8/46	6/45		1.30 (0.49, 3.46)
Total: (95% CI)	950	932		0.68 (0.46, 1.02)



Total events: 124 (NAC), 162 (Control)
Test for heterogenety: Ch=27.54 (P0.005), 1^2=56.4%
Test for overall effect: Z=1.88 (*P=0.05*)

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

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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	Low-osmolar, non-ionic
Iodixanol [Visipaque]	Iohexol [Omnipaque]
N=64	N=65
Mean Contrast Volume = 163 ml	Mean Contrast Volume = 162 ml
PTCA – 17%	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

(µmol/l) *p=0.002*

	Iodixanol (Visipaque)	Iohexol (Omnipaque)
	n=62	n=64
Mean	11.2 ±19.7	41.5 ± 68.6
Minimum	- 19.0	- 21.0
Max	74.0	331.0

The ICON Trial: Protocol

Patients With Chronic Renal Insufficiency to Undergo Angiography/PCI
n=130

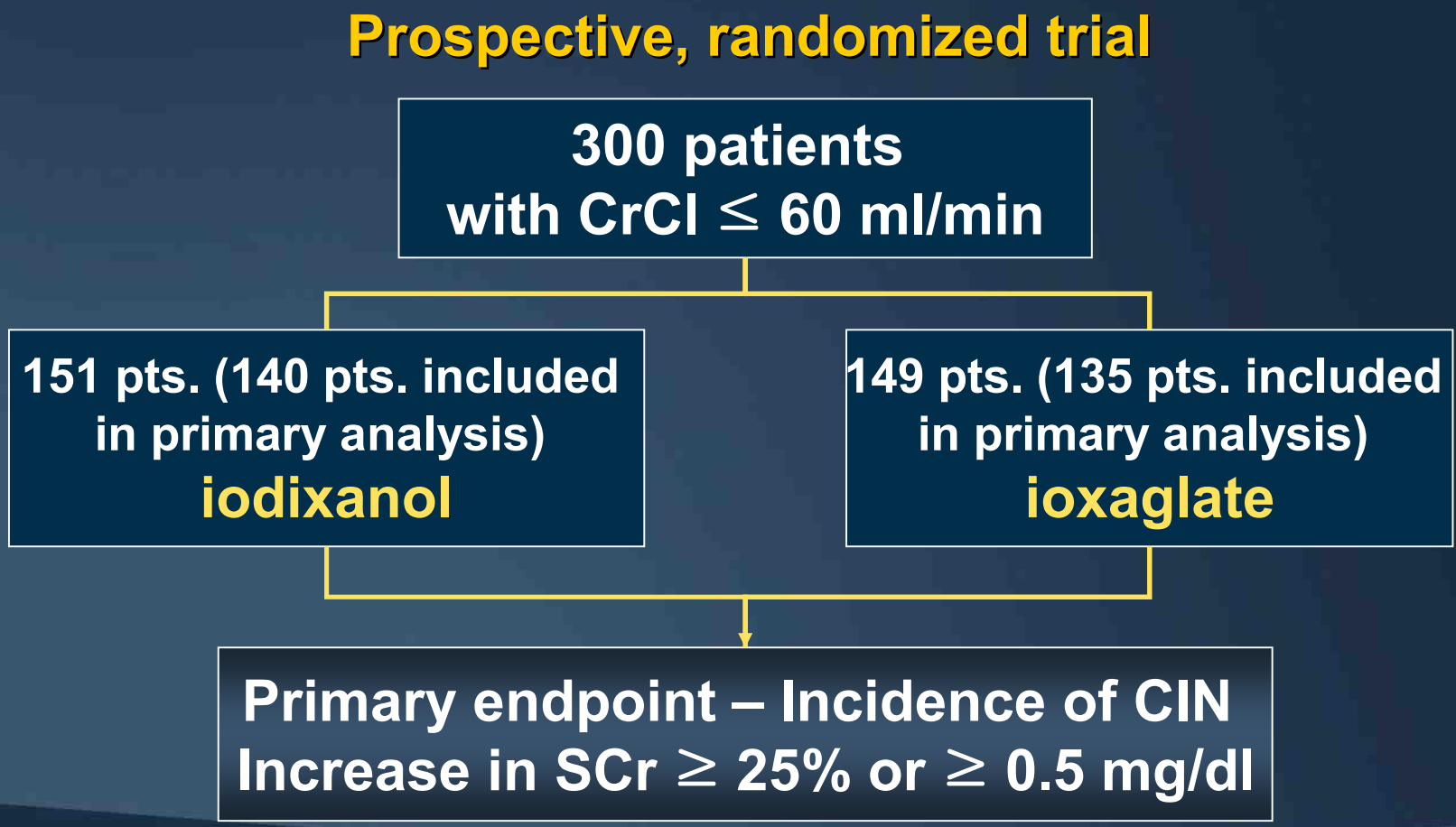
Ioxaglate (Hexabrix)	Iodixanol (Visipaque)
Low-osmolar, ionic	Isoosmolar, non-ionic

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

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

RECOVER Trial – Renal Toxicity Evaluation and Comparison Between Visipaque and Hexabrix in Patients With Renal Insufficiency Undergoing Coronary Angiography



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Jo et al. *JACC* 2006; 48:924-30

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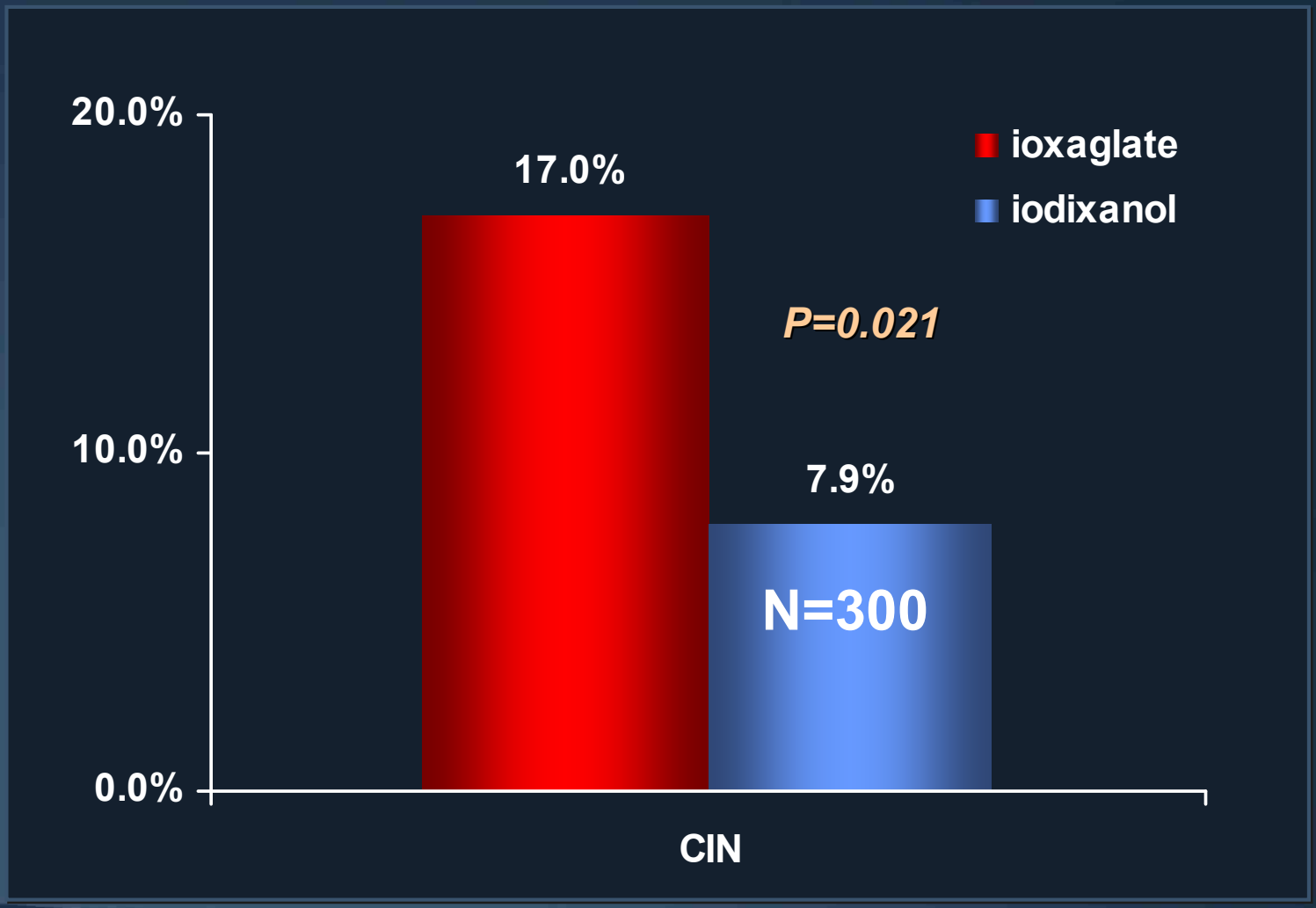
RECOVER Trial – Incidence of CIN



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Jo et al. *JACC* 2006; 48:924-30

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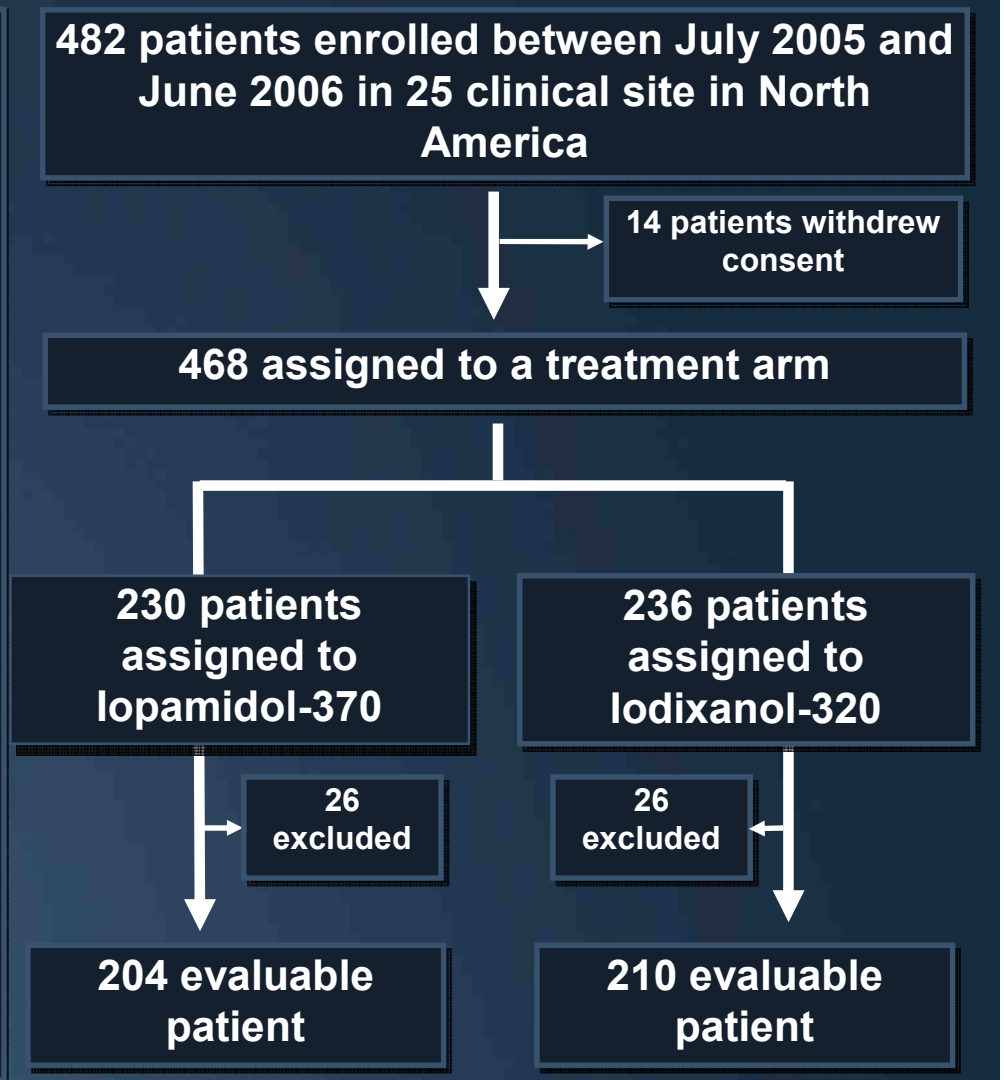
CARE

Design

- **DESIGN:** Prospective, randomized, double-blind, parallel-group, multi-center clinical evaluation ipamidol-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)

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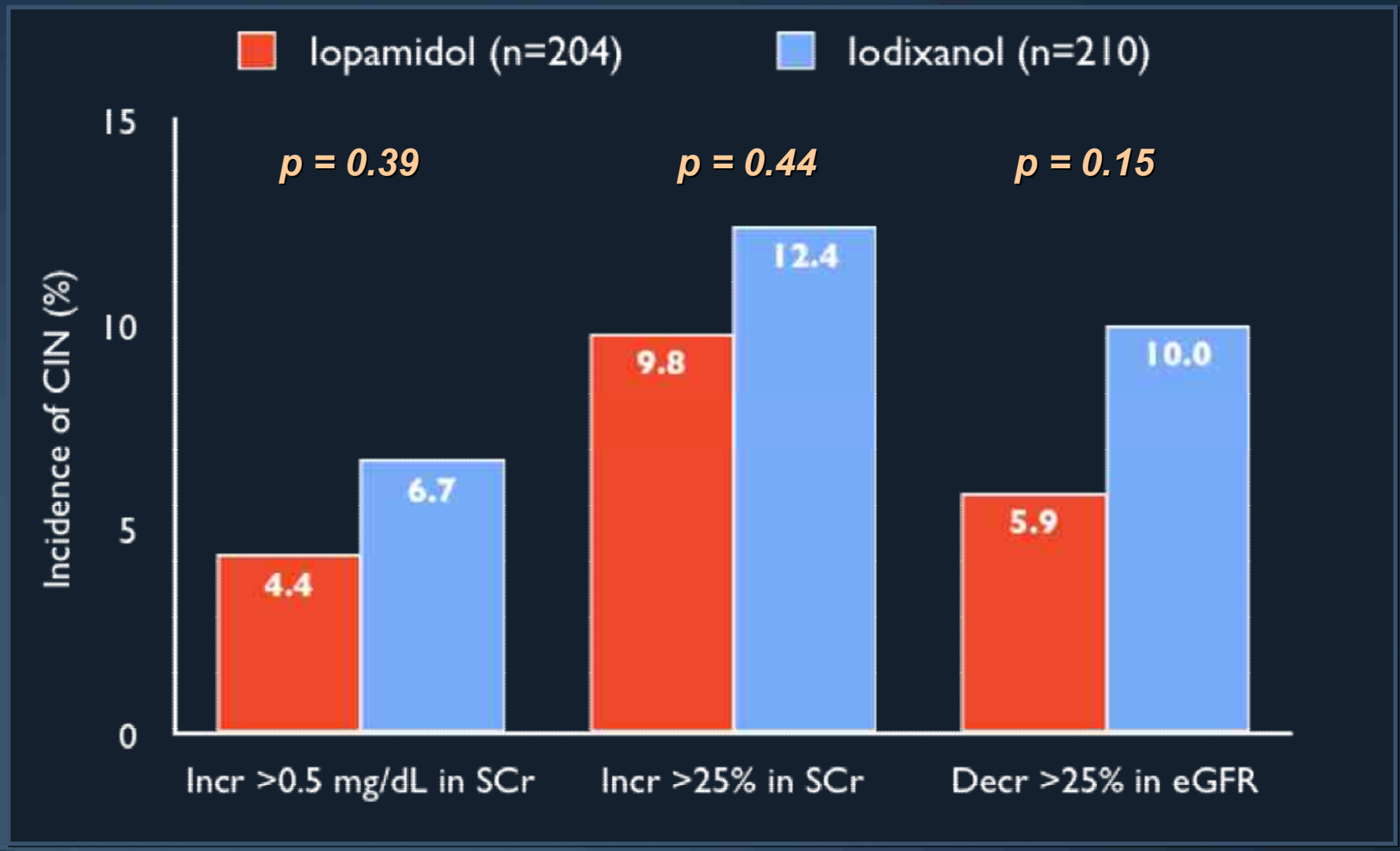

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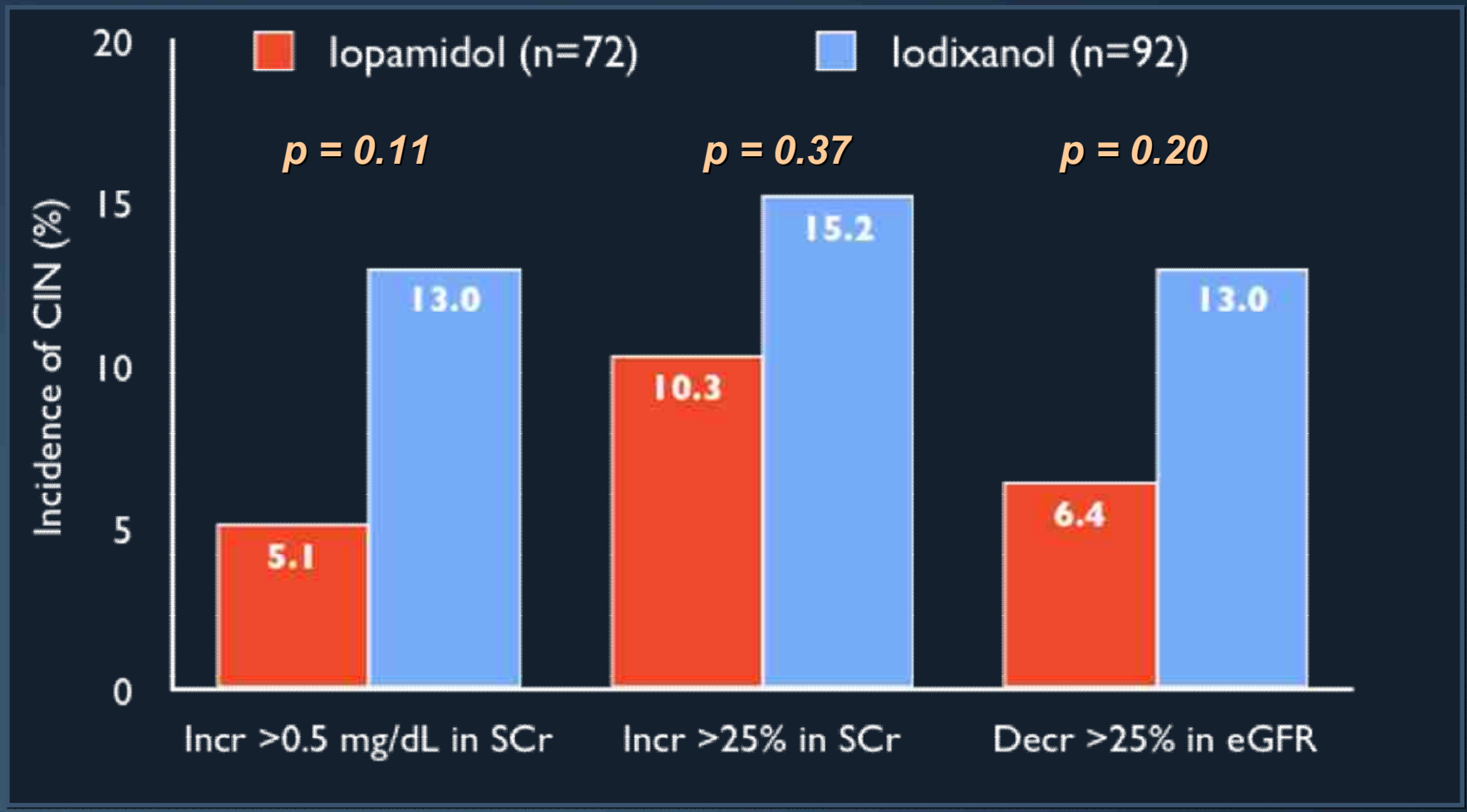
Diabetic Subgroup



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Conclusions (1)

- CKD is one of the most important independent predictors of poor outcome post PCI
- CI-AKI remains a frequent source of acute renal failure and is associated with increased morbidity and mortality, and higher resource utilization
- Several factors predispose patients to CI-AKI
- 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, antibiotics, etc)
- Role of n-acetylcysteine is disputable
- Sodium bicarbonate may be useful, but need more definitive data
- Limit contrast agent volume
- Low-osmolar agents are better than high-osmolar
  - Within non-ionic contrast, the data are contradictory