Contrast Issues in the Cath Lab 2009

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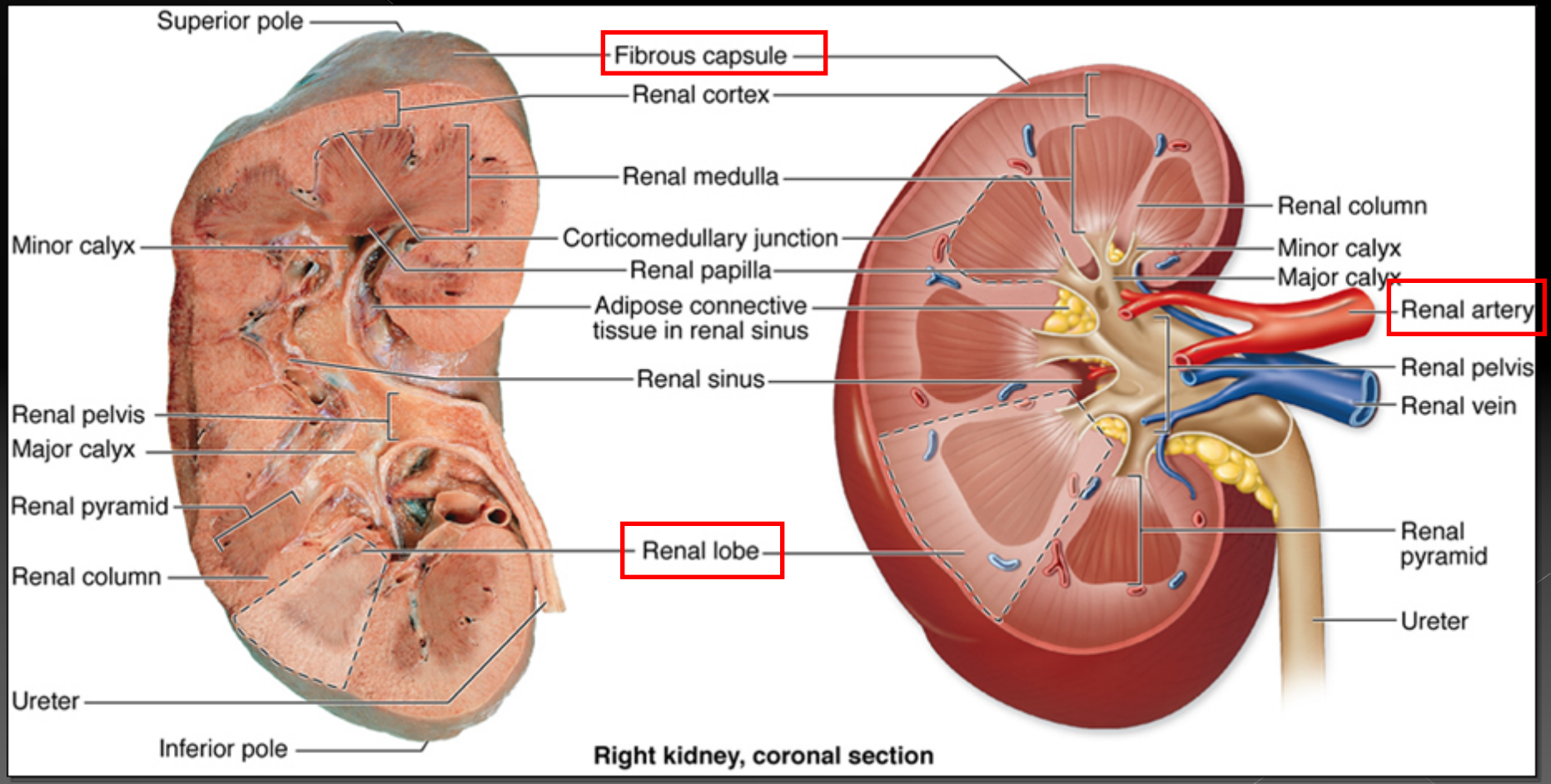
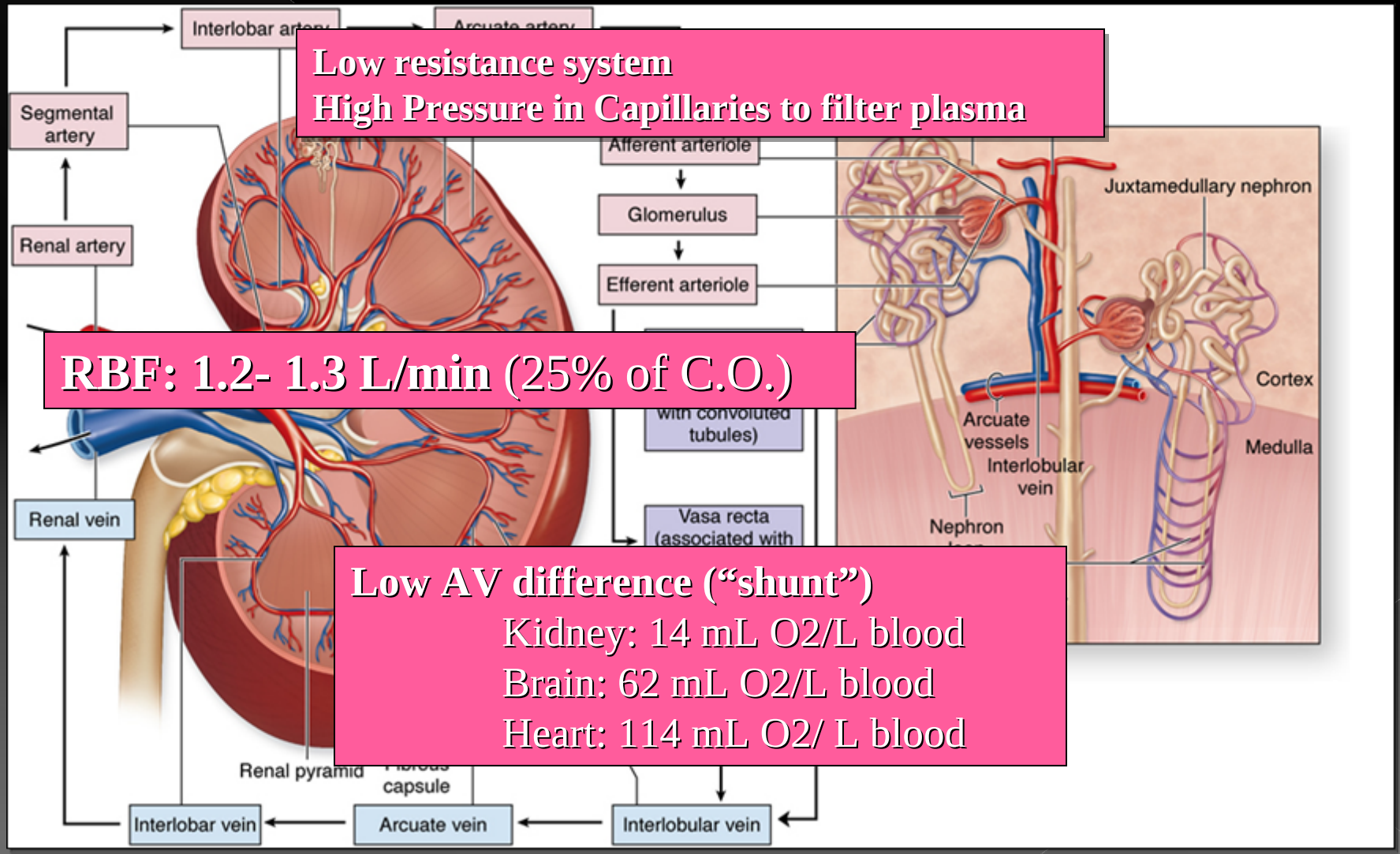
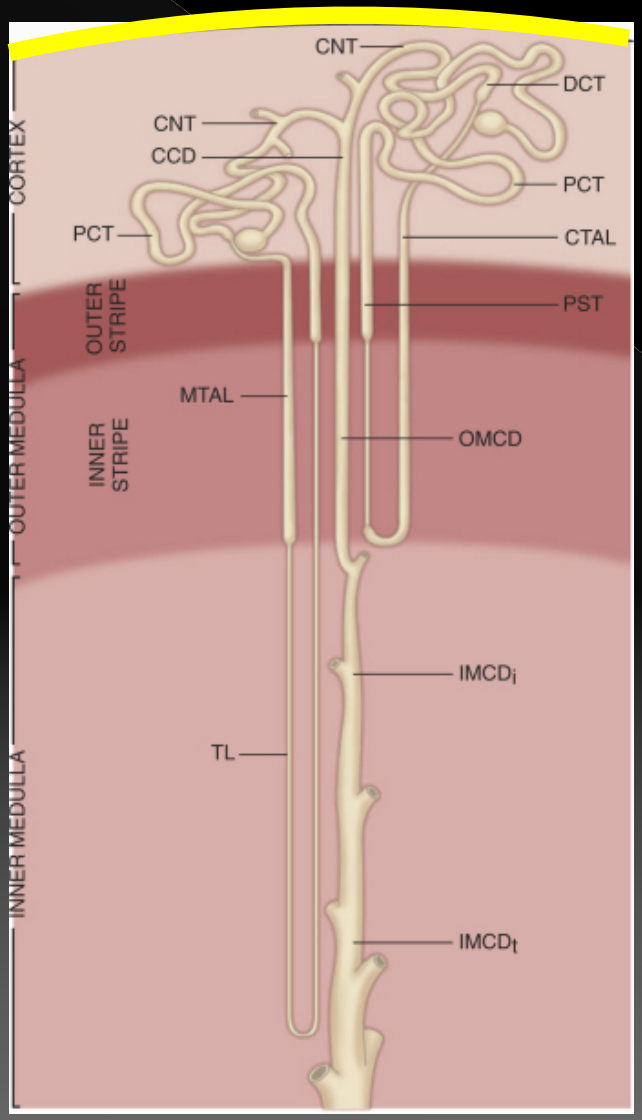
ANATOMY


Superior pole
Fibrous capsule
Renal cortex
Renal medulla
Minor calyx
Corticomedullary junction
Renal papilla
Adipose connective tissue in renal sinus
Renal sinus
Renal pelvis
Major calyx
Renal pyramid
Renal lobe
Renal column
Ureter
Inferior pole
Renal column
Minor calyx
Major calyx
Renal artery
Renal pelvis
Renal vein
Renal pyramid
Ureter
Right kidney, coronal section

Renal Vasculature



GFR: What is normal?



RBF: 1.2- 1.3 L/min (25% of C.O.)

RPF: 650-700 mL/min

Normal GFR: 125 mL/minute (10% lower in women).
or 7.5 L/hr or 180 L/day

Urine output: 1 L/day

Therefore, 99% of filtrate is reabsorbed

Chronic Kidney Disease

- Definition: GFR is the sum of the individual filtration rates of all functional nephrons
- Normally declines with age and is lower in women

CKD STAGE	DESCRIPTION	GFR (mL/min/1.73 m2)
1	Kidney damage with normal or increased GFR	> 90
2	Mild decrease in GFR	60-89
3	Moderate decrease in GFR	30-59
4	Severely decreased GFR	15-29
5	Kidney Failure (Dialysis stage)	< 15

INTEGRELIN: <60

LOVENOX: <50

ANGIOMAX: <30

How to Calculate GFR ?

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

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

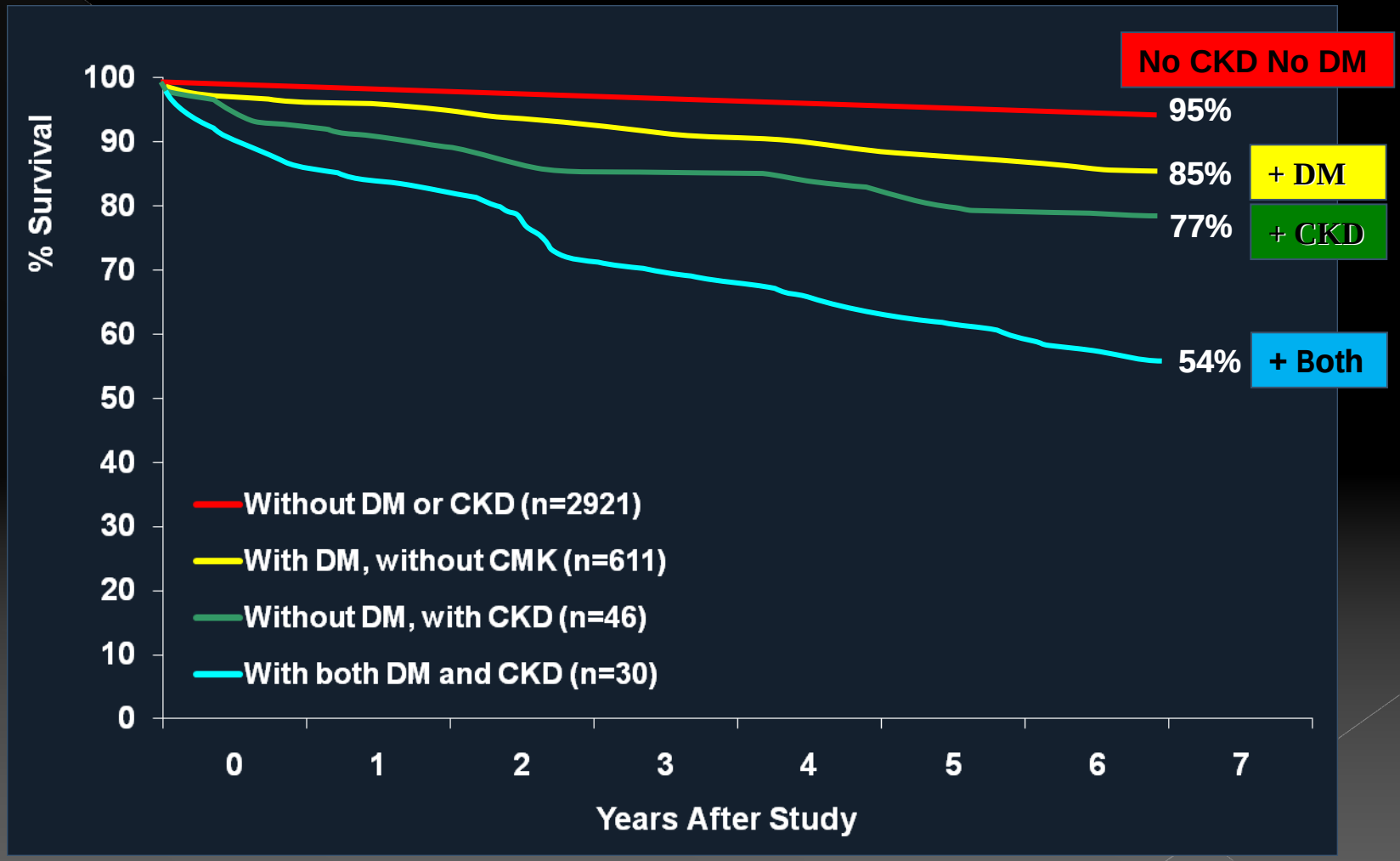
- **Cockcroft-Gault equation:**

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

*** Multiple by 0.8 in female**

www.mdrd.com

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

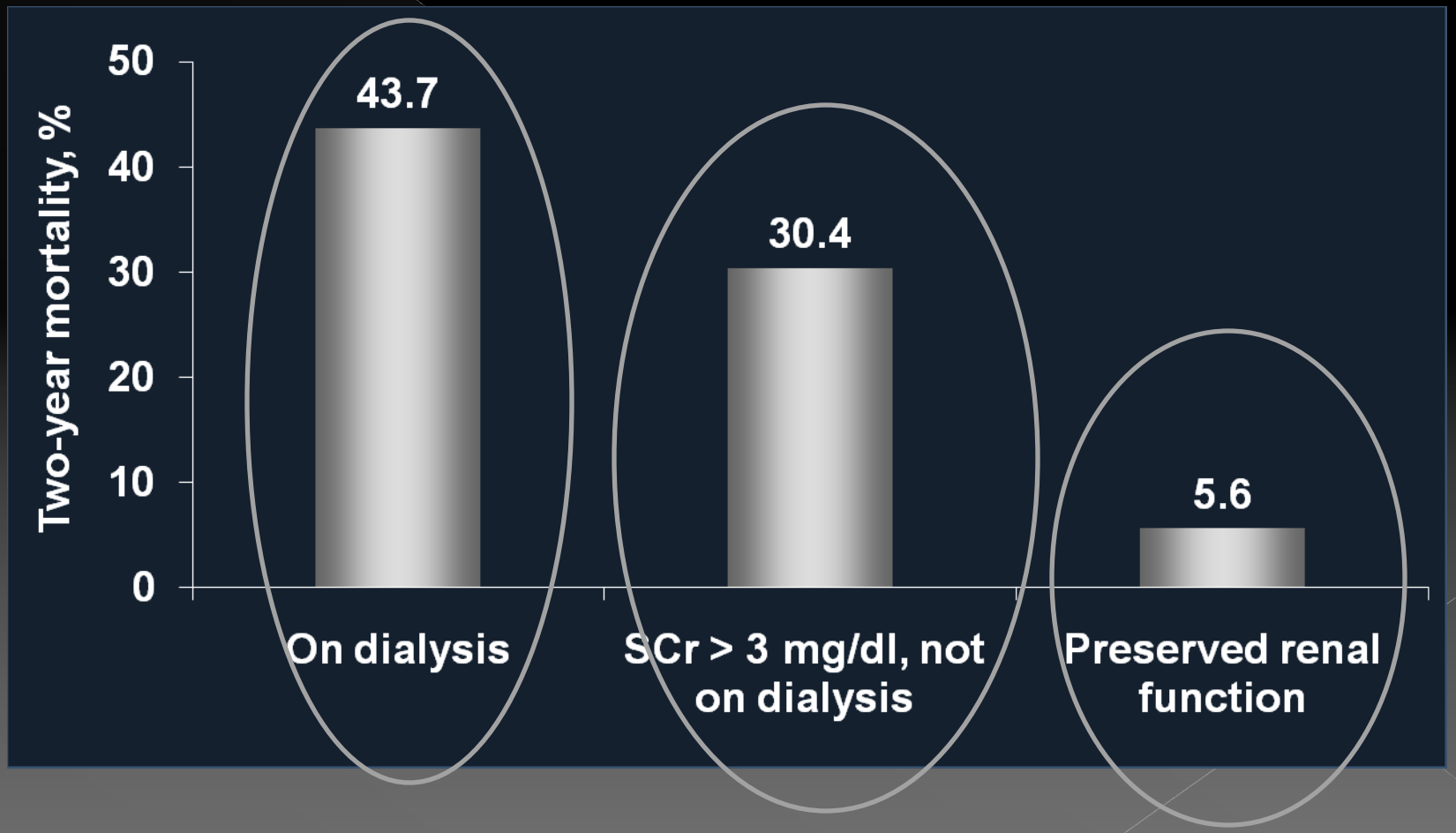


* CKD defined as baseline Cr > 1.5 mg/dl

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

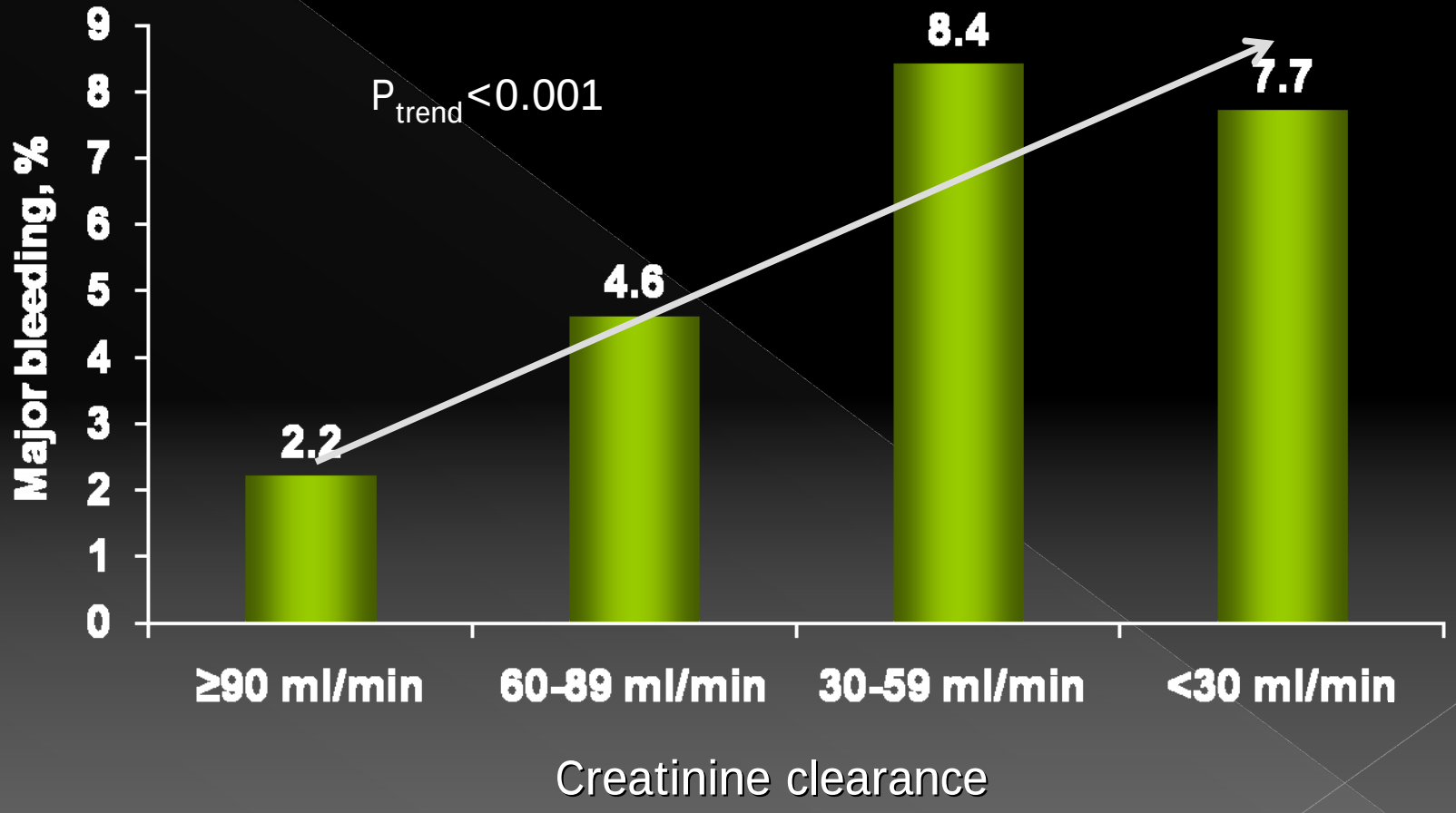
Two-year Mortality Post PCI in Relation to Renal Function

2650 consecutive patients from Mayo Clinic



Major Bleeding in Relation to Renal Function:

Meta-Analysis of 3 Randomized Trials



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

Predictors of Excessive Anticoagulation in ACS Patients: CRUSADE Registry

- Older age
- Female gender
- Lower weight
- **Chronic renal insufficiency**
- Diabetes mellitus
- Congestive heart failure

Alexander KP et al, JAMA 2005;294:3108-3116.

GFR using MDRD (mL/min/1.73 m2)

Integrelin: <60
Lovenox: <50
Angiomax:<30

60 years old woman of average size

CREATININE	African American	All Other races
0.8	94	78
1.0	73	60
1.2	59	49
1.5	46	38
1.8	37	31
2.0	33	27

Contrast-Induced Acute Kidney Injury (AKI) or Contrast-Induced Nephropathy (CIN)

Definition

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

increase by > 25%

or

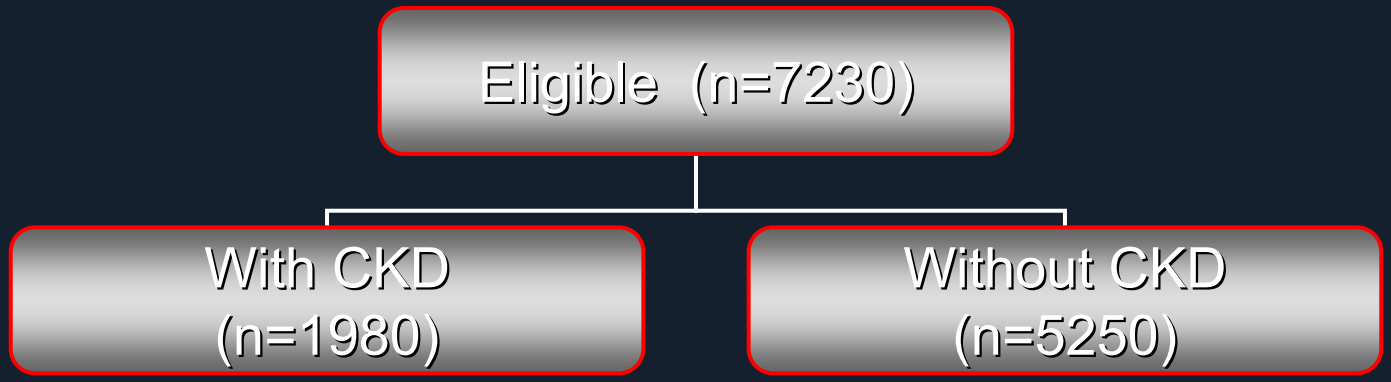
absolute ↑ of > 0.5 mg/dL

} from baseline serum creatinine within 24-48 hrs

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

Is CIN bad for our patients?

n = 7230 consecutive patients who underwent first PCI over a period of 5 years

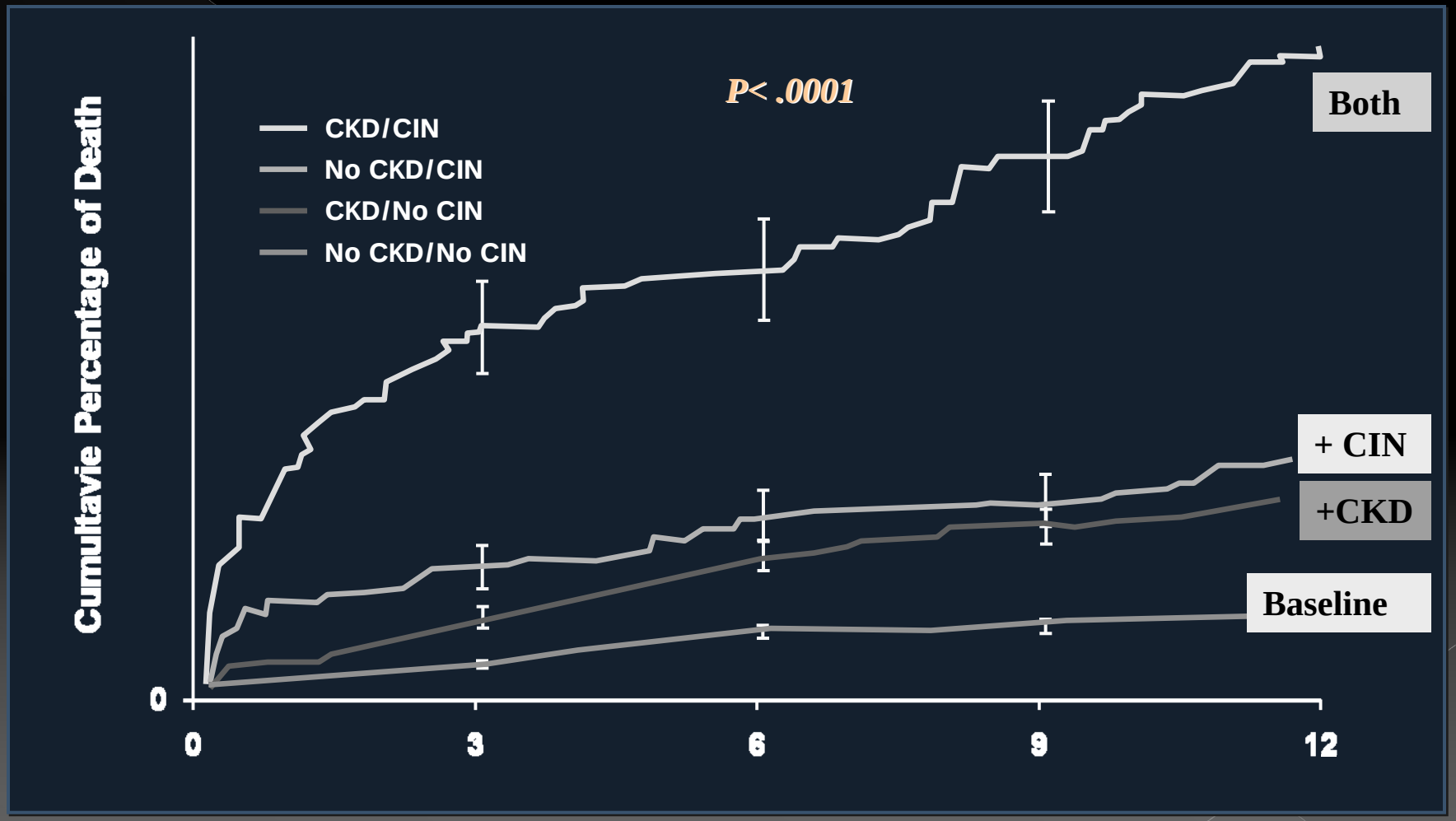


- FACTORS FOR CIN: Peri-procedural hypotension, lower eGFR, older age, diabetes, greater amount of contrast medium and atherosclerosis
- CONCLUSION: CIN was related to higher mortality in both groups (with or without CKD).

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

CIN after PCI

One-year mortality after PCI



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

CKD and CIN: Poor prognosis

Risk Factors for CIN

Patient-related Risk Factors
• Chronic Kidney Disease • Diabetes mellitus • Older age • Anemia • Volume depletion • Low cardiac output • Advanced CHF • Nephrotoxic drugs (NSADIs) • Renal transplant

Procedure-related Risk Factors
• Contrast Volume • Hypotension • Blood loss • Multiple procedures within 72 hrs • High-Osmolar Contrast

Treatment Modalities Assessed in Randomized Trials on Prevention of CIN

Treatment	Effect
Hydration	+
Hemofiltration	+
Prostaglandin E_1	+/–
Sodium bicarbonate	+/–
N-acetyl-l-cysteine	+/–
Dopamine	+/–
Fenoldopam	+/–
Theophylline	+/–
Calcium channel blockers	+/–
Hemodialysis	+/–
Atrial natriuretic peptide	+/–
Statins	+/–

+ positive effect; – no effect; +/– conflicting data or not enough data

Hydration

Avoid CHF:

Assess patient's LV Systolic and diastolic function

Right heart catheterization may help in some patients

Hydration

Patient at Risk (GFR < 60 mL/min/1.73m^2)

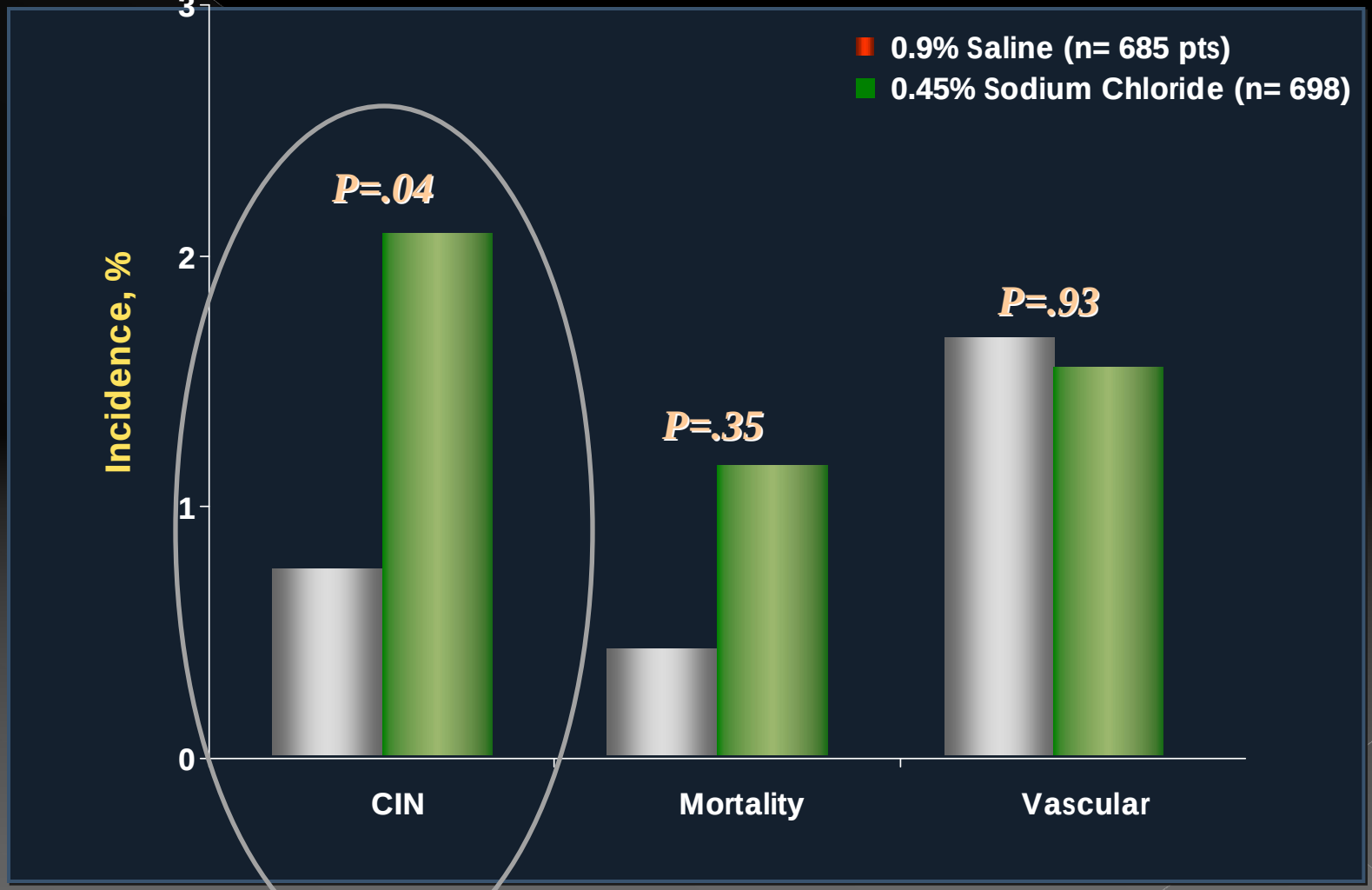
0.9 NS at 1-1.5 mL/Kg/h for 12 hrs before and 12 hrs after procedure

OR

0.9 NS 3 mL/kg, 1 hour prior to procedure and 1.5mL/Kg/h for 4-6 hrs after procedure

May use sodium bicarbonate 3 amps (150 mEq) in 1 L D5W instead of NS

Optimal Hydration: 0.9 NS vs 0.45 NS



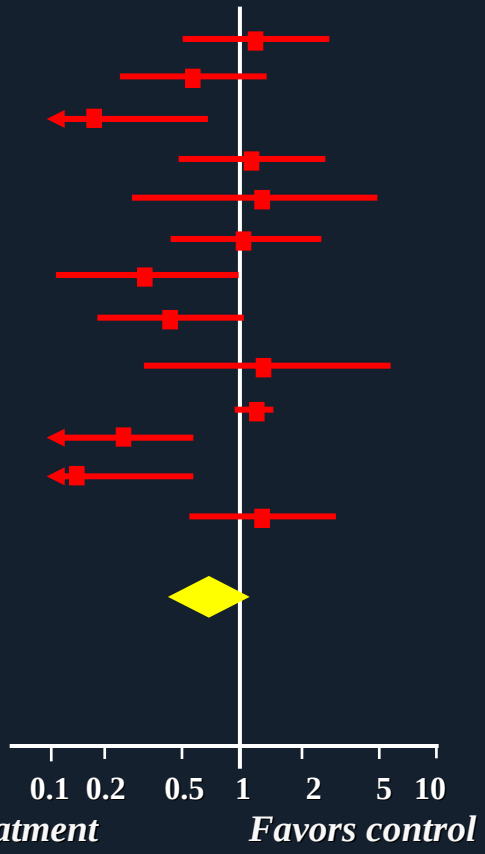
Mueller et al *Arch Intern Med* 2002

Sodium Bicarbonate

Study	N (Saline, Bicarb)	Procedure	Baseline Function (mL/min/1.73m2)	Fluid protocol	CIN rate (%)	p
RANDOMIZED						
Brar (MEENA)	353 (175, 178)	Cardiac	48 48	Saline Bicarbonate	13.6 13.5	0.97
Briguori (REMEDIAL)	219 (108, 111)	Cardiac Peripheral	32 35	Saline Bicarbonate	9.9 1.9	0.02
Merten	119 (59, 60)	Cardiac Peripheral	45 41	Saline Bicarbonate	13.7 1.7	0.02
Masuda*	59 (29, 30)	Emergency cardiac	39 40	Saline Bicarbonate	35 7	0.01
NON-RANDOMIZED						
CARE	414 (246,168)	Cardiac	50 50	Bicarbonate (-NAC) Bicarbonate (+NAC)	10.6 11.9	NS

N-Acetylcysteine: Metanalysis

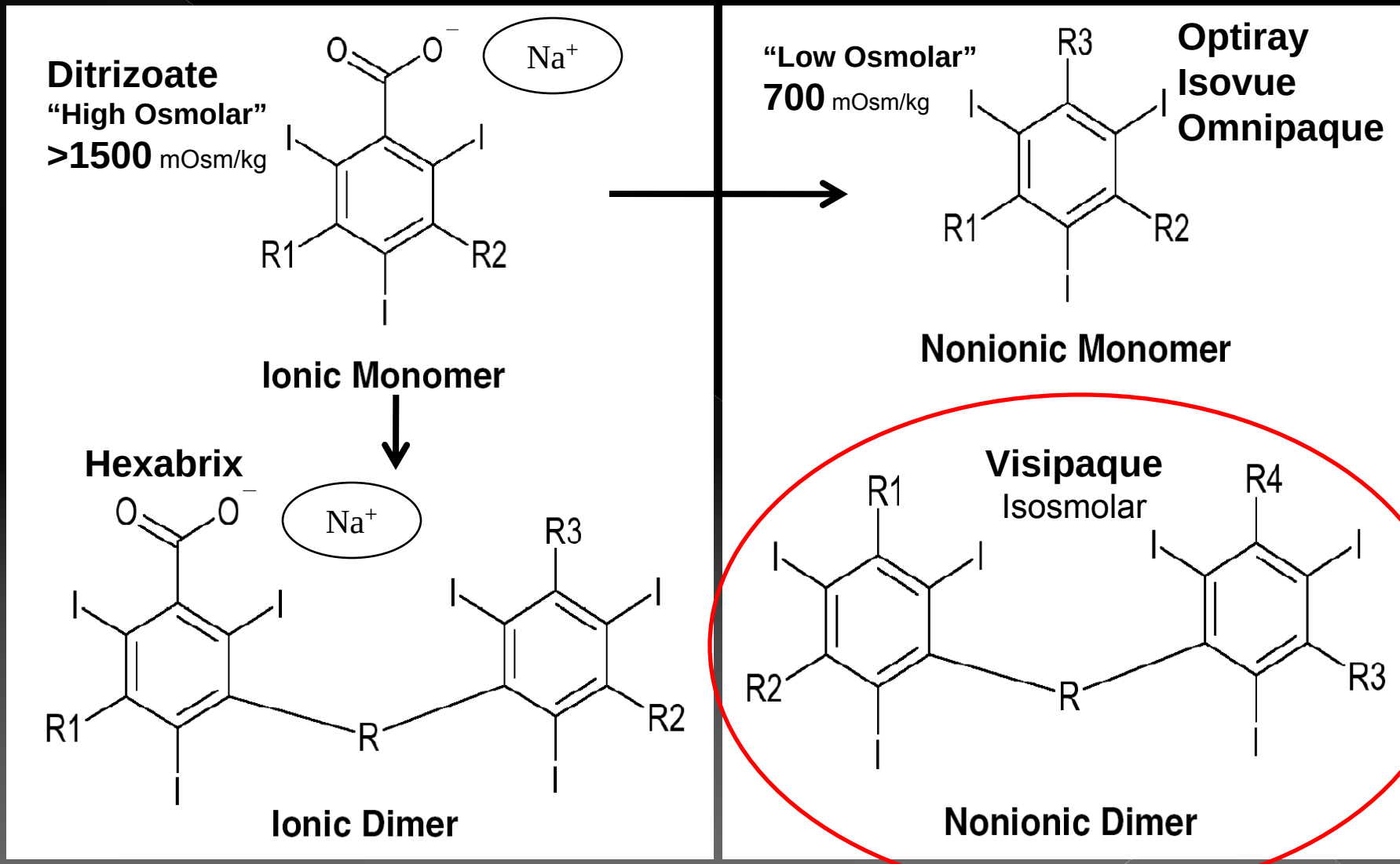
Study or substudy	NAC n/N	Control n/N	RR (Random) 95% CI	Risk Ratio (Random) 95% CI
Allaqaband et al	8/45	6/40		1.19 (0.45, 3.12)
Briguori et al	6/92	10/91		0.59 (0.23, 1.57)
Diaz-Sandoval et al	2/25	13/29		0.18 (0.04, 0.72)
Durham et al	10/38	9/41		1.20 (0.55, 2.63)
Goldenberg et al	4/41	3/39		1.27 (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*)

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

Contrast Media: Prototypic Structures

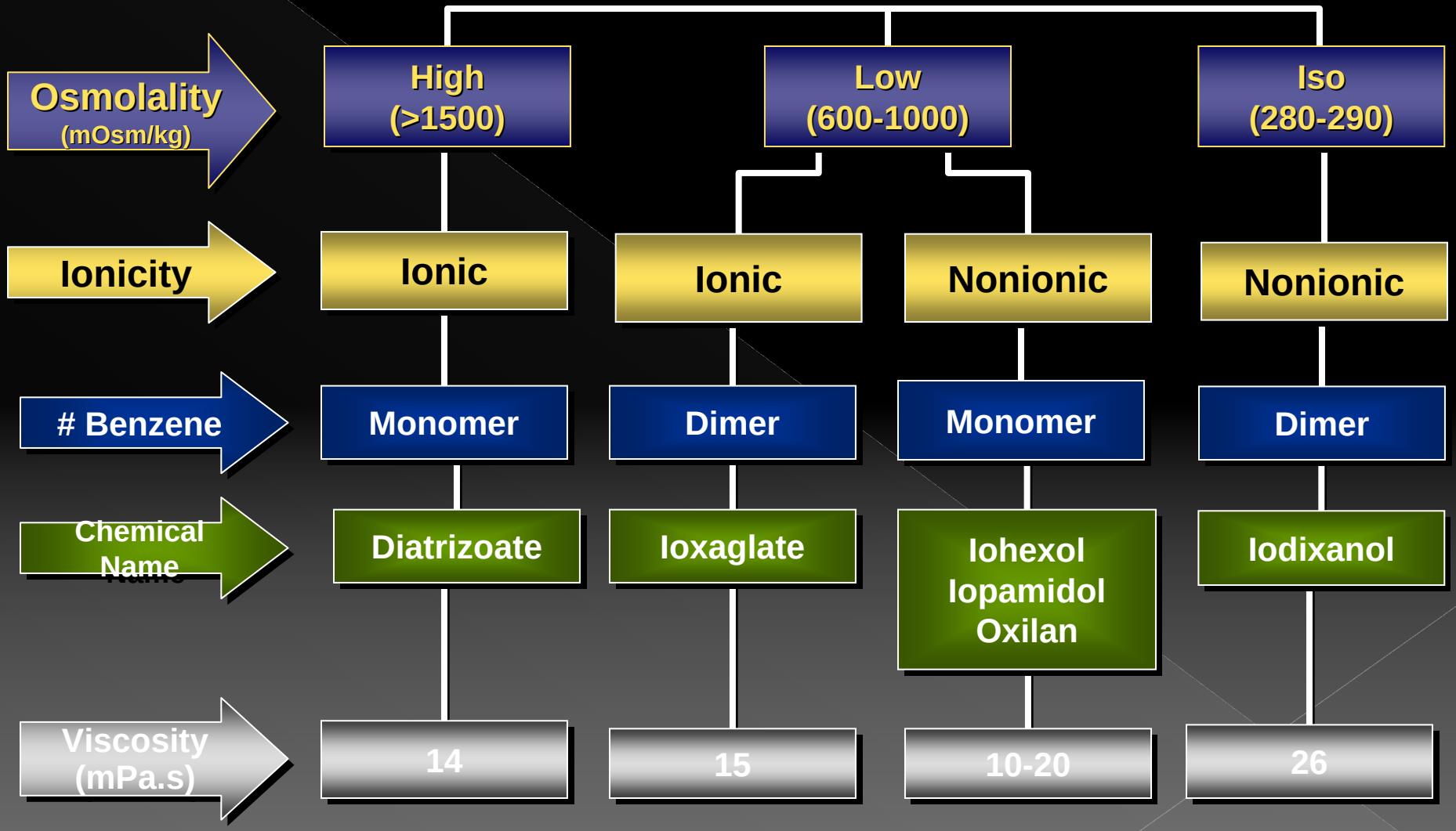


Voeltz MD, Nelson MA, McDaniel MC, Manoukian SV. J Invasive Cardiol 2007;19(Suppl A):1A-9A.

Products and Manufacturers

Product Name	Generic Name	Manufacturers	Approved Conc.(mgI/mL) for coronary injections
Oxilan®	ioxilan	Guerbet	350
Visipaque®	iodixanol	GE/Amersham	320
Omnipaque®	iohexol	GE/Amersham	350
Optiray®	ioversol	Mallinckrodt/ Tyco	320, 350
Hexabrix®	ioxaglate	Guerbet	320
Isovue®	iopamidol	Bracco	370
Ultravist®	iopromide	Berlex	370

Contrast Media Classification



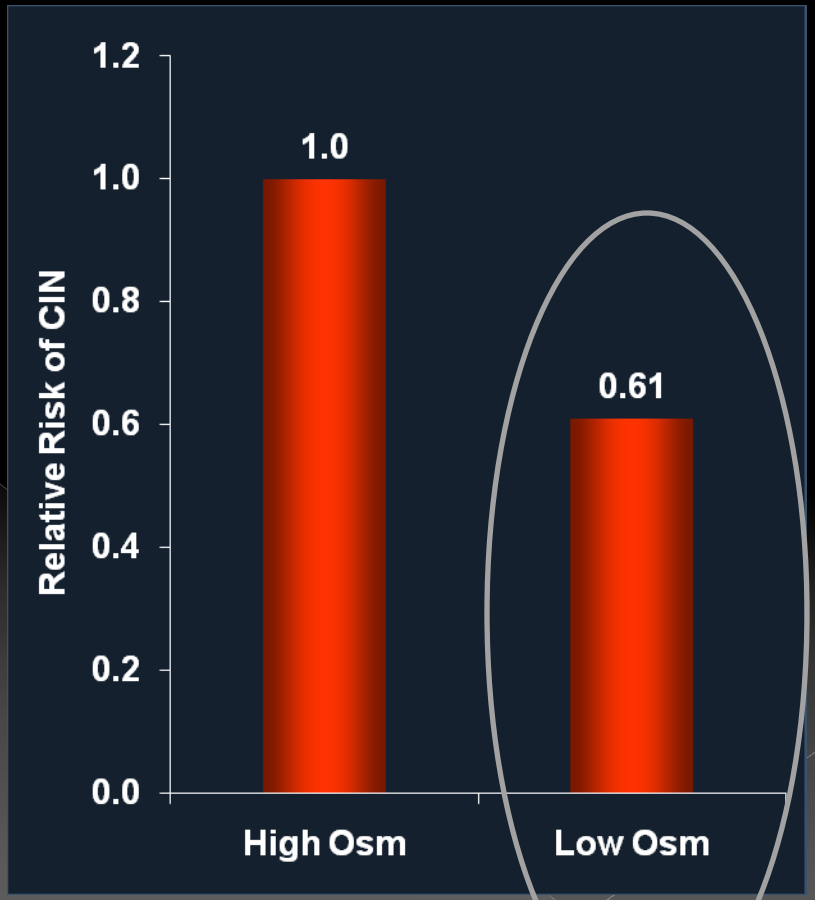
Abdominal Angio with 5F, Visipaque: Settings at 900 psi ……

Achieved values

VISIPAQUE: Isosmolar and well tolerated BUT viscous contrast

Meta-analysis: High vs. Low Osm Contrast Media

- 39 Trials - 5146 patients
- CIN > 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 included



Barrett BJ and Carlisle EJ Radiology. 1993;188:171-178.

CIN and Contrast Type

Prospective Randomized Trials

Low-osmolar	Iso-osmolar	Condition	Statistical result
Iohexol (844)	Iodixanol	Coronary, CKD (SCr* 3.1), 35% DM	No difference[1]
Iohexol (844)	Iodixanol	Coronary, CKD (SCr 1.5), 100% DM	Iodixanol superior to iohexol (NEPHRIC)[2]
Ioversol (792)	Iodixanol	Coronary, CKD (SCr 2.0), 52% DM	No difference[3]
Iopamidol (796)	Iodixanol	MDCT, CKD (SCr 1.6)	No difference[4]
Iopamidol (796)	Iodixanol	Coronary, CKD (SCr 1.45), 41% DM	No difference (CARE)[5]
Ioxaglate (600)	Iodixanol	Coronary, CKD (SCr 1.34, 48% DM	Iodixanol superior to ioxaglate (RECOVER)[6]
Ioxaglate (600)	Iodixanol	Coronary, CKD, contrast>150	No difference (ICON)[7]

[1]*Chalmer and Jackson, BJR 1999*

[2]*Aspelin et al (NEPHRIC), NEJM 2003*

[3]*Rudnick et al, (VALOR), ASN 2005*

[4]*Barrett et al (IMPACT), Invest Rad 2006*

[5]*Solomon et al (CARE), Circ 2007*

[6]*Jo et al (RECOVER), JACC 2006*

[7]*Mehran (ICON), TCT 2006*

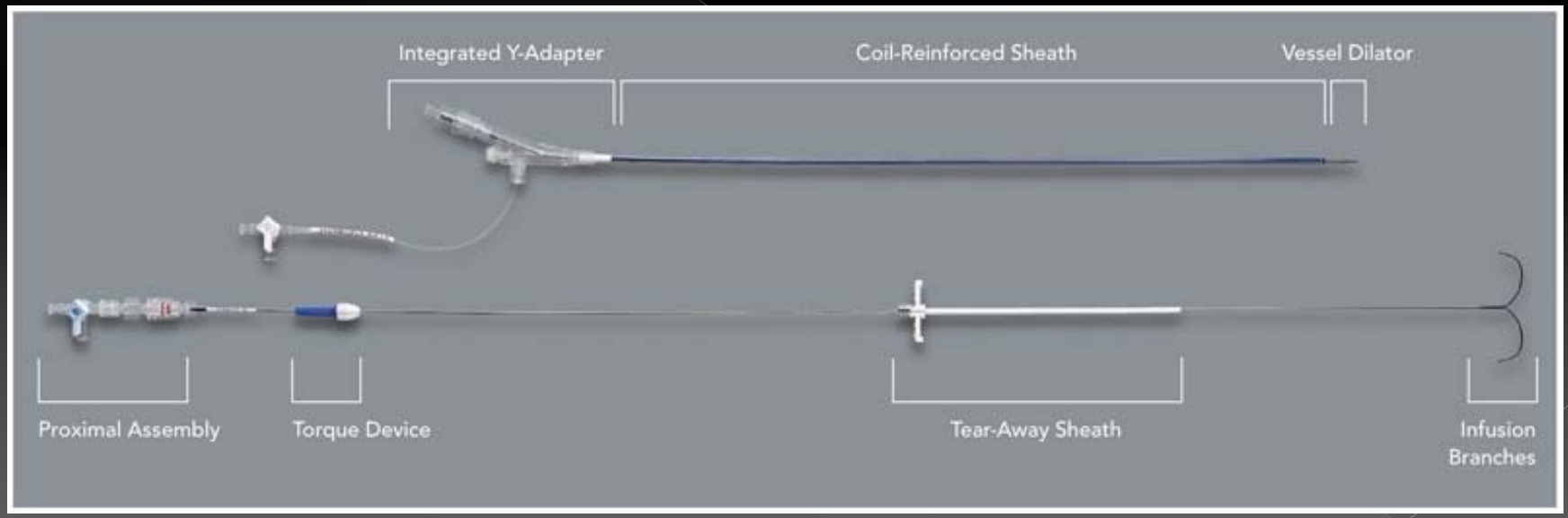
CONTRAST TYPE: Conclusion

- Low Osmolar better than High Osmolar Contrast.

- Isosmolar Contrast (Iodixanol, Visipaque™):
  - For CIN prevention: Not conclusively better than low-osmolar BUT 3.5 times more expensive per cc
  - Provides less osmotic load than low-osmolar agents (Advantage in CHF, acute MI or dialysis patients)
  - Most adequate than other agents for PERIHERAL angiography due to consistently LESS PAINFUL INJECTIONS.

Targeted Renal Therapy

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



CONTRAST Trial:

IV Fenoldopam for the Prevention of CIN

Design

- **DESIGN:** Prospective, placebo-controlled, double-blind, multicenter randomized trial
- **OBJECTIVE:** Examine the efficacy of IV fenoldopam in preventing CIN after invasive cardiovascular procedures.

A total of 315 pts with GFR<60mL/min at 28 centers in the US from 2001 to 2002

Randomization

IV fenoldopam (0.05 ugr/kg/min titrated to 0.10 ugr/kg/min) 1 hr pre- to 12 hrs post procedure

N=157

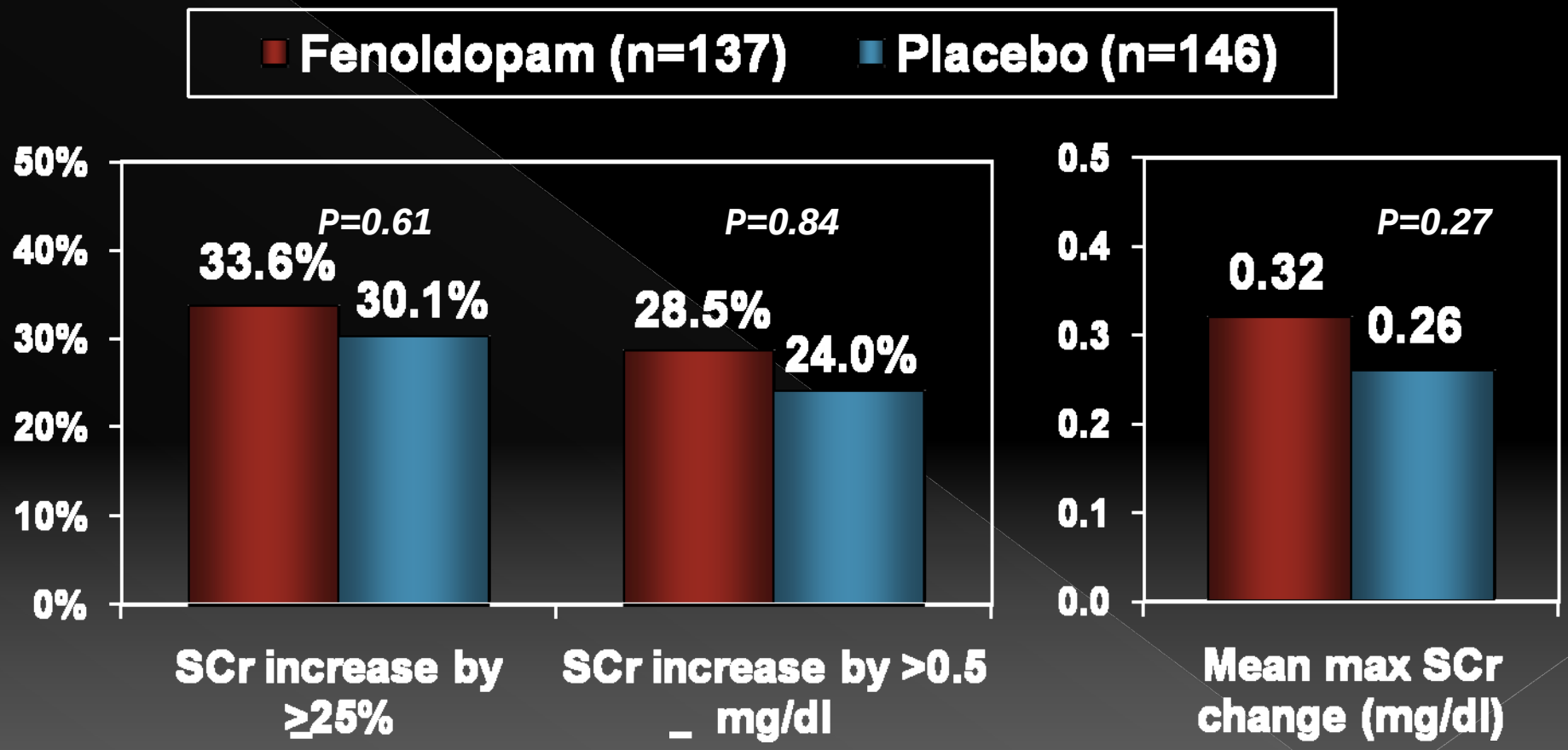
IV placebo 1 hr pre- to 12 hrs post procedure

N=158

Primary endpoint: **CIN** (increase of ≥25% in SCr level within 96 hours post-procedure).

Stone G. et al. JAMA. 2003 ;290:2284-2291

CONTRAST Trial



Stone G. et al. JAMA. 2003 ;290:2284-2291

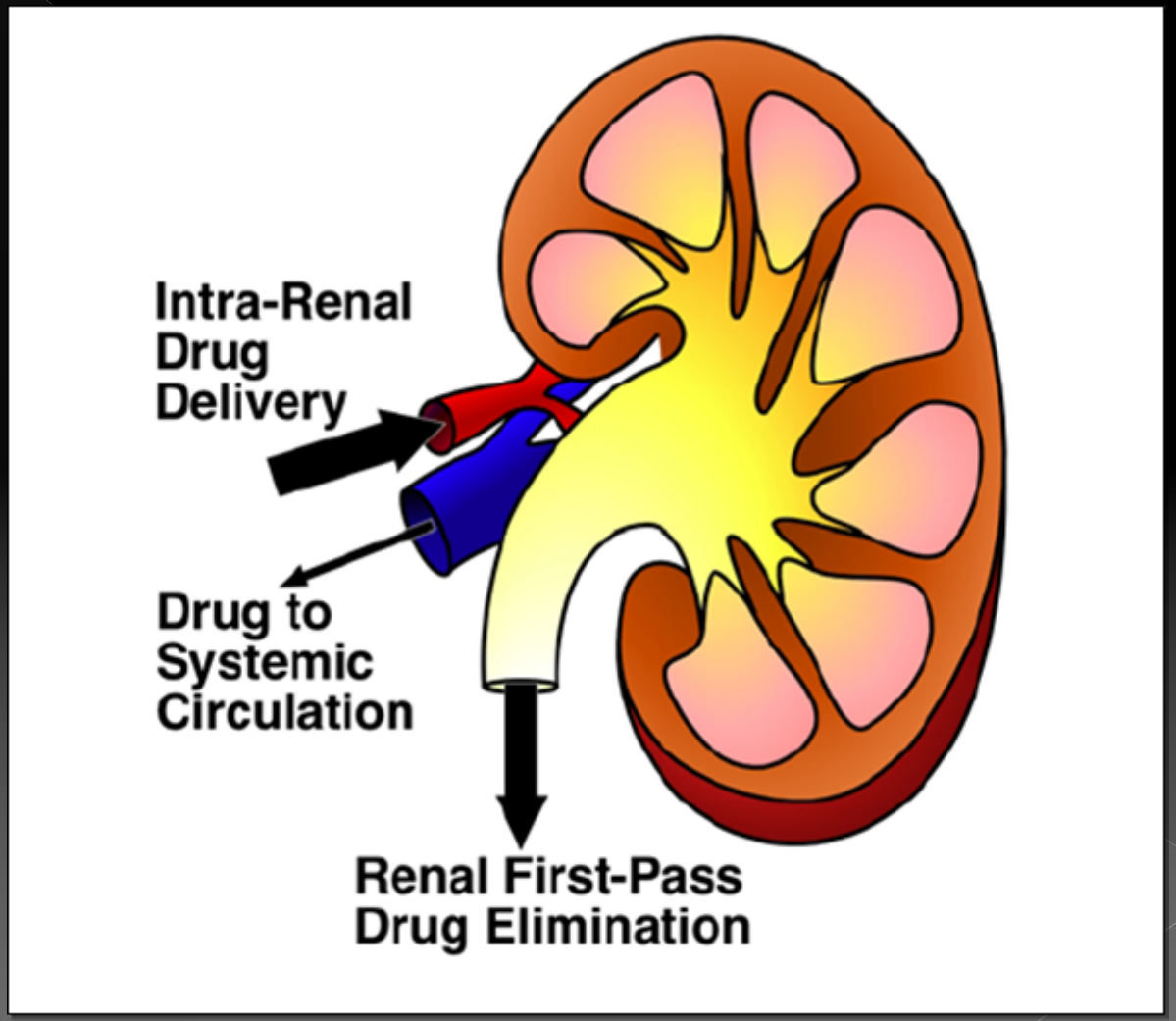
Fenoldopam

- Short acting Dopamine-1 agonist, vasodilator of BOTH renal cortical and medullary blood flow.
- NEGATIVE effect of IV fenoldopam in CIN prevention (CONTRAST trial)
  - Problems: First pass metabolism
  - Hypotension limits IV dose

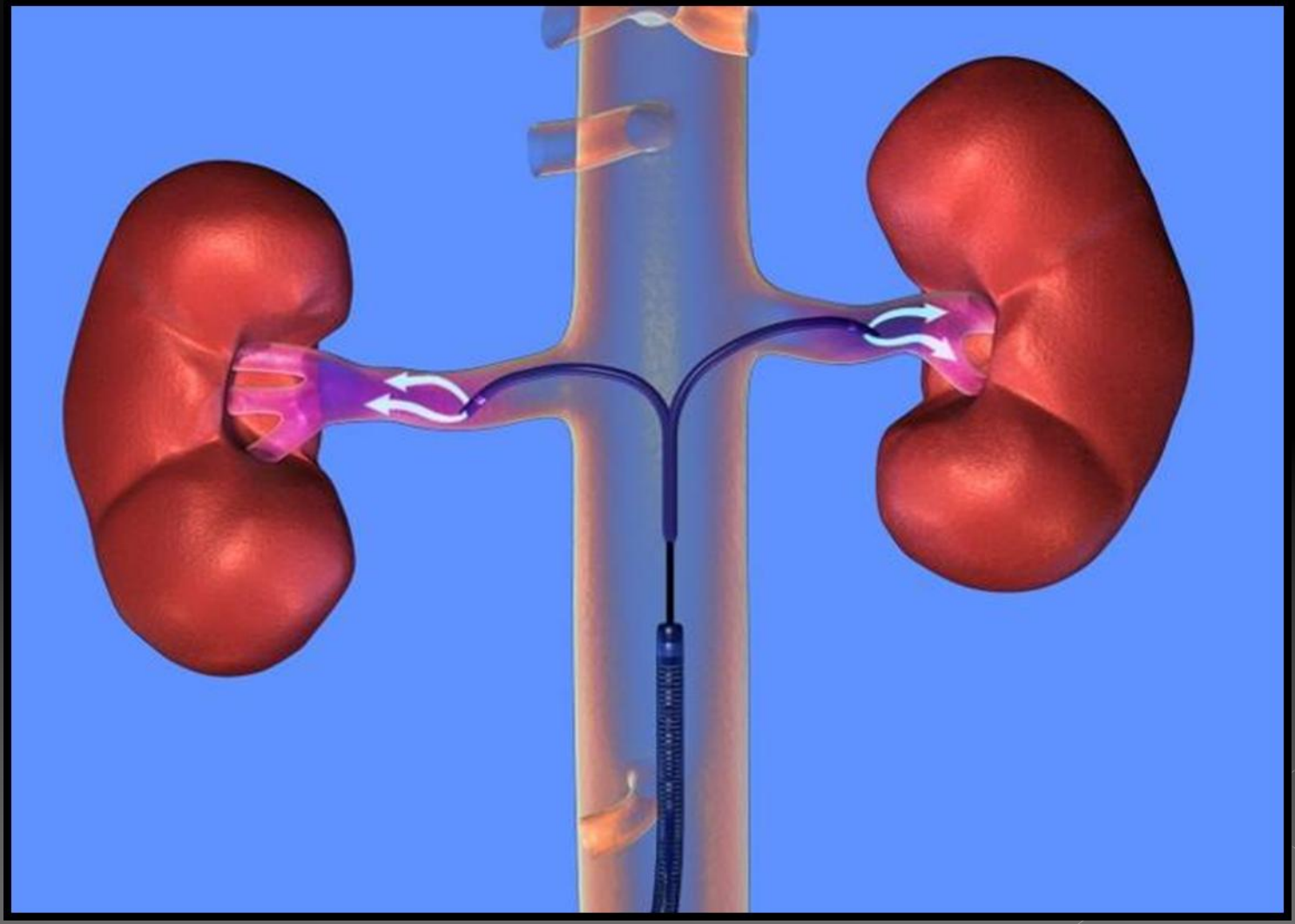
Intrarenal Fenoldopam

- Serum Fenoldopam levels are 30-50% lower by IR infusion.
- Less hypotension allows higher doses.
- GFR significantly increased by IR infusion and not by IV infusion (and persists few hrs. after IR infusion)

Targeted Renal Delivery



Renal Infusion Catheter



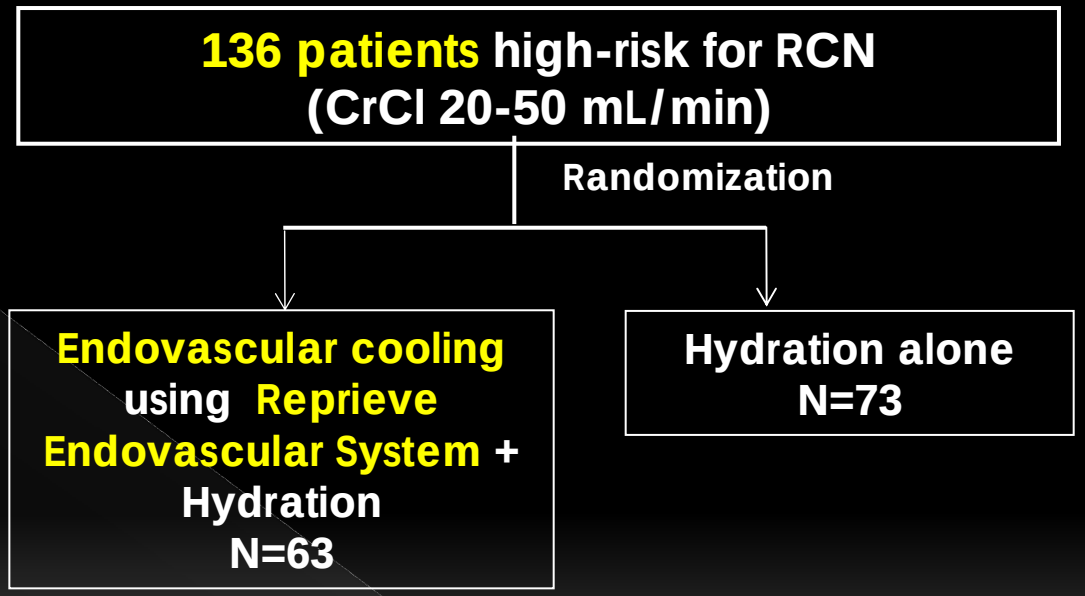
COOL-RCN:

Cooling to Prevent Radiocontrast Nephropathy

Design

Prospective, randomized, open label, active control, parallel assignment

OBJECTIVE: Evaluate whether endovascular cooling can reduce the incidence of CIN in high-risk patients undergoing diagnostic or interventional catheterization procedures

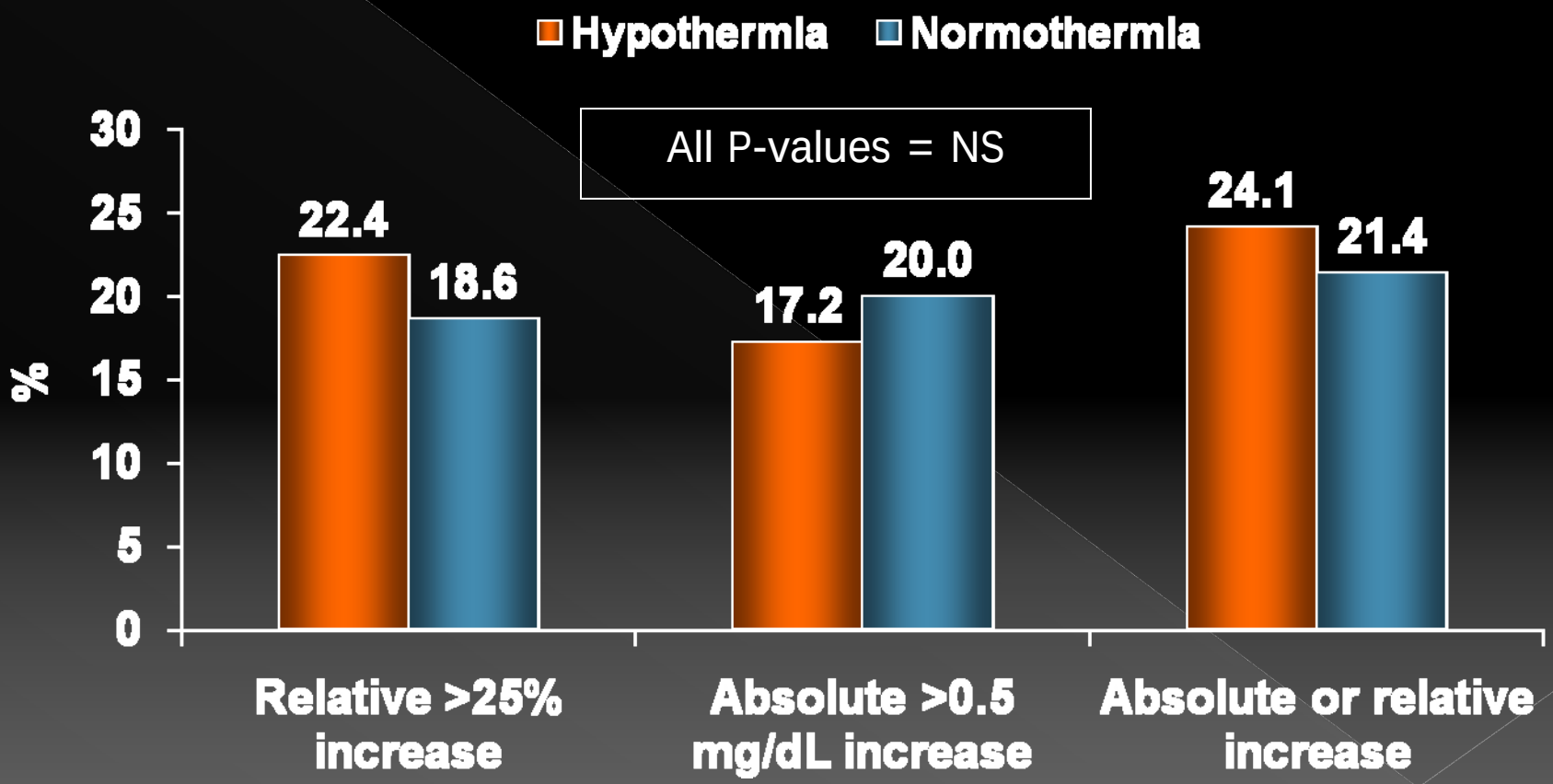


Primary endpoint: rates of CIN

Stone GW et al, TCT 2008

COOL-RCA: Results

Increase in SCr from baseline to 96 hours



Stone GW et al, TCT 2008

Conclusions (1)

- CKD is one of the most powerful predictors of poor outcome post PCI
- CIN remains a frequent source of acute renal failure and is associated with increased morbidity and mortality.
- Several patient and procedural factors predispose patients to CIN
- Preventive measures pre procedure, as well as careful post procedure management should be routine in all patients

Conclusions (2)

- Hydration 0.9 NS pre-cath (12 hours recommended).
- Hold nephrotoxic drugs (NSAIDS, antibiotics, etc)
- Role of N-acetylcysteine is disputable
- No role for IV Fenoldopam
- Sodium bicarbonate may be useful, but need more definitive data
- Limit contrast agent volume
- Low-osmolar agents are better than high-osmolar
- Within low or ISO osmolar, the data are contradictory
- Role of local drug delivery (e.g. Fenoldopam) for prevention of CIN requires further investigation
- No role of Cooling Therapy (COOL CIN Study)