

# L'insufficienza renale acuta nel paziente critico

Inquadramento clinico dell'IRA nel paziente cardiopatico critico.  
La nefropatia da contrasto.

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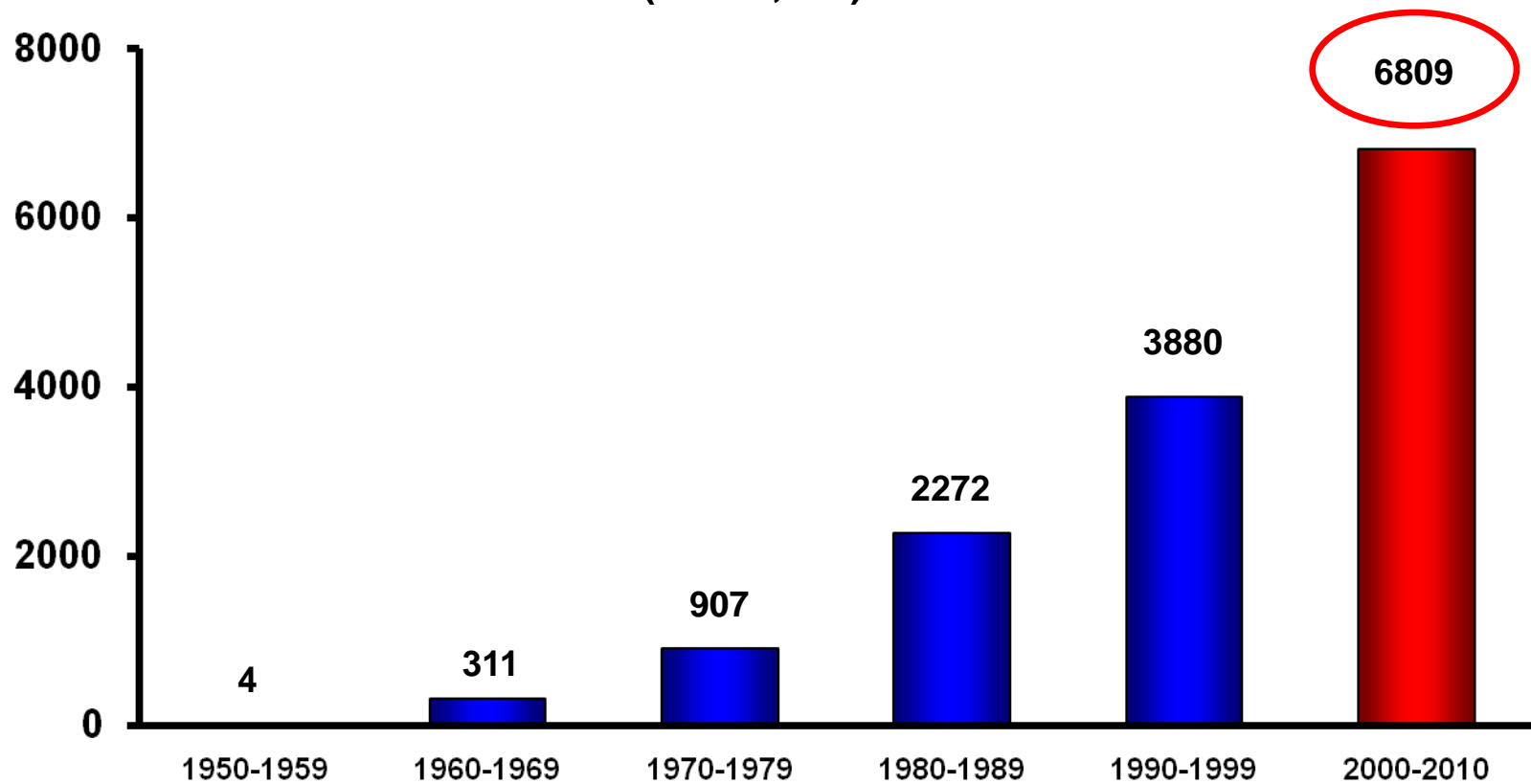
Giancarlo Marenzi, MD



# Contrast-Induced Nephropathy

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CIN literature (PubMed)  
(1951- 2010)  
(n = 14,163)



# Incidence of CIN is higher following cath lab studies

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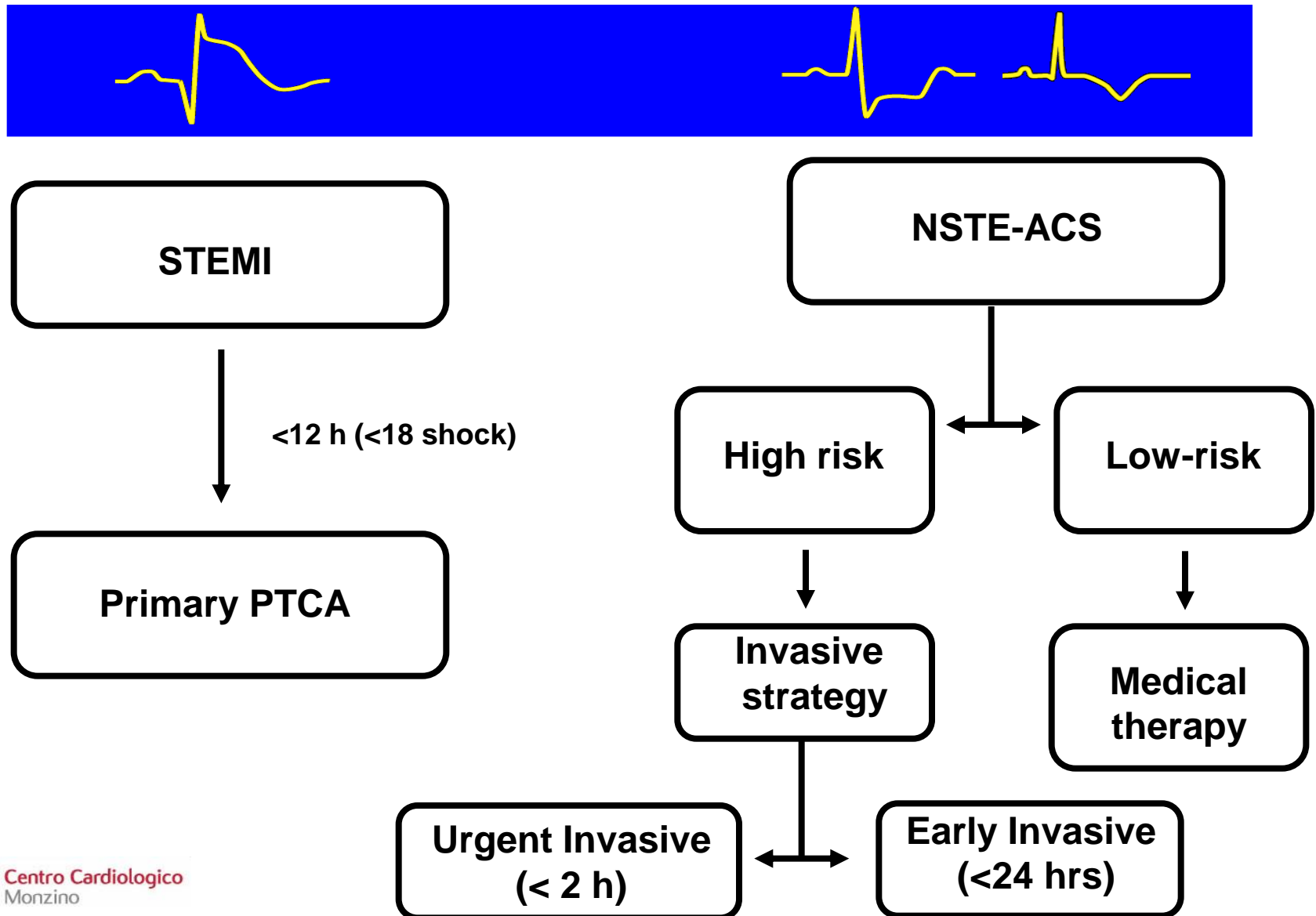
- ❑ Complex procedures
- ❑ Larger volumes of contrast
- ❑ Contrast going undiluted to renal aa. when injection is made above the emergency of the renal aa.
- ❑ Radiologists can choose to perform alternative imaging procedures (MRI, US) in risk patients
- ❑ Greater awareness in the cardiology setting – risk patients are usually followed-up, with measurement of serum creatinine at 24-48 hrs post-contrast

# Incidence of CIN following emergency/urgent PCI

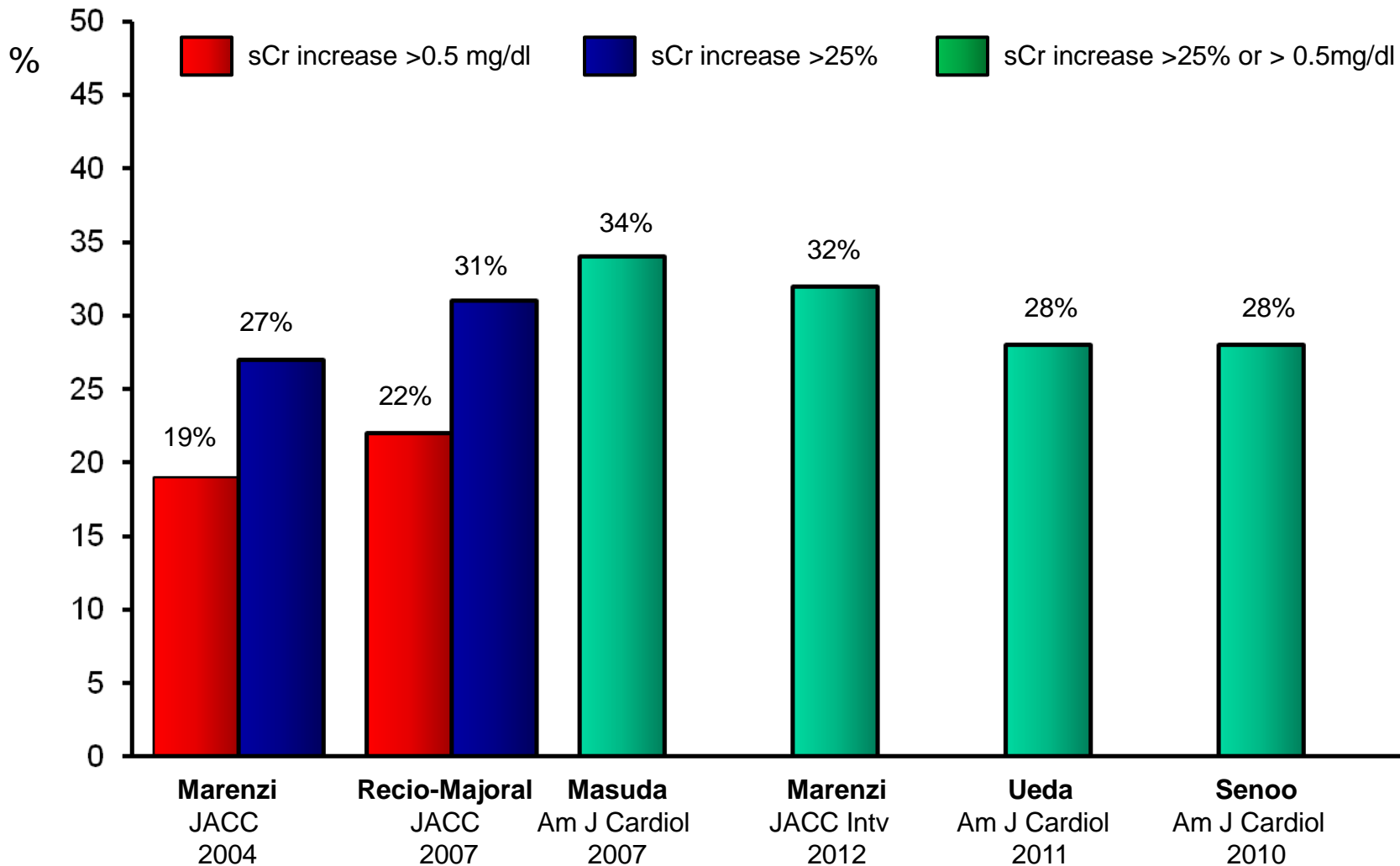
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- ❑ Complex procedures
- ❑ Larger volumes of contrast
- ❑ Hemodynamic instability
- ❑ Impossibility of starting a renal prophylactic therapy
- ❑ No time for stratifying the baseline risk of the patient

# European Society of Cardiology Guidelines



# Incidence of CIN in urgent or emergency angiography for ACS



# Risk Factors for Contrast-Induced Nephropathy

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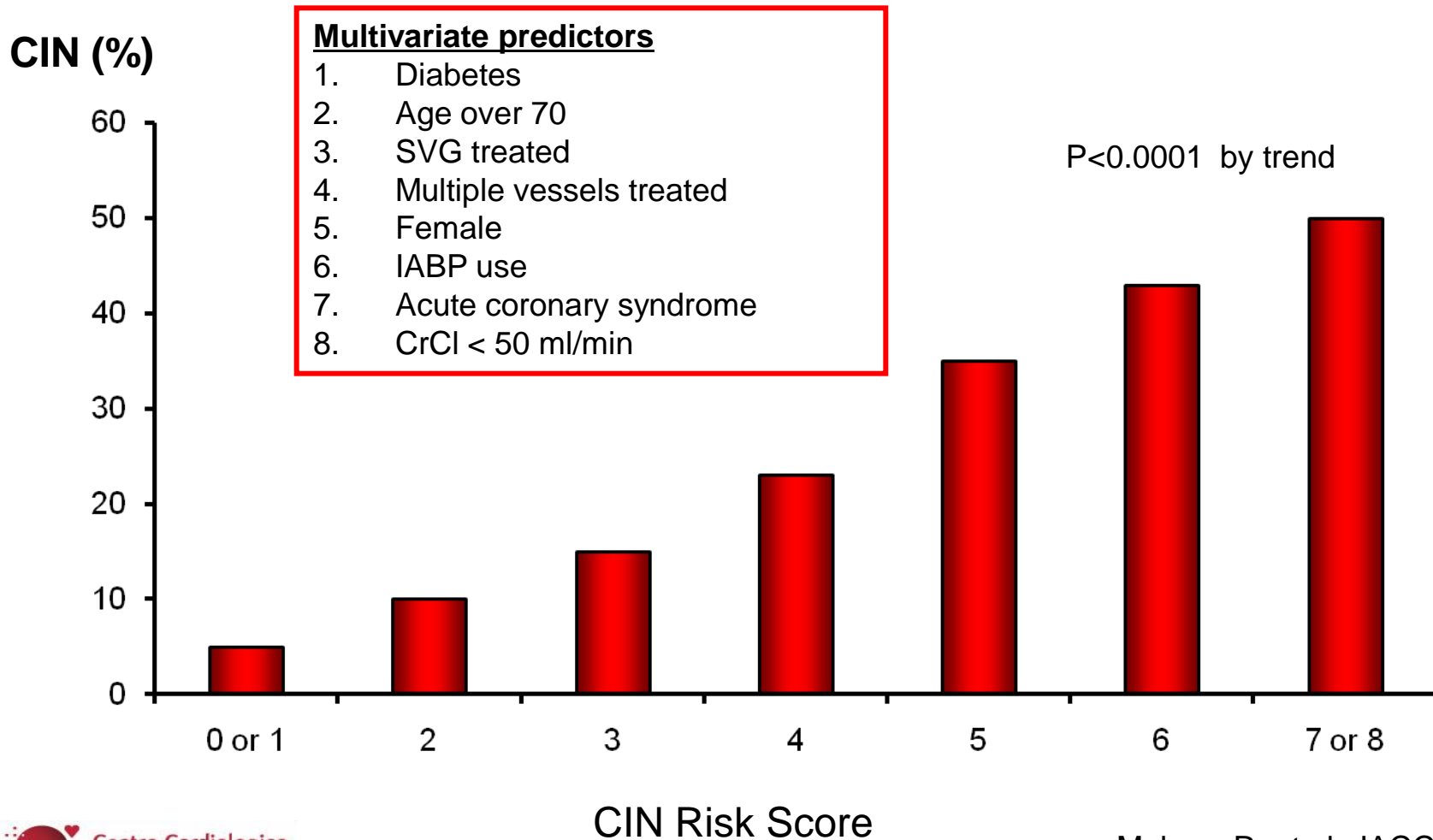
## Patient Related

- ❑ Chronic kidney disease ( $\geq$ stage III)
- ❑ Diabetes mellitus (type 1 or 2)
- ❑ Volume depletion
- ❑ Older age
- ❑ Congestive heart failure (or LVEF < 40%)
- ❑ Hypertension
- ❑ Anemia and blood loss
- ❑ Hypoalbuminemia (<35 g/l)
- ❑ Nephrotoxic drug use
  - NSAIDs,
  - cyclosporine,
  - aminoglycosides
  - diuretics
  - ACE inhibitors
- ❑ Hypotension or hemodynamic instability
- ❑ Urgent procedure
- ❑ IABP use
- ❑ Renal transplant

## Not Patient Related

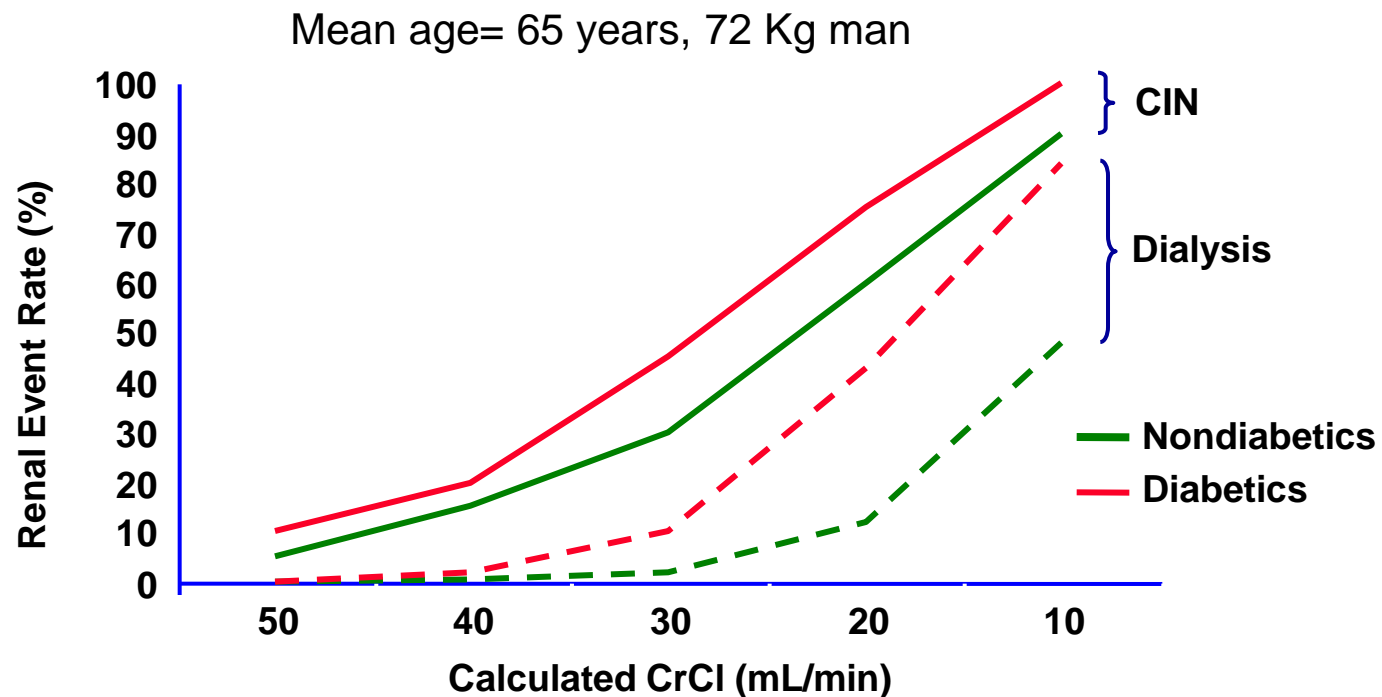
- ❑ Contrast properties
  - High osmolar contrast
  - Ionic contrast
  - Contrast viscosity
  - Contrast volume
  - Intra-arterial administration

# A Risk Score for Prediction of CIN





# Prediction of CIN and Dialysis After PCI

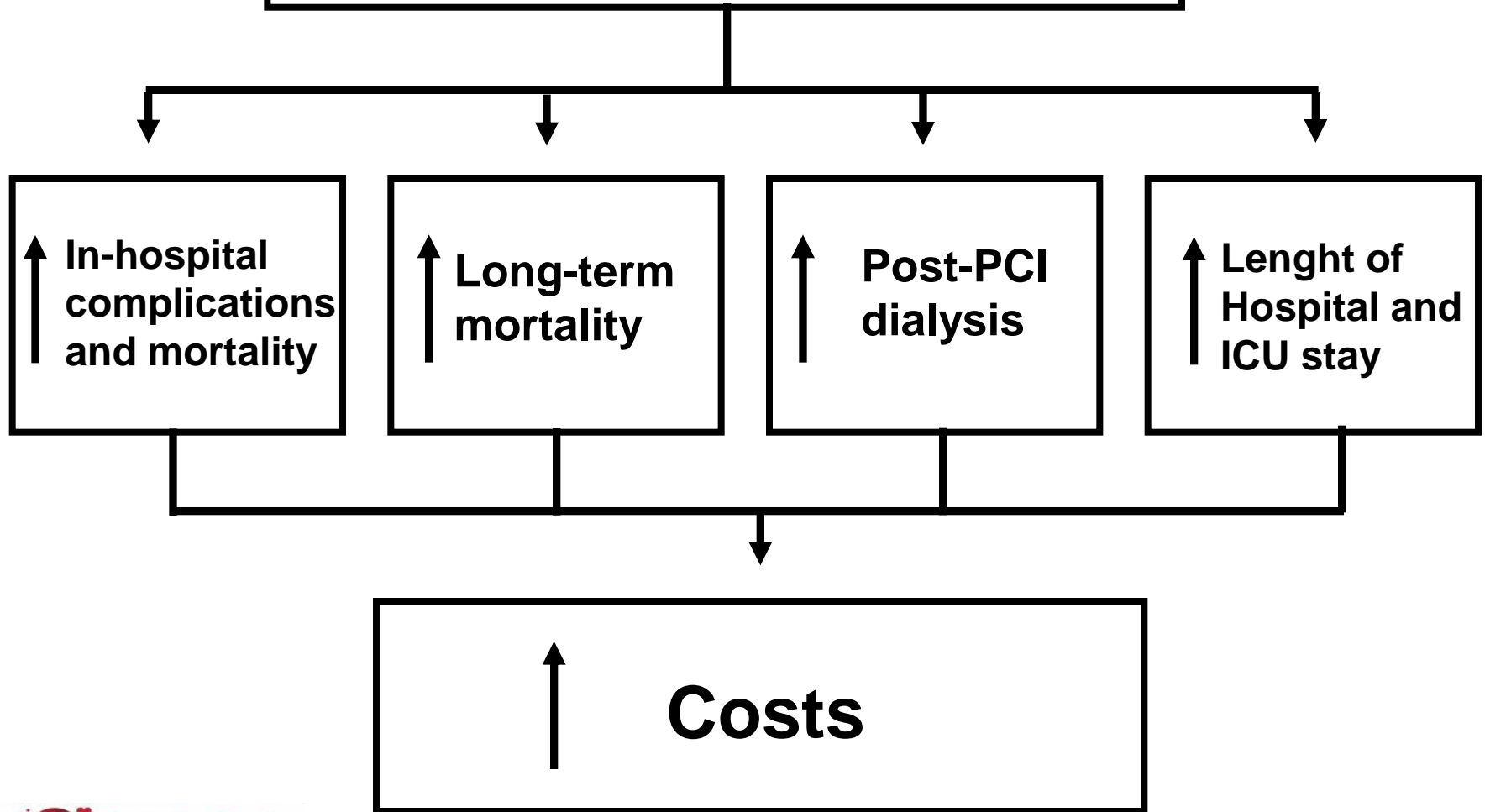


# Patients at “*Very High Risk*” for CIN after PCI

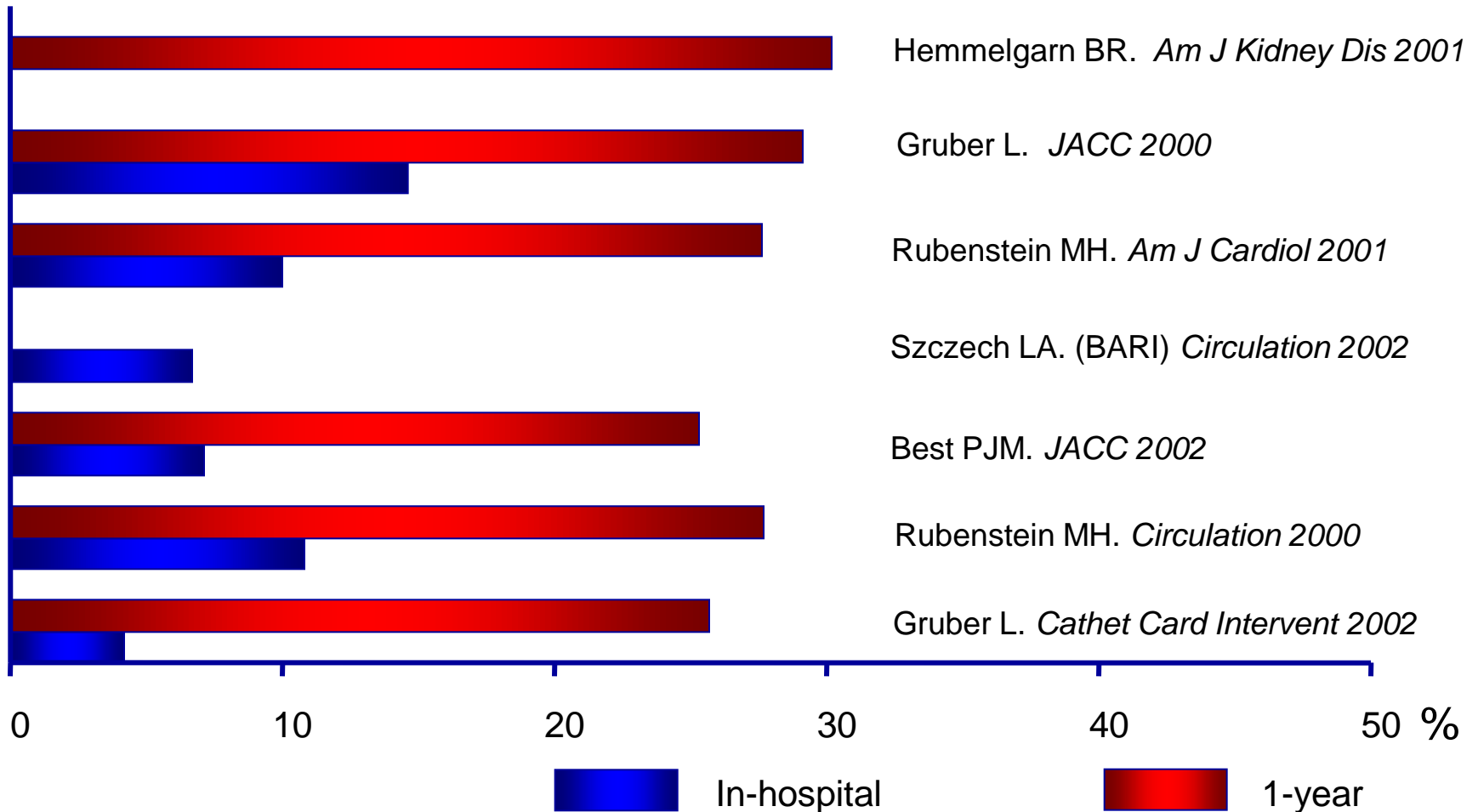
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- ❑ Patients with multiple risk factors
- ❑ Patients with severe chronic renal insufficiency (CrCl<30 ml/min)
- ❑ Patients undergoing emergency (primary) PCI
- ❑ Patients combining these three characteristics

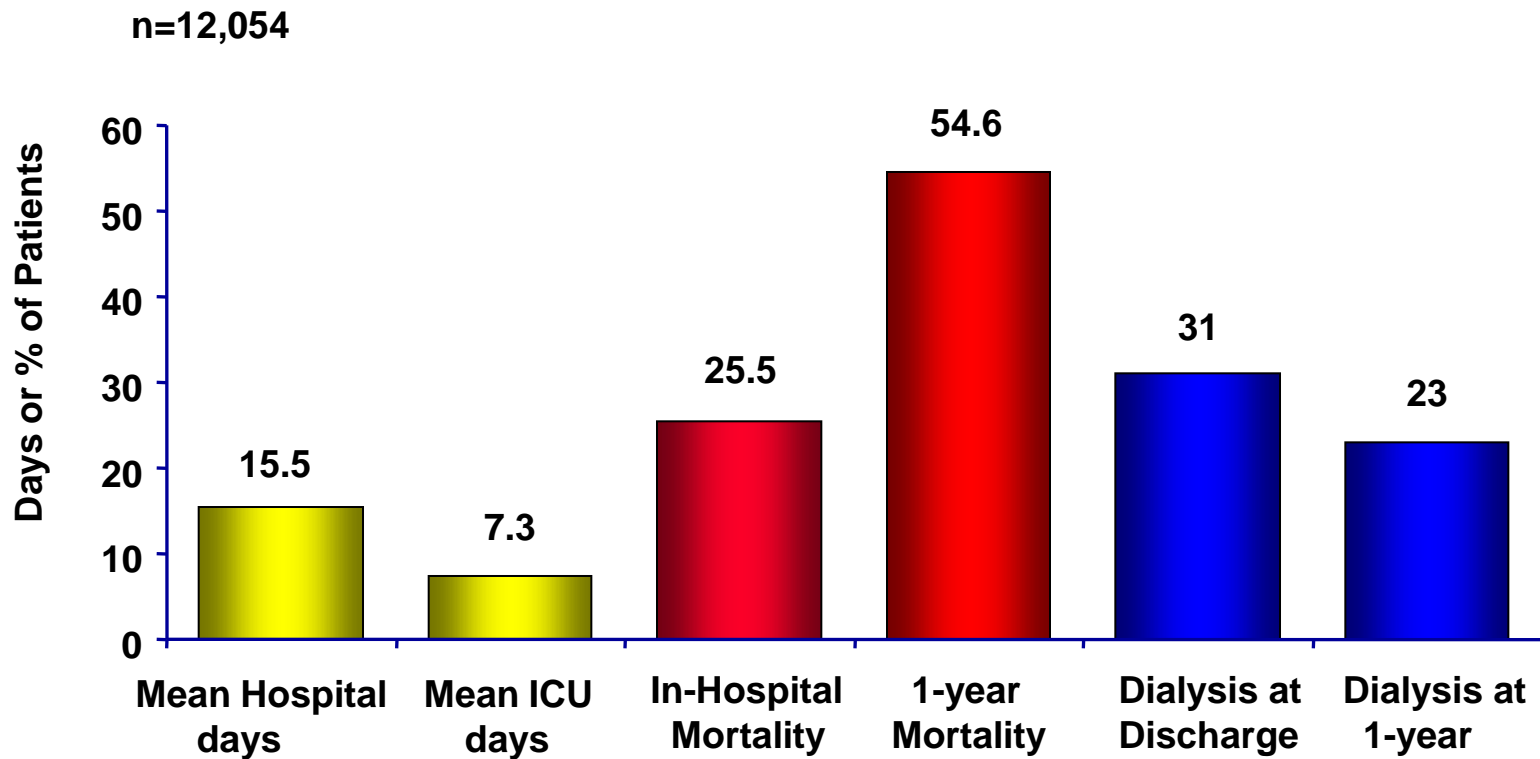
# IMPLICATIONS OF CIN



# In-Hospital and 1-Year Mortality in Patients Developing CIN after PCI

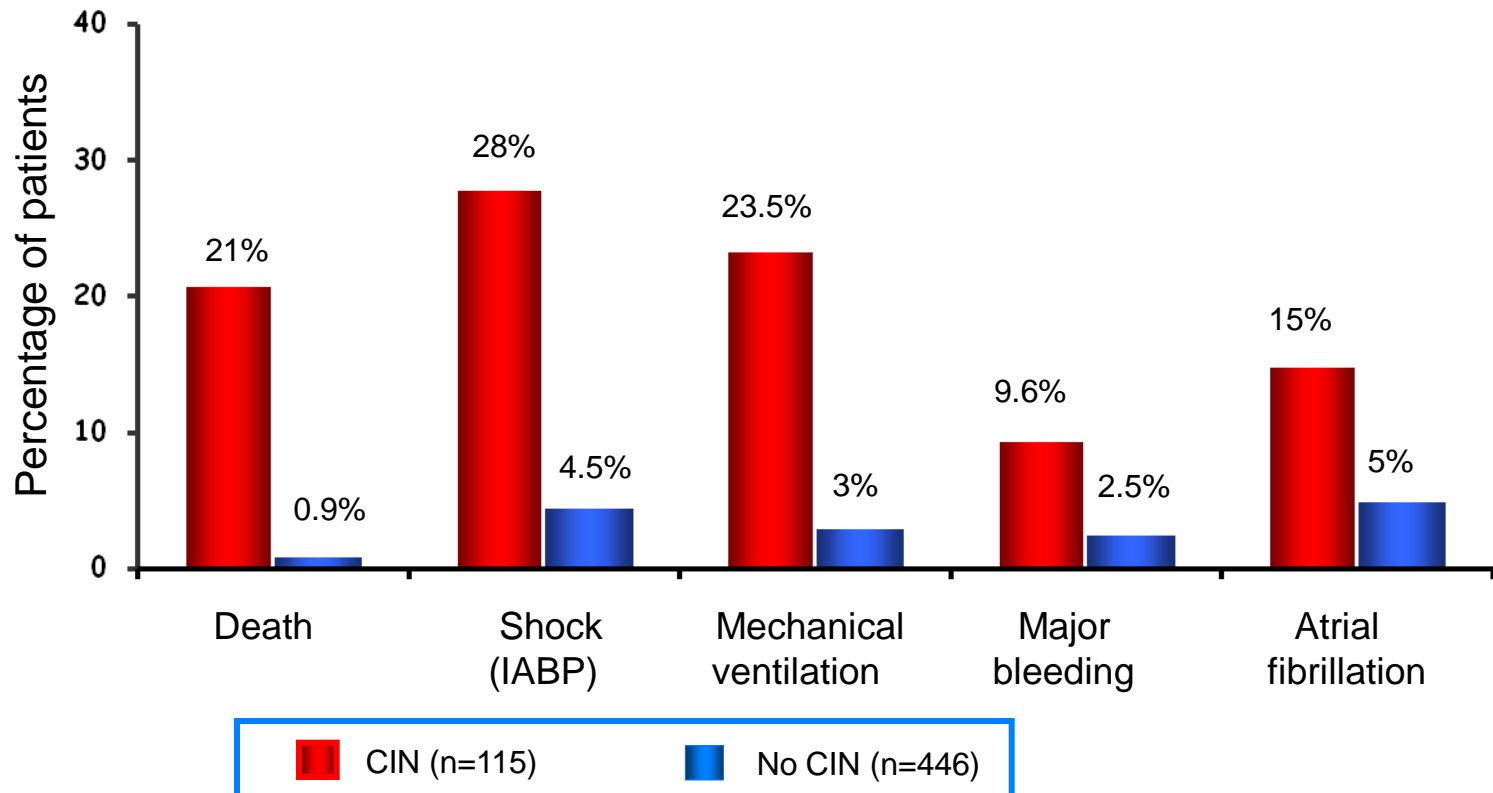


# Outcomes of Patients Requiring Dialysis Following PCI



# Contrast Volume During Primary Percutaneous Coronary Intervention and Subsequent Contrast-Induced Nephropathy and Mortality

561 patients with STEMI who were undergoing primary PCI



# CIN Prevention Trials

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Agent	Design	Results
Furosemide	Pro-Ran	Worsened CIN
Mannitol	Pro-Ran	Worsened CIN
Hydration (½ saline)	Pro-Ran	Benefit vs. furosemide & mannitol
Hydration (saline)	Pro-Ran	Benefit vs. ½ saline
Atrial natriuretic peptide	Pro-Ran	No benefit
Dopamine	Pro	No benefit
Endothelin antagonist	Pro-Ran	No benefit
Adenosine antagonist	Pro-Ran	No benefit
Calcium channel block.	Pro	No benefit
LOCM-IOCM	Pro-Ran	Benefit vs. HOCM
Fenoldopam	Pro-Ran	No benefit
N-Acetylcysteine	Pro-Ran	Benefit
Ascorbic acid	Pro-Ran	Benefit
NaHCO <sub>3</sub>	Pro-Ran	Benefit
Statins	Pro-Ran	Benefit
Hemodialysis	Pro-Ran	No benefit

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# Guidelines on myocardial revascularization

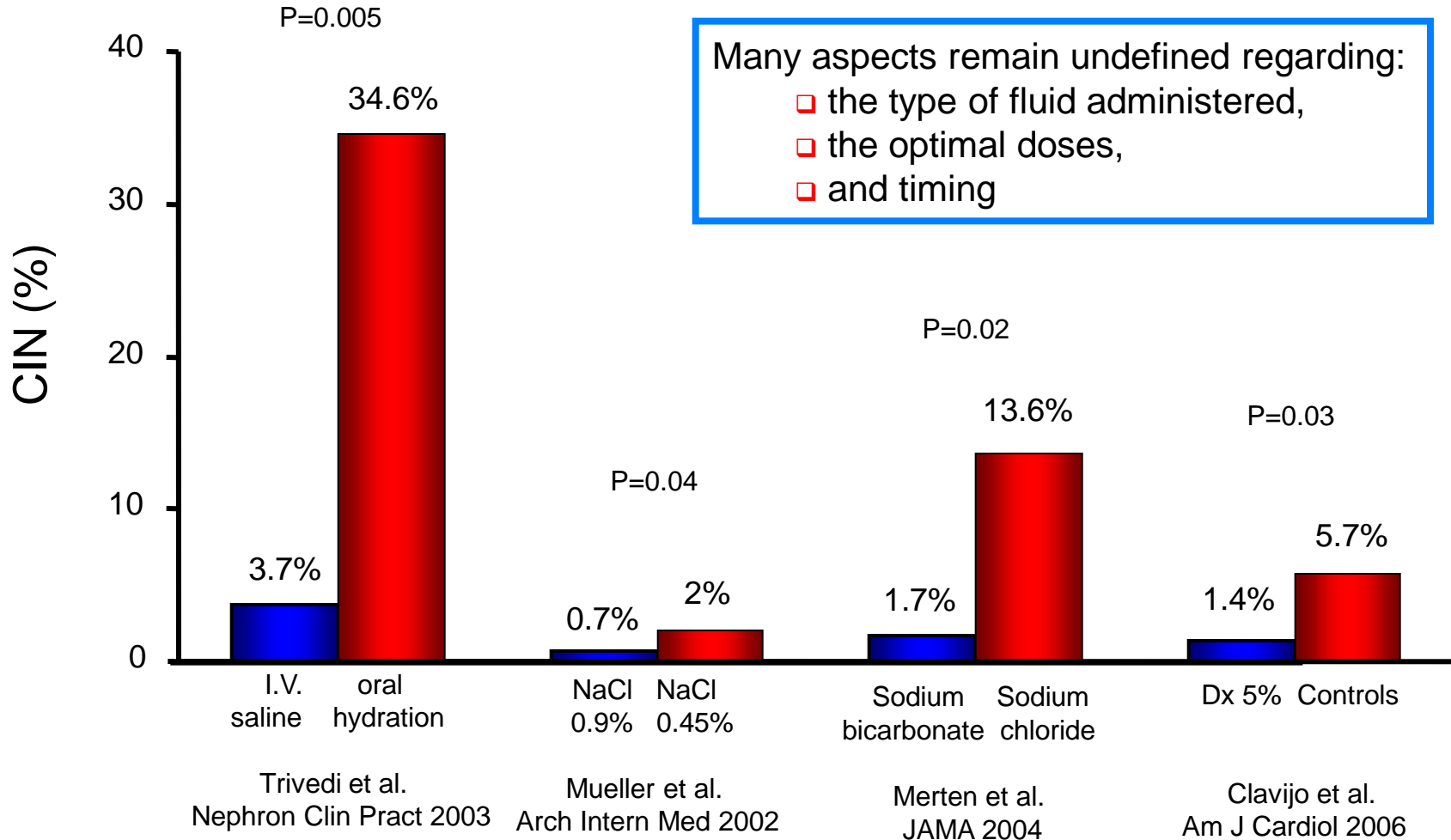
## The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

**Table 17** Recommendations for prevention of contrast-induced nephropathy

Intervention	Dose	Class <sup>a</sup>	Level <sup>b</sup>	Ref. <sup>c</sup>
<b>All patients with CKD</b>				
OMT (including statins, β-blockers, and ACE inhibitors or sartans) is recommended.	According to clinical indications.	I	A	123
Hydration with isotonic saline is recommended.	1 mL/kg/h 12 h before and continued for 24 h after the procedure (0.5 mL/kg/h if EF <35% or NYHA >2).	I	A	127–130
N-Acetylcysteine administration may be considered.	600–1200 mg 24 h before and continued for 24 h after the procedure.	IIb	A	128, 129
Infusion of sodium bicarbonate 0.84% may be considered.	1 h before: bolus = body weight in kg x 0.462 mEq i.v. infusion for 6 h after the procedure = body weight in kg x 0.154 mEq per hour.	IIb	A	127, 128, 130
<b>Patients with mild, moderate, or severe CKD</b>				
Use of LOCM or IOCM is recommended.	<350 mL or <4 mL/kg	I <sup>d</sup>	A <sup>d</sup>	124, 131–133
<b>Patients with severe CKD</b>				
Prophylactic haemofiltration 6 h before complex PCI should be considered.	Fluid replacement rate 1000 mL/h without weight loss and saline hydration, continued for 24 h after the procedure.	IIa	B	134, 135
Elective haemodialysis is not recommended as a preventive measure.		III	B	136



# Hydration



# Idratazione o prevenzione della disidratazione?

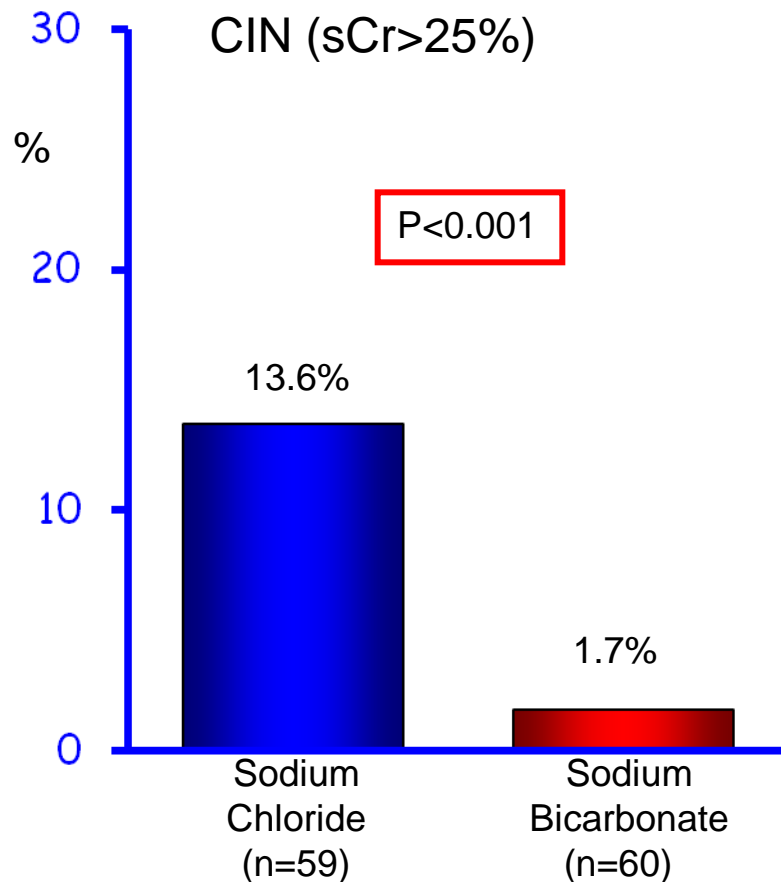
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Il fabbisogno idrico quotidiano di una persona normale, di corporatura media, sana, che si trovi in un ambiente a temperatura ideale, varia da 2,5 a 3 litri di acqua.

1 ml/kg/h per una persona di 70 kg corrisponde a 1.680 litri nelle 24 ore

# Prevention of Contrast-Induced Nephropathy With Sodium Bicarbonate

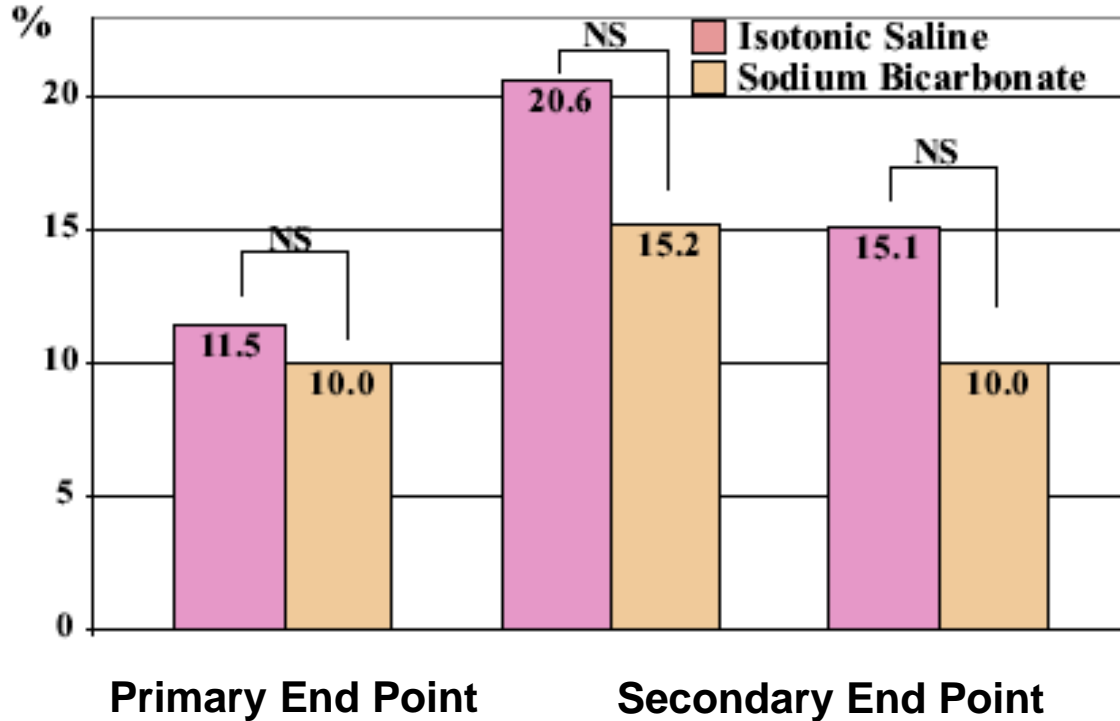
## A Randomized Controlled Trial



- 119 pts with sCr >1.1mg/dl undergoing coronary procedures or CT scan.
- 3 ml/kg/h for 1 h before and 1 ml/kg/h for 6h after contrast exposure

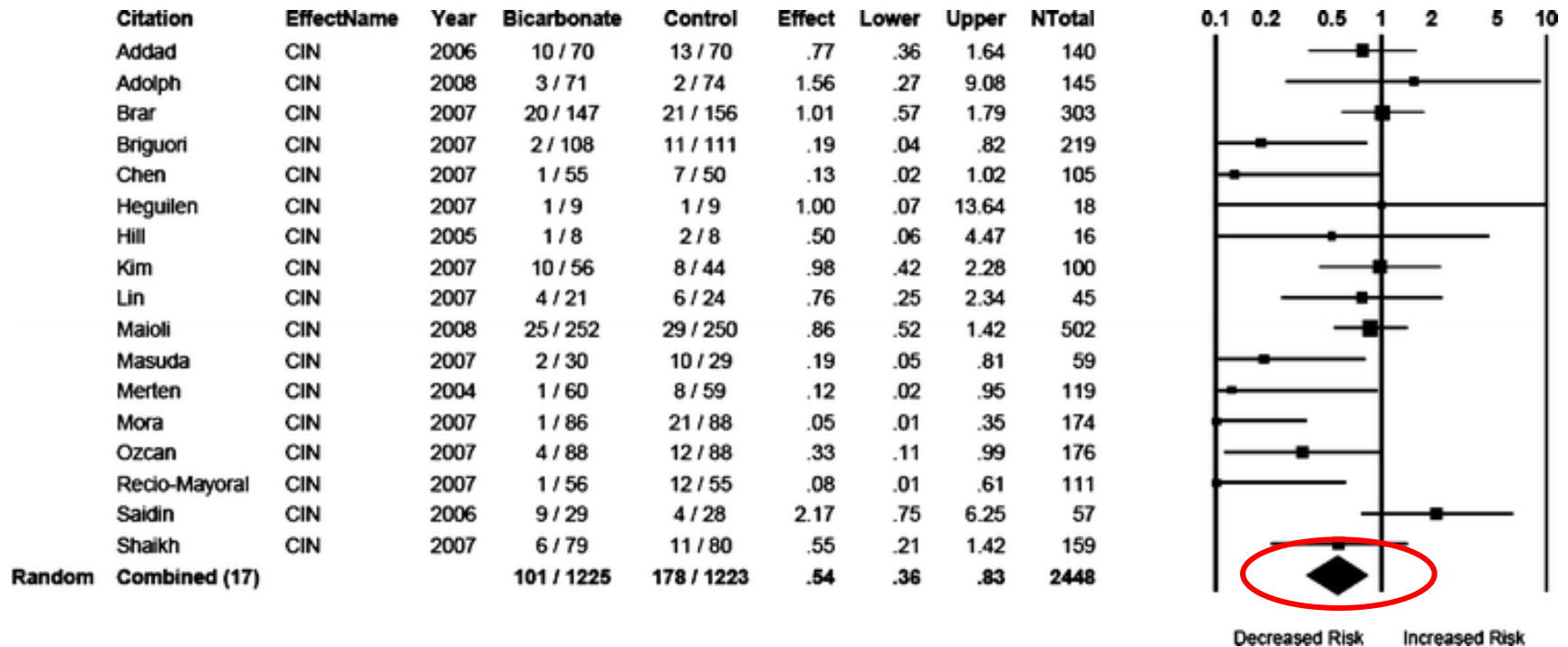
# Sodium Bicarbonate Versus Saline for the Prevention of Contrast-Induced Nephropathy in Patients With Renal Dysfunction Undergoing Coronary Angiography or Intervention

502 patients with CrCl<60ml/min undergoing PCI, randomized to saline+NAC or bicarbonate+NAC



# Sodium bicarbonate for the prevention of contrast-induced nephropathy: a meta-analysis of 17 randomized trials

17 trials (2,448 patients) OR 0.54 (95% CI, 0.36–0.83)



# Sodium bicarbonate-based hydration prevents contrast-induced nephropathy: a meta-analysis

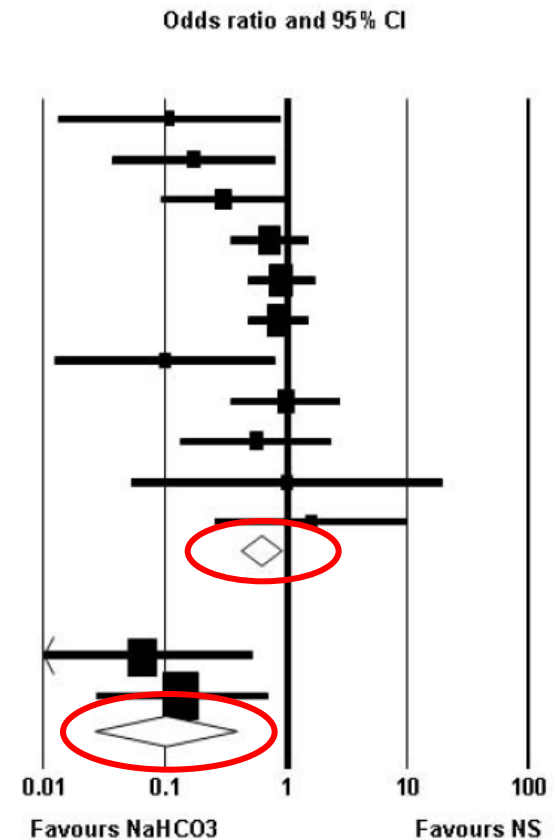
17 trials (2,633 patients) OR 0.52 (95% CI, 0.34–0.80; P=0.003)

Study	Statistics for each study				CIN / Total	
	OR	95% CI	p-Value	NaHCO3	NS	
Elective procedures	Merten	0.11	0.01 0.89	0.039	1 / 60	8 / 59
	REMEDIAL	0.17	0.04 0.79	0.024	2 / 108	11 / 111
	Ozcan	0.30	0.09 0.97	0.045	4 / 88	12 / 88
	Shaikh	0.72	0.35 1.49	0.380	14 / 159	19 / 161
	Brar	0.90	0.48 1.69	0.745	21 / 158	24 / 165
	Maioli	0.85	0.49 1.50	0.586	25 / 250	29 / 252
	Tamura	0.10	0.01 0.80	0.030	1 / 72	9 / 72
	Kim	0.98	0.35 2.73	0.967	10 / 56	8 / 44
	Lin	0.56	0.14 2.28	0.414	4 / 40	5 / 30
	Heguilen	1.00	0.05 18.91	1.000	1 / 9	1 / 9
	REINFORCE	1.59	0.26 9.80	0.618	3 / 71	2 / 74

**Summary elective procedures 0.63 0.43 0.92 0.017**

Emergency procedures	RENO	0.07	0.01 0.52	0.010	1 / 56	12 / 55
	Masuda	0.14	0.03 0.69	0.016	2 / 30	10 / 29

**Summary emergency procedures 0.10 0.03 0.39 0.001**



# Effects of Hydration in Contrast-Induced Acute Kidney Injury After Primary Angioplasty

## A Randomized, Controlled Trial

	Control Group (n=150)	Late Hydration Group (n=150)	Early Hydration Group (n=150)	P Value for Trend
Primary and secondary end points				
Serum creatinine increase by $\geq 0.5$ mg/dL and/or by $\geq 25\%$ within 72 h, n (%)	41 (27.3)*	34 (22.7)†	18 (12.0)*†	0.001

**Control group:** no hydration

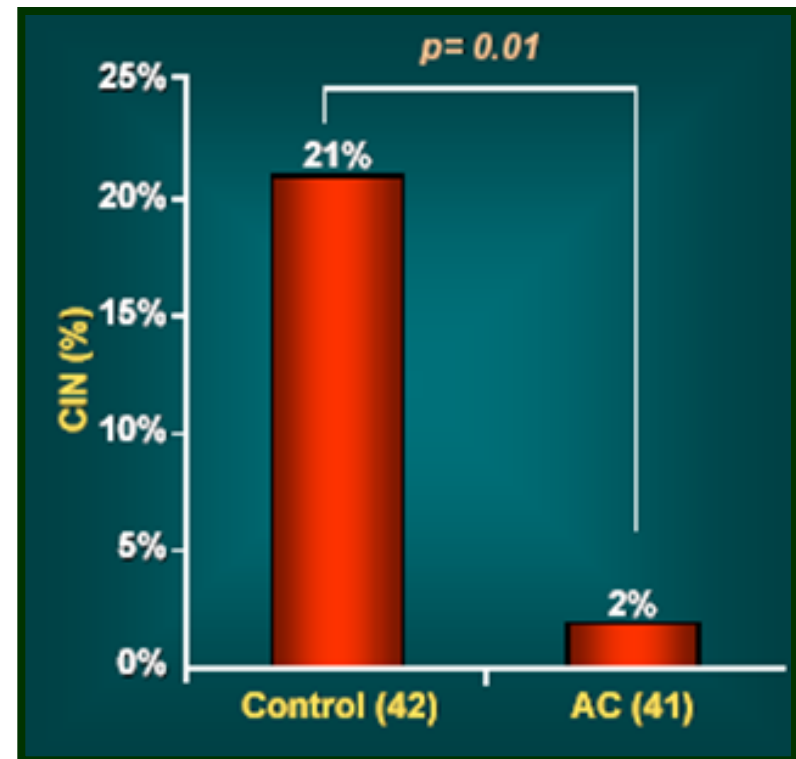
**Late hydration group:** isotonic saline (1 ml/kg/h) for 12 hours after PCI

**Early hydration group:** a bolus of 3 ml/kg of sodium bicarbonate solution in 1 hour, starting in the emergency room, followed by infusion of 1 ml/kg/hr for 12 hours after PCI.

# PREVENTION OF RADIOGRAPHIC-CONTRAST-AGENT-INDUCED REDUCTIONS IN RENAL FUNCTION BY ACETYLCYSTEINE

Antioxidant agent that improves renal hemodynamics and may prevent direct oxidative tissue damage

- ❑ Prospective randomized trial
- ❑ 83 high-risk patients:
  - ❑ CrCl <50 ml/min
  - ❑ Diabetes 33%
  - ❑ IV contrast for CT (75 ml of low-osmolar CM)
  - ❑ NAC 600 mg bid x 2 days
  - ❑ Hydration with 0.45% 1 ml/kg/h x 24 h
  - ❑ CIN definition: sCr >0.5 mg/dl





# Meta-analyses of NAC for CIN Prevention Trials

Source	Procedure	Type of Study	No. of Trials	No. of Patients	Heterogeneity (p value)	Pooled Estimate (95% CI)	Author Conclusions
Birk et al..	CT or angiography	A	7	805	Present (p=.02)	RR, 0.44 (0.22-0.88)	<u>Beneficial</u>
Isenbarger et al.	CT or angiography	A	7	805	Present (p=.01)	OR, 0.37 (0.16-0.84)	<u>Beneficial</u>
Alonso et al.	CT or angiography	A, B	8	805	Not reported	RR, 0.41 (0.22-0.79)	<u>Beneficial</u>
Kshirsager et al.	CT or angiography	A, B	16	1538	Present (p<.001)	Not reported	<u>Inconclusive</u>
Pannu et al.	CT or angiography	A, B, D	15	1776	Present (p=.02)	RR, 0.65 (0.43-1.0)	<u>Inconclusive</u>
Guru and Fremes	CT or angiography	A, C	11	1213	Present (p=.01)	OR, 0.46 (0.32-0.66)	<u>Beneficial</u>
Bagshaw and Ghail	Angiography	A	14	1261	Present (p=.03)	OR, 0.54 (0.32-0.91)	<u>Inconclusive</u>
Misra et al.	Angiography	A	5	643	Present (p=.05)	RR, 0.30 (0.11-0.82)	<u>Beneficial</u>
Nallamotheu et al.	CT or angiography	A, D	20	2195	Present (p=.01)	RR, 0.73 (0.52-1.0)	<u>Inconclusive</u>
Liu et al.	CT or angiography	A, B	9	1028	Present (p=.03)	RR, 0.43 (0.24-0.75)	<u>Beneficial</u>
Duong et al.	CT or angiography	A, C	14	1584	Present (p=.01)	RR, 0.57 (0.37-0.84)	<u>Beneficial</u>

A= RCT (articles), B= RCT (abstracts), C= NRT (articles), D= unpublished

# NAC for CIN Prevention

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- ❑ Disparate conclusions, with 7 meta-analyses finding a beneficial effect and 4 demonstrating inconclusive results
- ❑ This may partially reflect differences in:
  - ❑ Patient population,
  - ❑ renal dysfunction severity,
  - ❑ number of additional risk factors,
  - ❑ clinical setting,
  - ❑ Type of invasive procedure,
  - ❑ hydration protocols,
  - ❑ type and volume of contrast agent,
  - ❑ definition of CIN,
  - ❑ wide range of oral or i.v. dosage of NAC.

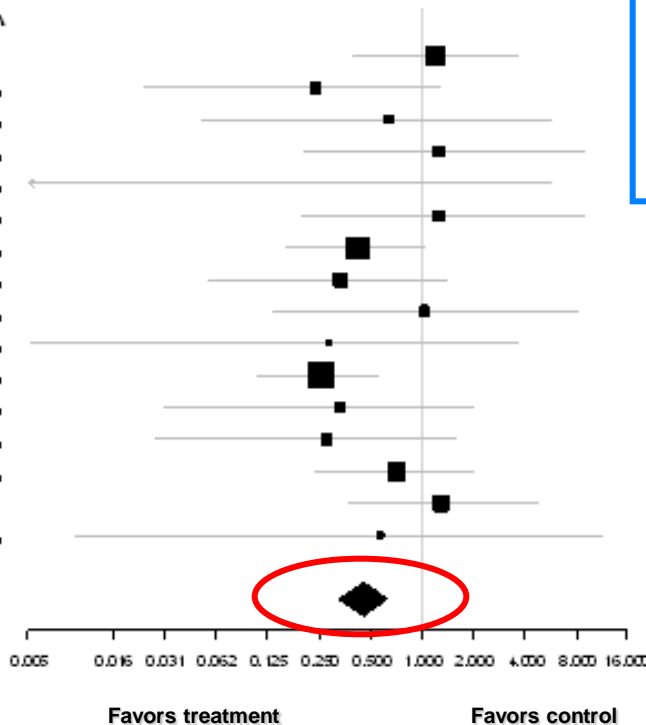
# High-dose N-acetylcysteine for the Prevention of Contrast-induced Nephropathy

Hariprasad Trivedi, MD,<sup>a</sup> Sumanth Daram, MD,<sup>b</sup> Aniko Szabo, PhD,<sup>c</sup> Antonio L. Bartorelli, MD,<sup>d</sup> Giancarlo Marenzi, MD<sup>d</sup>

OR of 0.46 (95% CI: 0.33 0.63, P<0.0001) for the occurrence of CIN with the use of high-dose NAC (daily dose greater than 1200 mg or single peri-procedural dose within 4 hours of contrast exposure greater than 600 mg)

## Incidence of CIN

Study	Total N	Control <sup>^</sup>	NAC <sup>^</sup>
Durham (2002)	79	22.0%	26.3%
Baker (2003)	80	20.5%	4.9%
Kefer (2003)	104	5.9%	3.8%
Oldemeyer (2003)	96	6.4%	8.2%
Efrati (2003)*	49	8.0%	0.0%
Goldenberg (2004)	80	7.7%	9.8%
Miner (2004)	180	22.4%	9.5%
Ochoa (2004)	80	25.0%	8.3%
Rashid (2004)	94	6.2%	6.5%
Balderramo (2004)	61	10.7%	3.0%
Marenzi (2006)	237	32.8%	8.5%
Khalili (2006)	70	17.1%	5.7%
Poletti (2007)	87	16.3%	4.5%
Shaikh (2007)	161	13.8%	9.9%
Shaikh (2007)	159	7.6%	10.0%
Heng (2007)	60	6.2%	3.6%



- 16 studies, 1677 pts
- Most patients with CKD
- High-dose NAC in 842 pts
- Control arm: 835 pts

## Summary

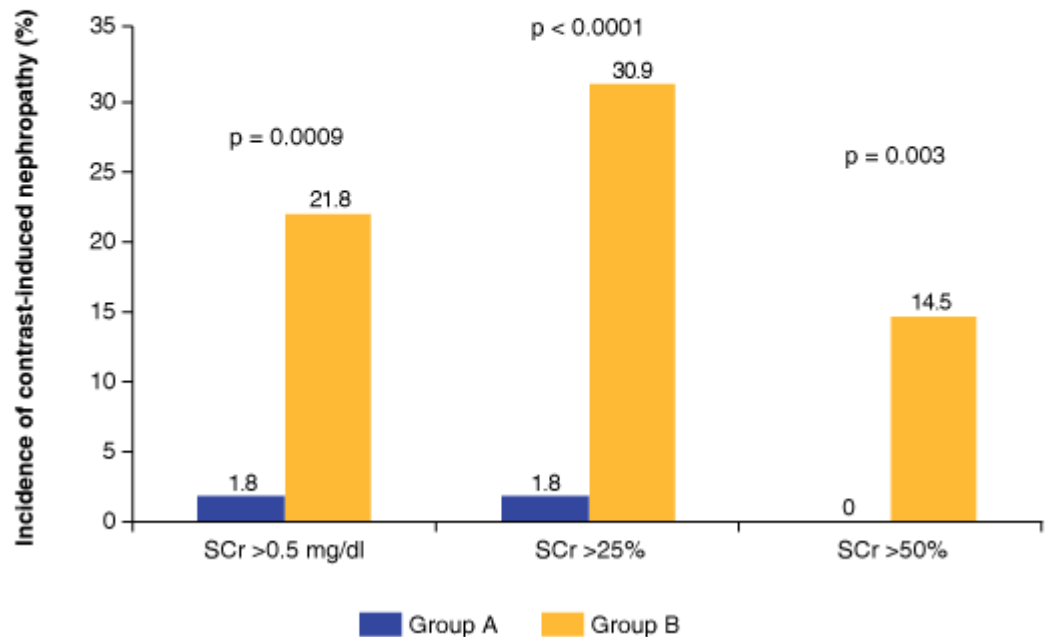
<sup>^</sup>Incidence of CIN

# The Reno-Protective Effect of Hydration With Sodium Bicarbonate Plus N-Acetylcysteine in Patients Undergoing Emergency Percutaneous Coronary Intervention

The RENO Study

- 111 ACS pts
- Group A (n=56) received infusion of sodium bicarbonate plus NAC started just before CM injection and continued for 12h after PCI
- Group B (n=55) received isotonic saline for 12h after PCI
- In both groups, oral NAC was given after PCI

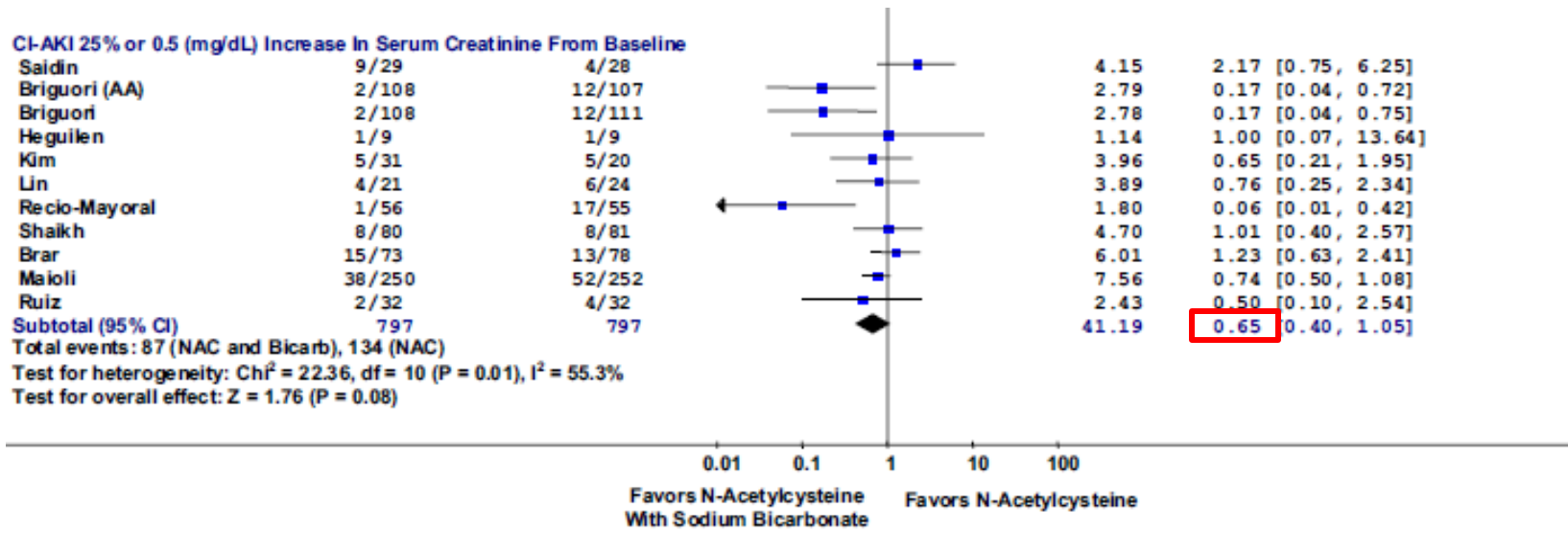
Incidence of Contrast-Induced Nephropathy Based on the Criteria Used in RENO



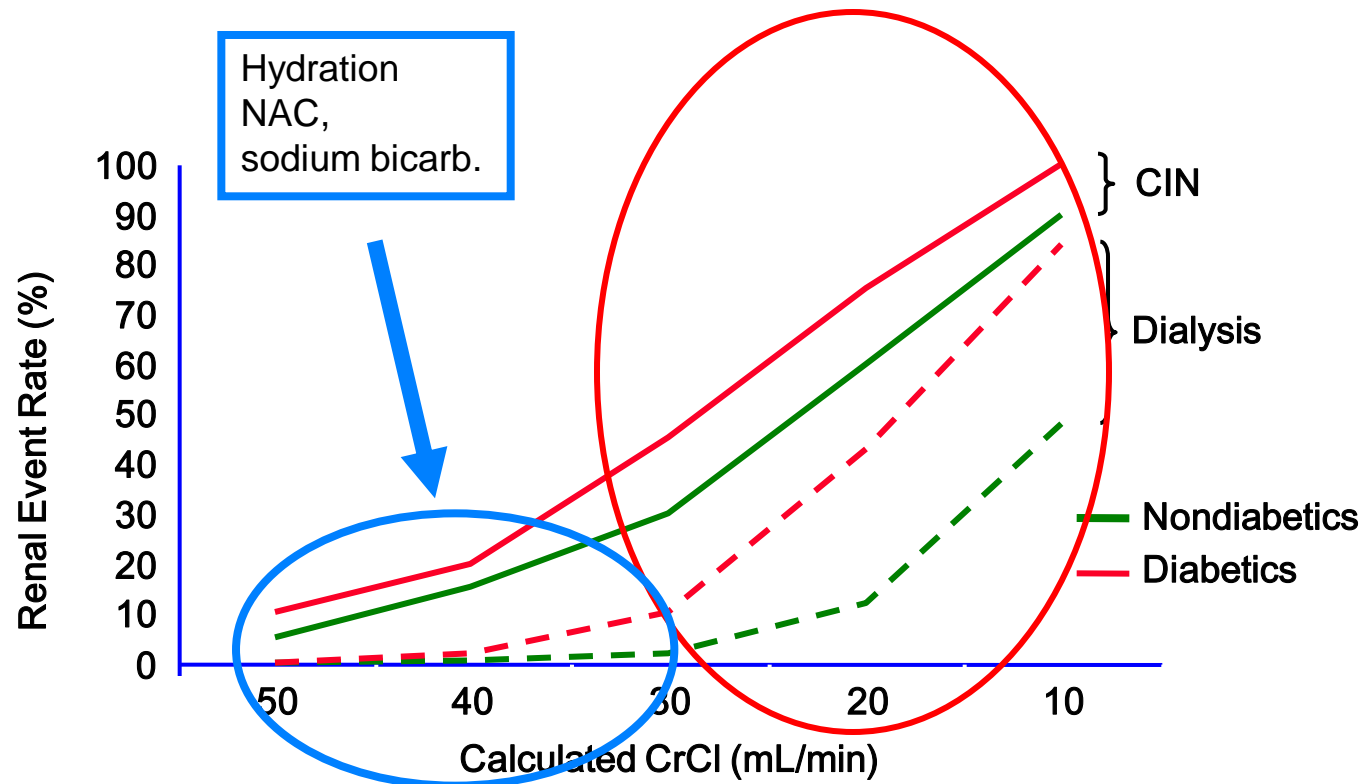
# Sodium Bicarbonate Plus N-Acetylcysteine Prophylaxis

## A Meta-Analysis

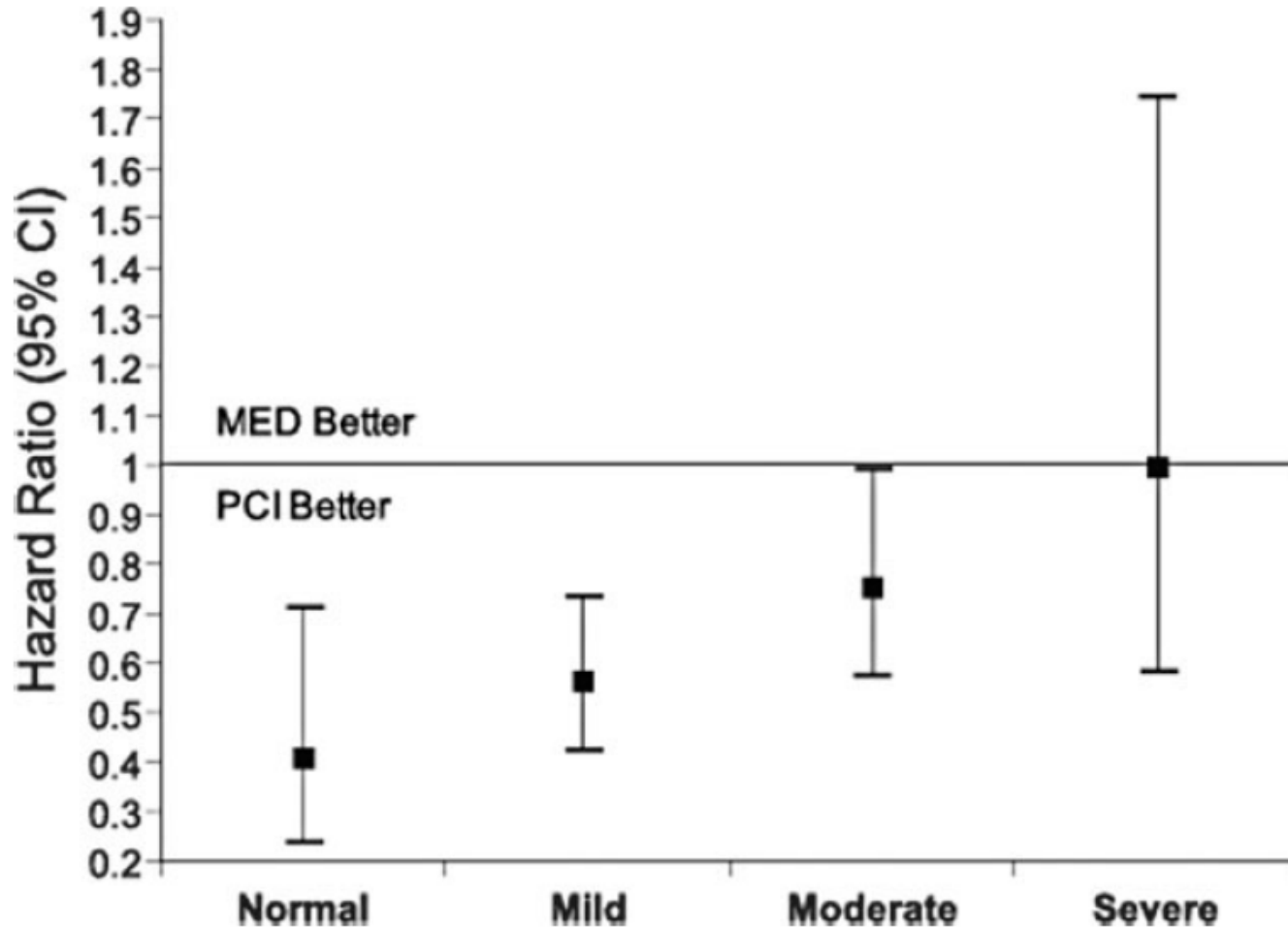
### Contrast-induced nephropathy



# Prediction of CIN and Dialysis After PCI



# Hazard Ratios for Mortality as a Function of Renal Function in Patients Treated Medically or with PCI (Registry data over a 5-year period)



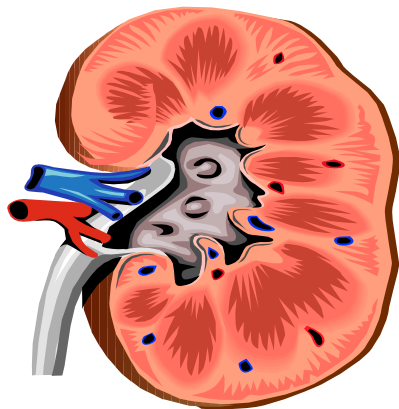
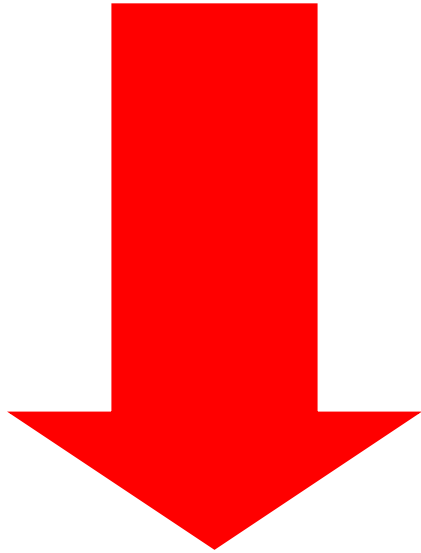
# Rationale for Renal Replacement Therapies (RRT) in CIN Prevention

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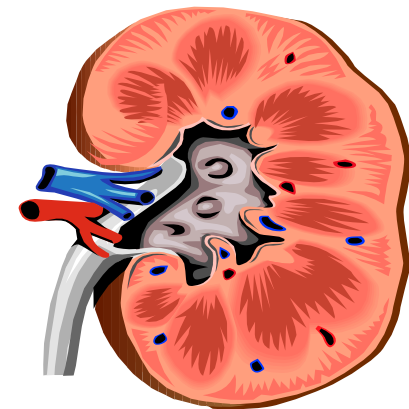
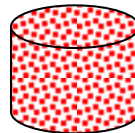
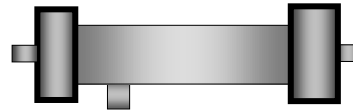
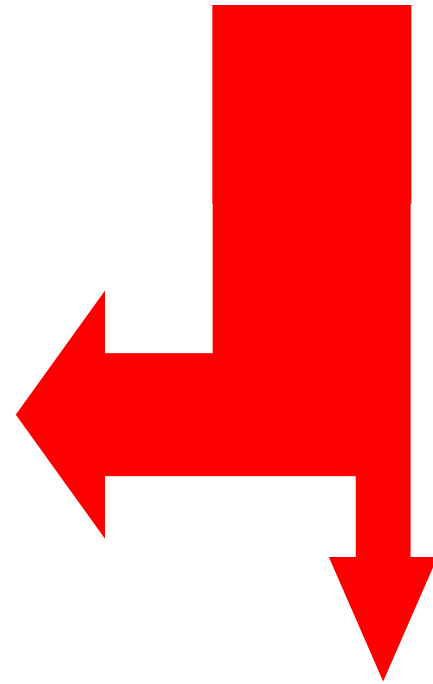
- ❑ Contrast media are mainly excreted by glomerular filtration.
- ❑ Effective contrast removal by the artificial membranes used with RRTs, through a process similar to spontaneous glomerular filtration, has been demonstrated in renal failure patients (*Schindler R, et al. Nephrol Dial Transplant 2001;16:1471*)

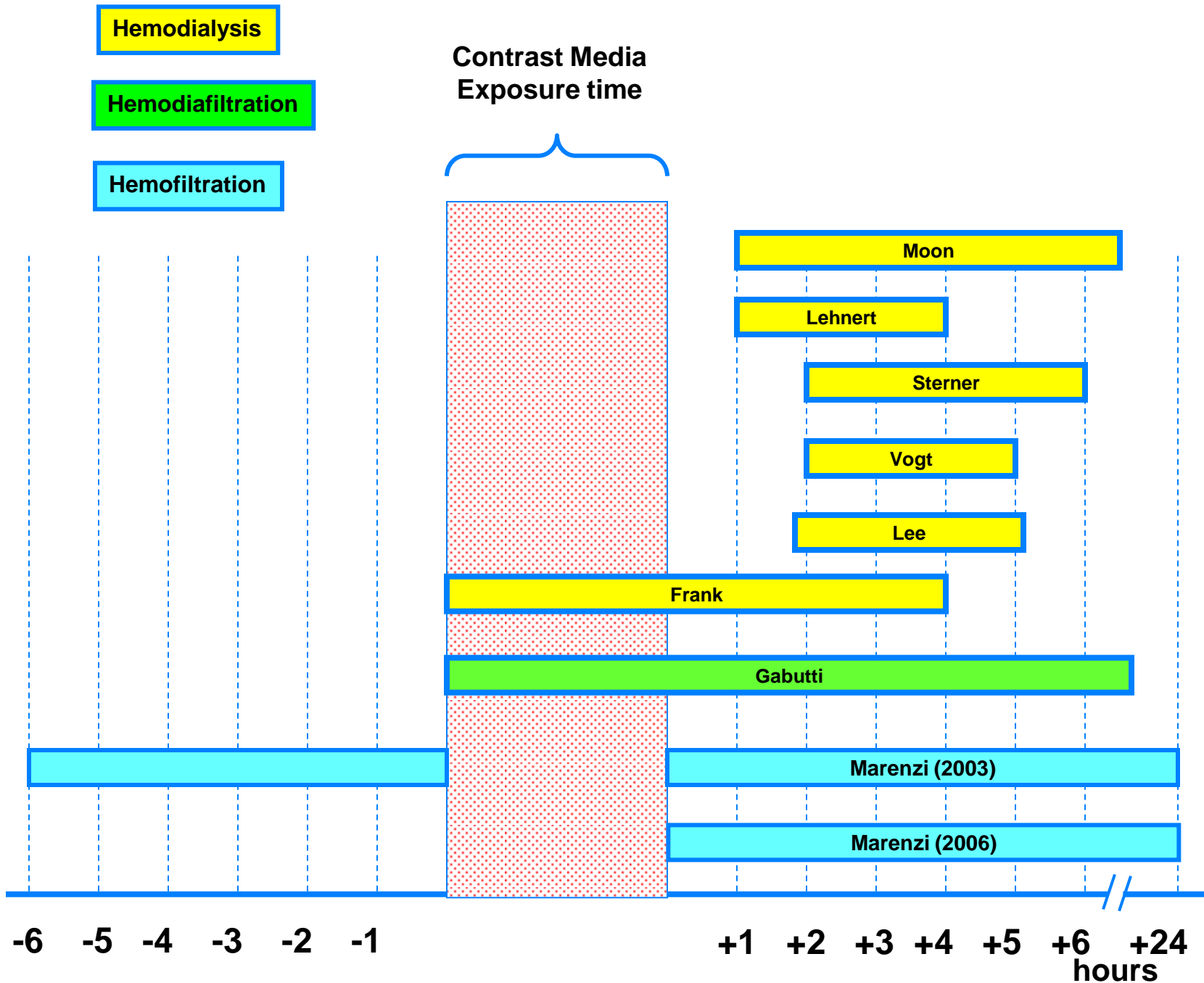


**Contrast**



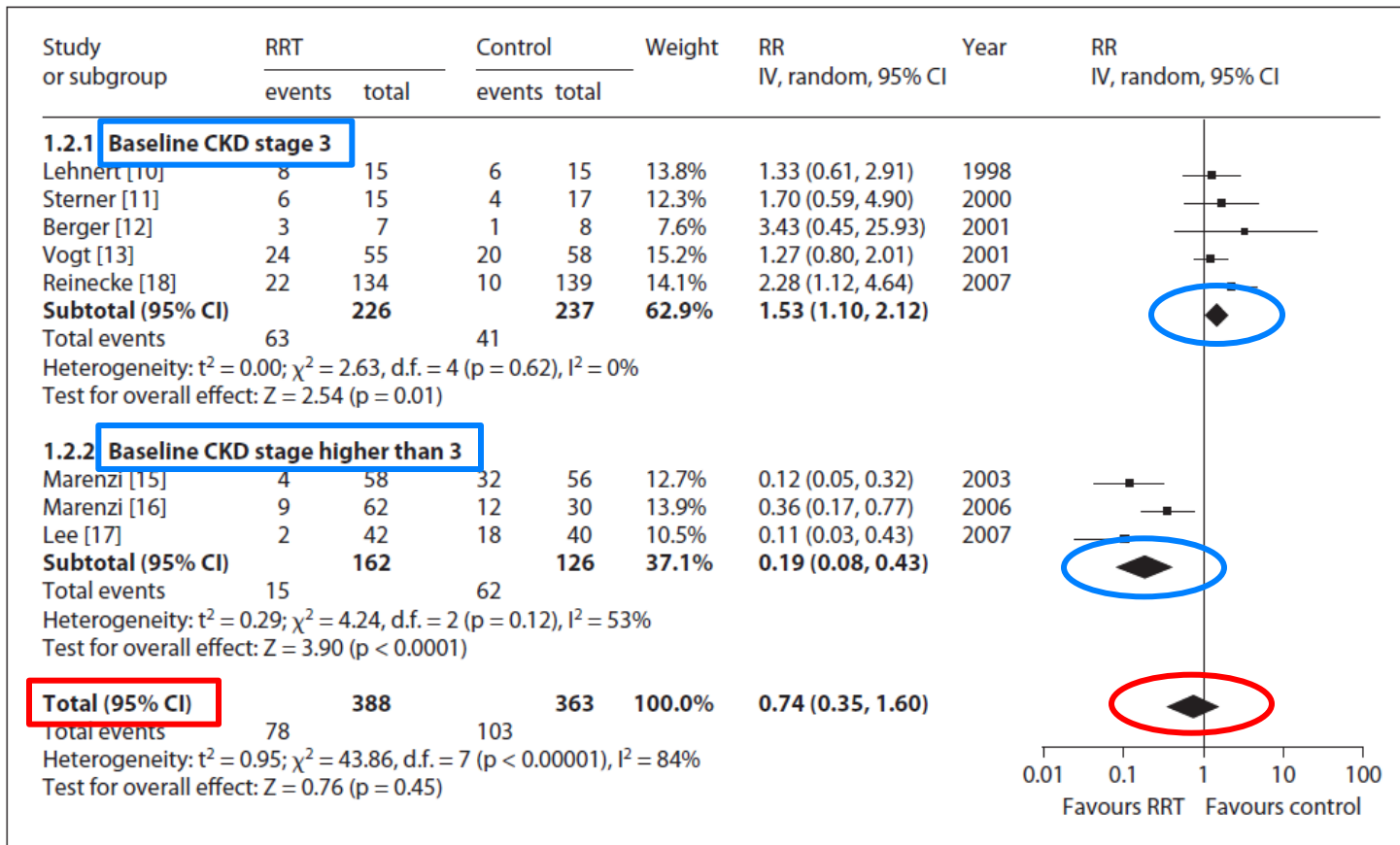
**Contrast**





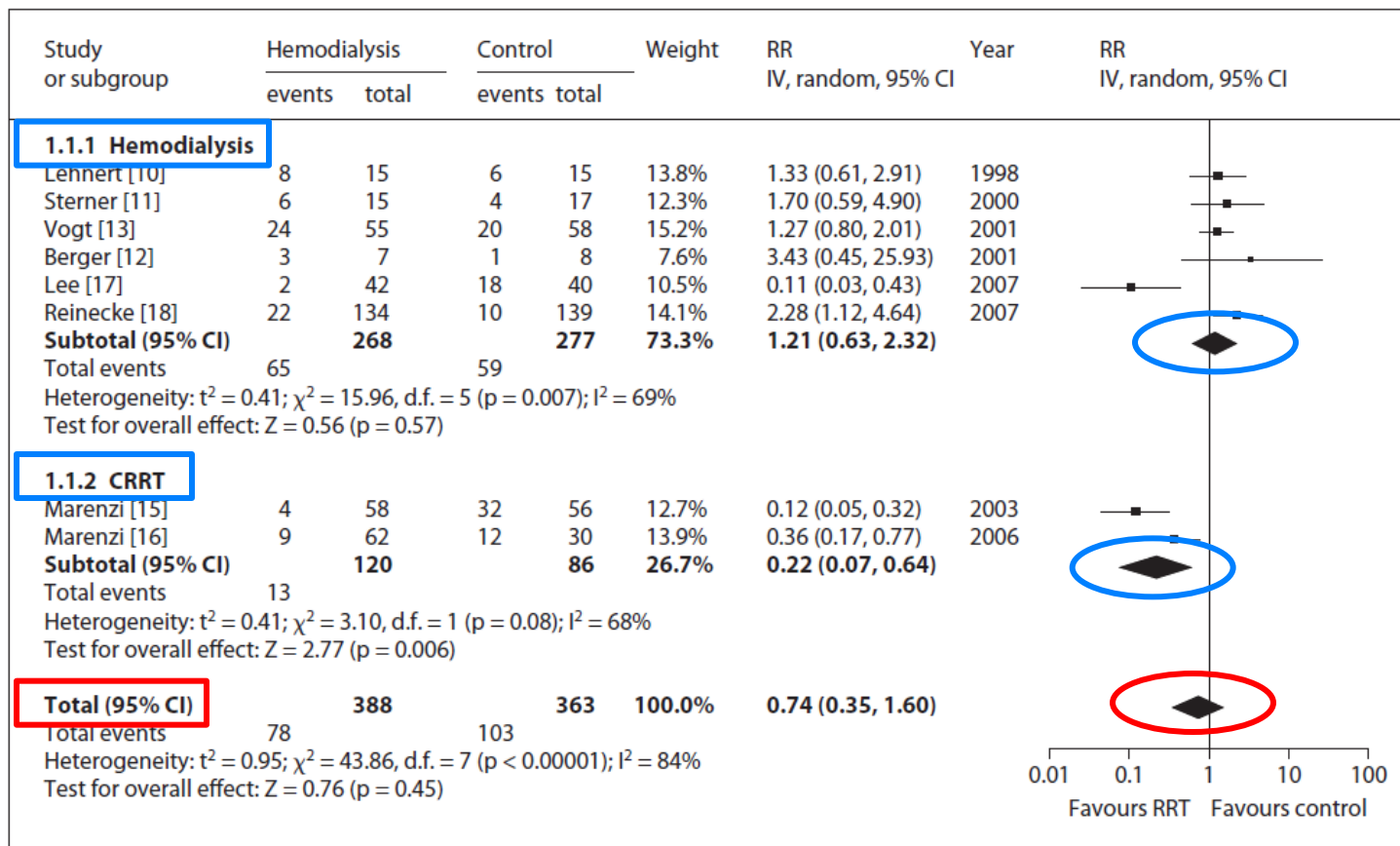
# Renal Replacement Therapy for Prevention of Contrast-Induced Acute Kidney Injury: A Meta-Analysis of Randomized Controlled Trials

## Effect of baseline CKD stage on CIN



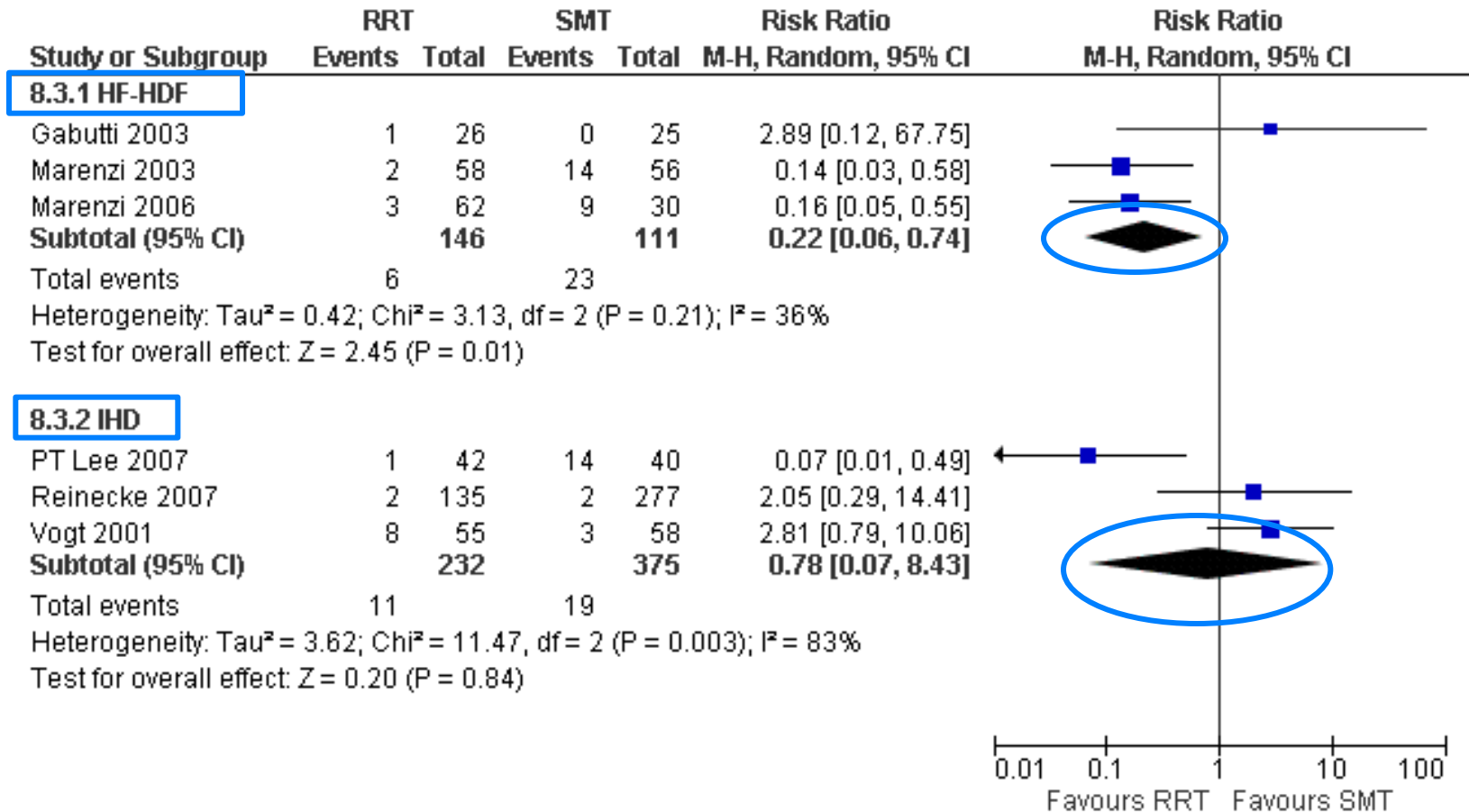
# Renal Replacement Therapy for Prevention of Contrast-Induced Acute Kidney Injury: A Meta-Analysis of Randomized Controlled Trials

## Effect of modality of RRT on CIN



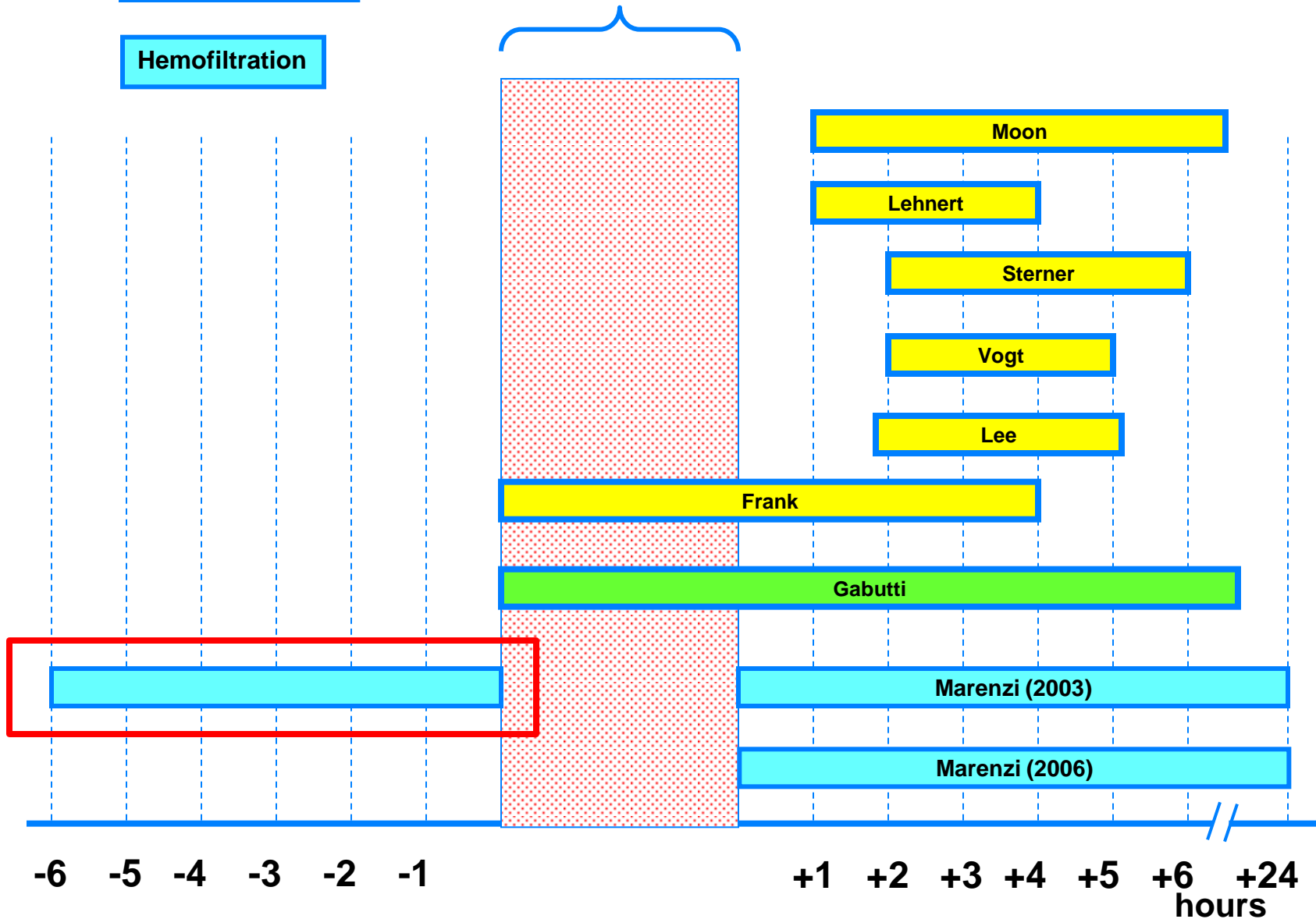
# Renal replacement therapies for prevention of radiocontrast-induced nephropathy. A systematic review.

Risk for acute RRT: Renal Replacement Therapy vs Standard Medical Therapy, by RRT modality



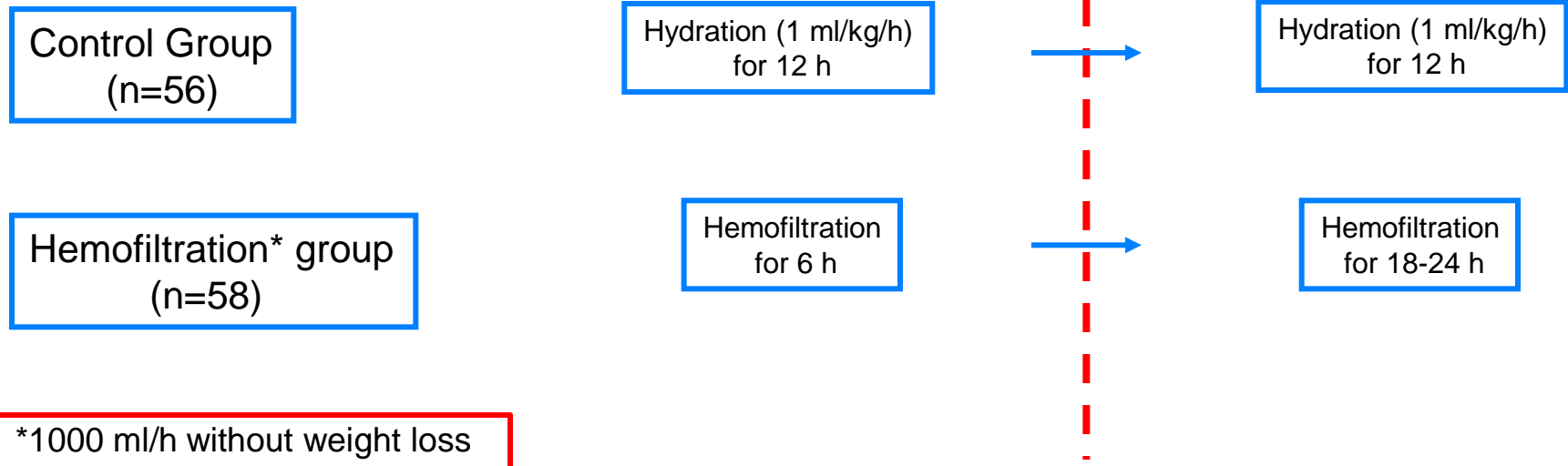
- Hemodialysis
- Hemodiafiltration
- Hemofiltration

Contrast Media Exposure time



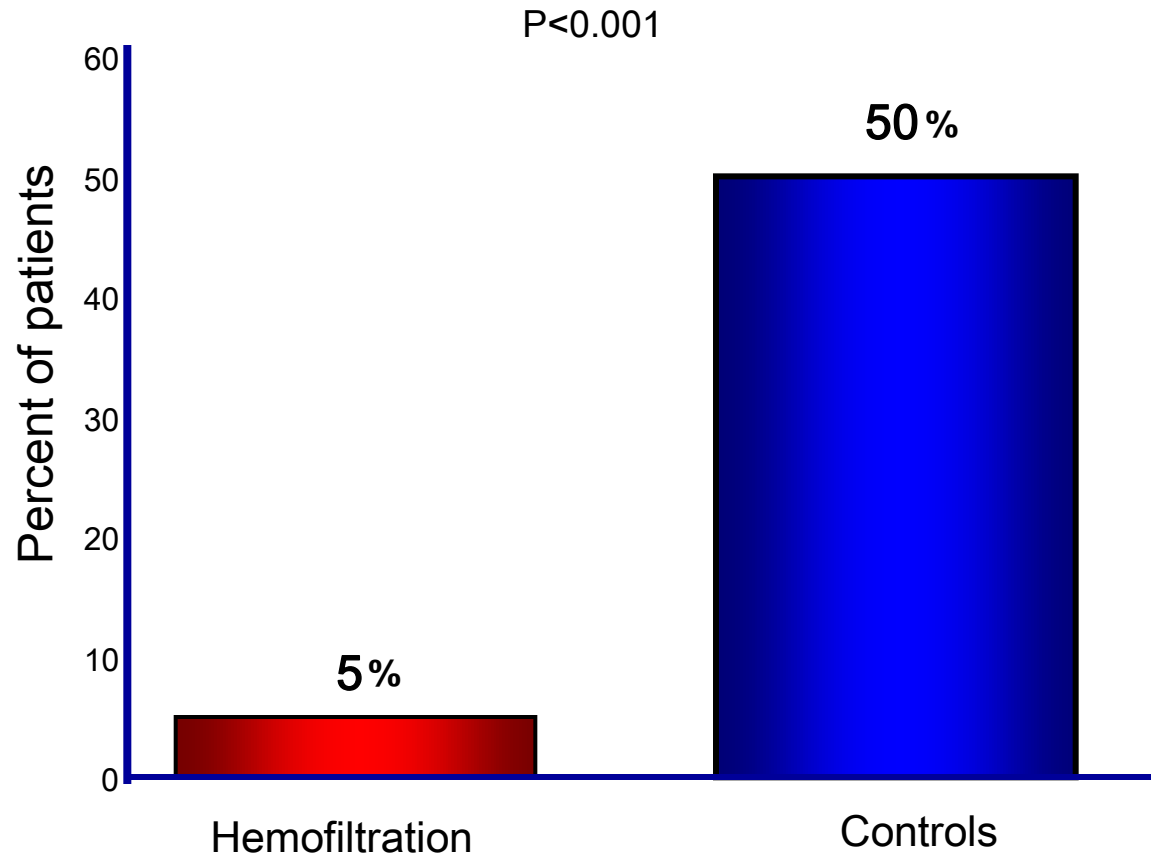
# The Prevention of Radiocontrast-Agent-Induced Nephropathy by Hemofiltration

114 pts with CKD (creatinine > 2.0 mg/dl)  
scheduled for elective angiographic procedures



# Hemofiltration to Prevent CIN

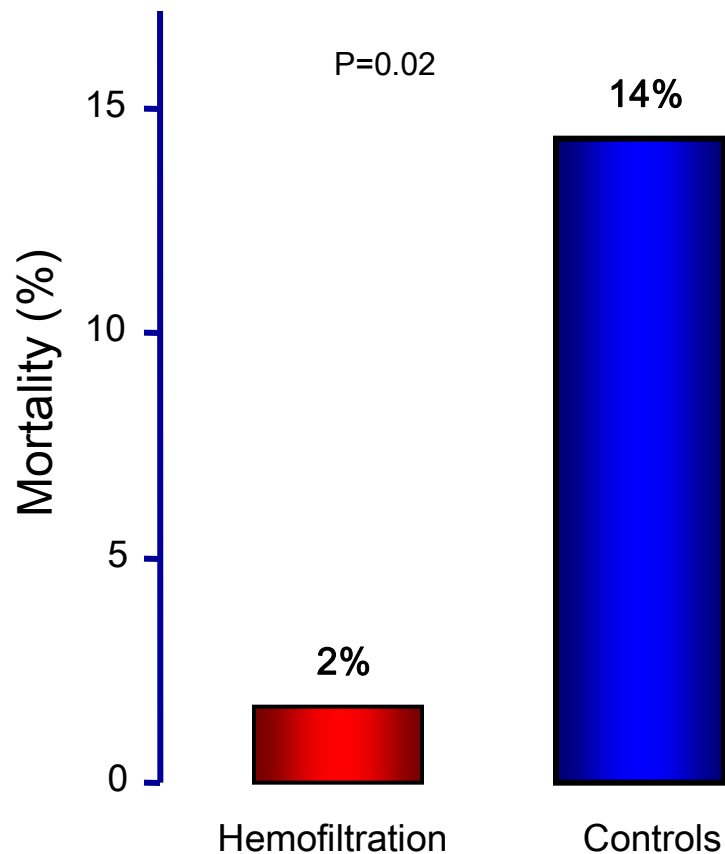
Incidence of CIN



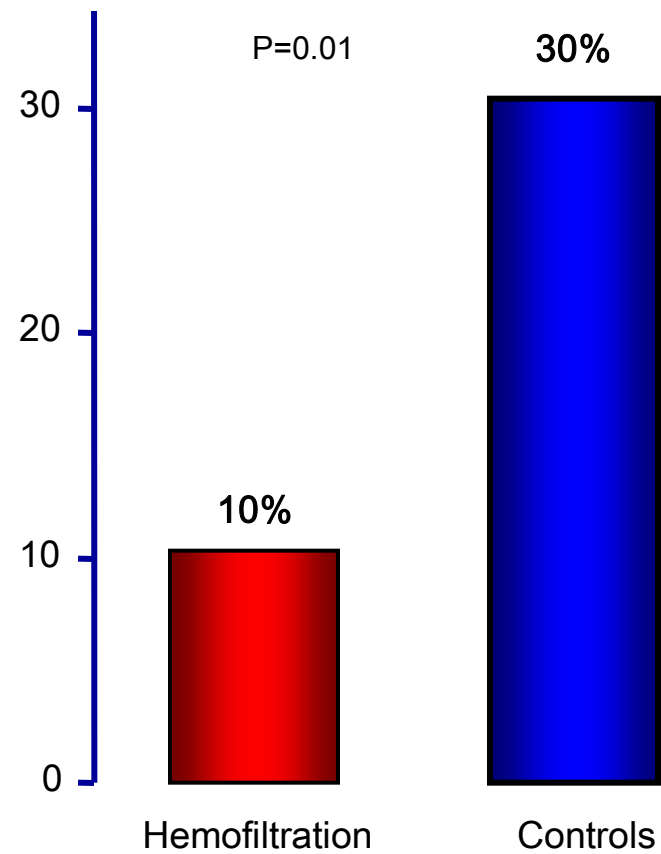


# The Prevention of Radiocontrast-Agent-Induced Nephropathy by Hemofiltration

In-hospital mortality



One-Year  
(cumulative)



# Guidelines on myocardial revascularization

The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

**Table 17** Recommendations for prevention of contrast-induced nephropathy

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Use of LOCM or IOCM is recommended.	<350 mL or <4 mL/kg	I <sup>d</sup>	A <sup>d</sup>	124, 131–133
<b>Patients with severe CKD</b>				
Prophylactic haemofiltration 6 h before complex PCI should be considered.	Fluid replacement rate 1000 mL/h without weight loss and saline hydration, continued for 24 h after the procedure.	IIa	B	134, 135
Elective haemodialysis is not recommended as a preventive measure.		III	B	136

# Furosemide and Matched Hydration

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- ❑ Furosemide administration may have some positive effects when associated with hydration.
  - ❑ It enhances contrast dilution in the renal tubule through increased urine flow.
  - ❑ it blocks tubular sodium reabsorption in the medulla and, as a consequence, reduces tubular workload and concomitant oxygen requirement at a time when contrast is expected to decrease medullary oxygen delivery.
  - ❑ it may reduce renal vascular resistance, increasing renal blood flow
  - ❑ it prevents fluid overload, reducing the risk of heart failure.
- ❑ On the other hand, these positive actions may be thwarted by furosemide-induced reduction of the effective circulating volume
- ❑ Indeed, previous clinical studies demonstrated that the net effect of prophylactic furosemide seems to be an increased CIN rate.

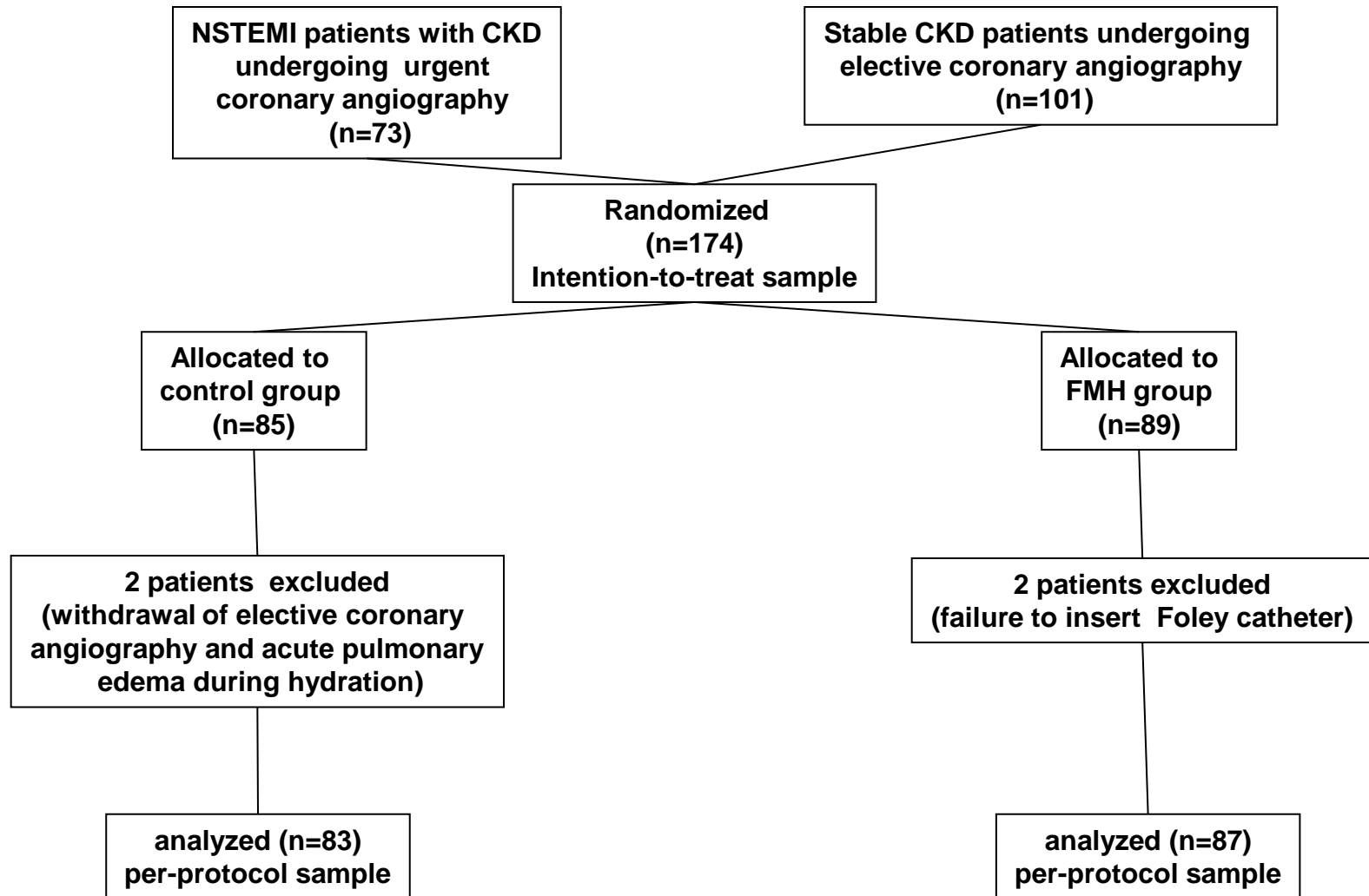
# The RenalGuard System

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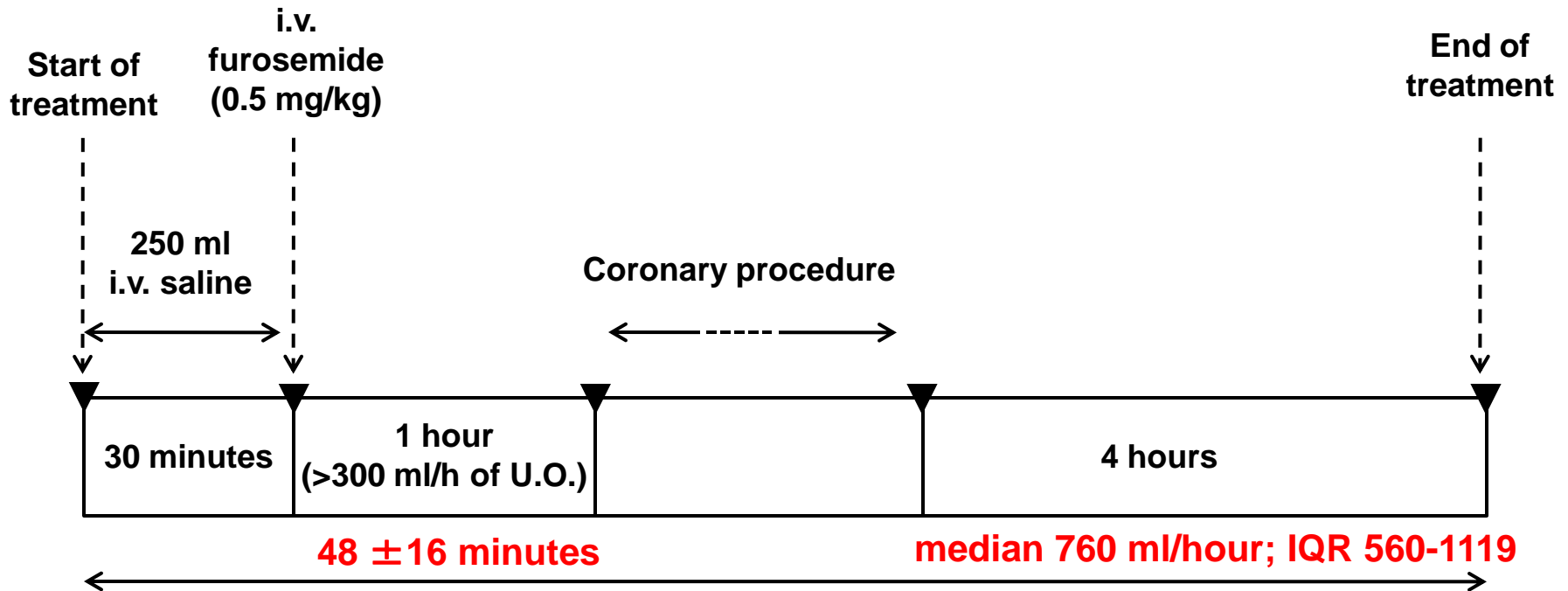
- ❑ RenalGuard therapy is designed to:
  - ❑ Automatically match i.v. fluid replacement to urine volume in real-time during furosemide-induced forced diuresis
  
- ❑ This treatment may:
  - ❑ Reduce the risk of over- or under-hydration
  - ❑ Dilute contrast agent in the renal tubules
  - ❑ Limit kidneys exposure to contrast agent



# The MYTHOS trial

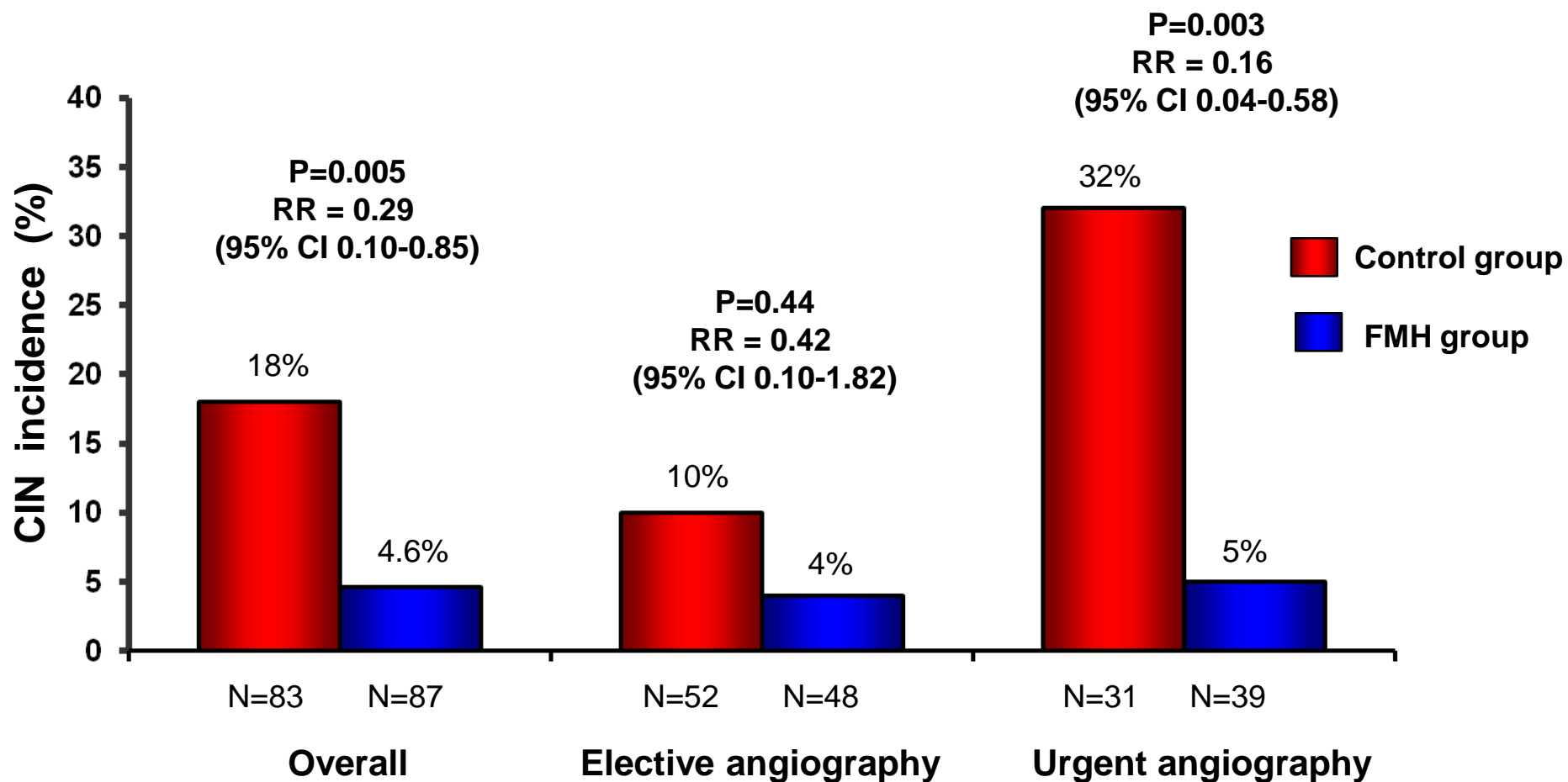


# The MYTHOS trial



Continuous infusion of isotonic saline solution matched with urine output

# The MYTHOS trial



# The MYTHOS trial

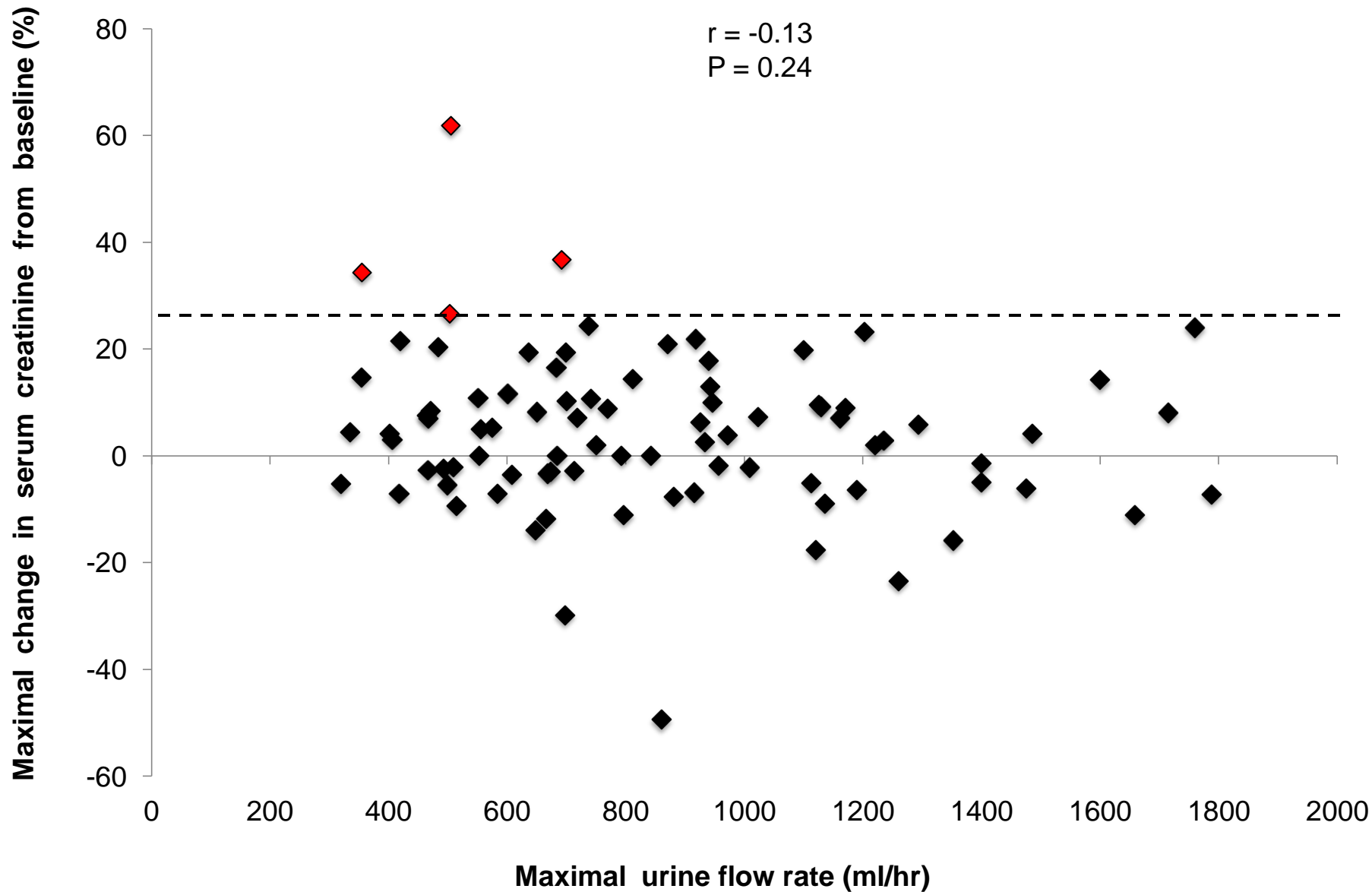
## Post-procedural complications.

	FMH group (n=87)	Control group (n=83)	P value
CIN requiring RRT, n (%)	1 (1.1%)	3 (4%)	0.29*
Acute myocardial infarction, n (%)	0 (0%)	1 (1.2%)	0.30*
AF/VT, n (%)	1 (1.1%)	2 (2.4%)	0.53*
Emergency CABG, n (%)	0 (0%)	0 (0%)	-
Acute pulmonary edema, n (%)	5 (6%)	10 (12%)	0.15*
Hypotension/shock, n (%)	0 (0%)	0 (0%)	-
In-hospital death, n (%)	1 (1.1%)	3 (4%)	0.29*
Patients with $\geq 2$ events, n (%)	1 (1.1%)	3 (4%)	0.29*
All clinical events (per protocol), n (%)	7 (8%)	15 (18%)	0.052
All clinical events (intention to treat), n (%)	7 (8%)	17 (20%)	0.02

AF = atrial fibrillation; CABG = coronary artery bypass graft surgery; CIN = contrast-induced nephropathy; FMH = furosemide-induced diuresis with matched hydration; RRT = renal replacement therapy, VT = ventricular tachycardia.

\*By Fisher exact test.





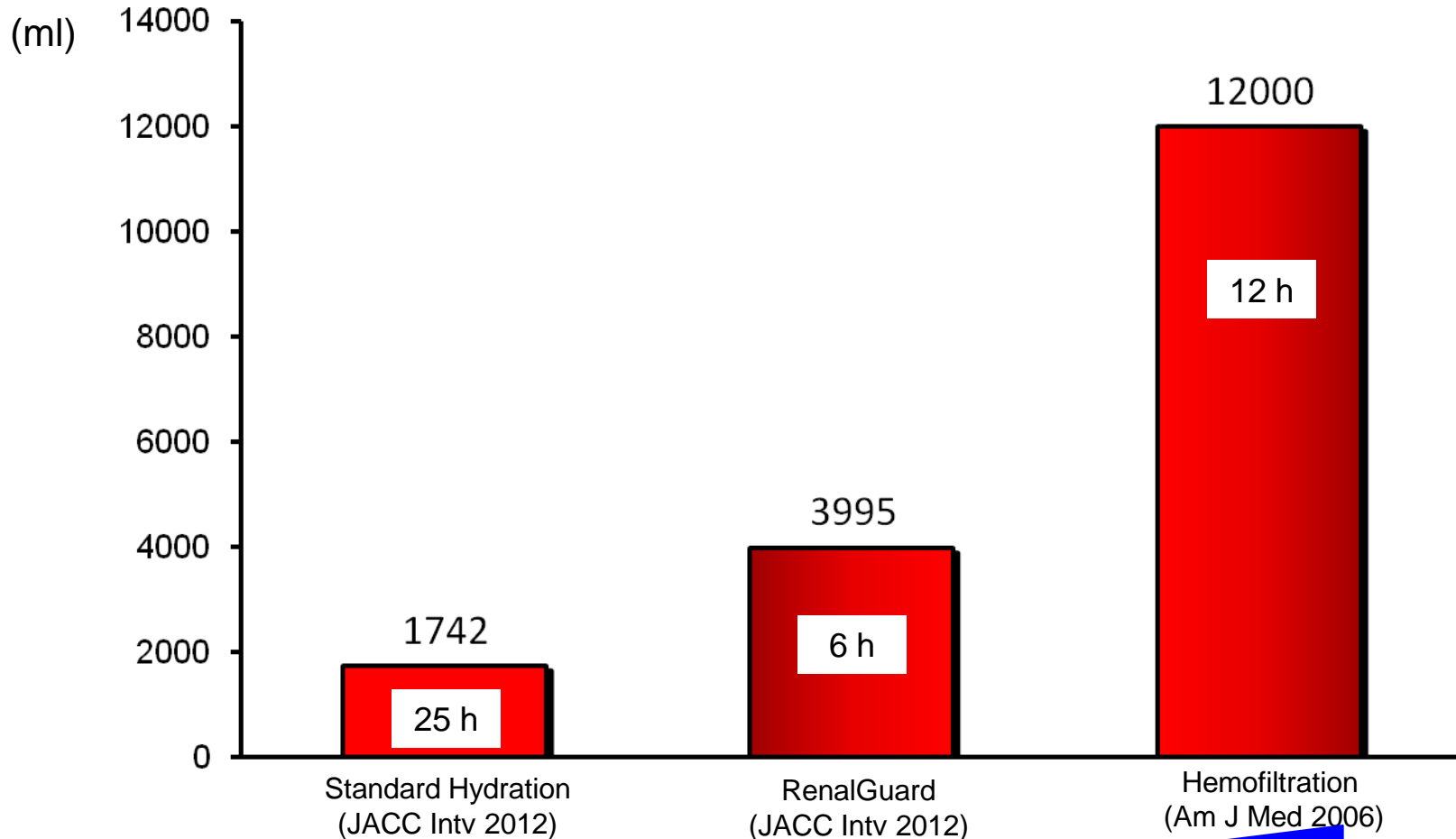
# Furosemide and Matched Hydration

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  - ❑ It enhances contrast dilution in the renal tubule through increased urine flow.
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- ❑ On the other hand, these positive actions may be thwarted by furosemide-induced reduction of the effective circulating volume
- ❑ Indeed, previous clinical studies demonstrated that the net effect of prophylactic furosemide seems to be an increased CIN rate.
- ❑ Matched hydration allows for a high-volume (800 mL/hour as a average) controlled hydration.

# Cumulative i.v. saline hydration volume during the treatment period

eGFR (ml/min/1.73 m <sup>2</sup> )	38 ± 11	41 ± 10	18 ± 4
CIN incidence (%)	18%	5%	3%



# A new concept is emerging for CIN prevention

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- ❑ The hydration volume should be commensurate to the patient's risk
- ❑ A high volume (~1 L/hr) of controlled hydration is likely required in high-risk patients
- ❑ This goal can be achieved by:
  - ❑ Exactly matching fluid removal to i.v. hydration to prevent fluid overload (*Hemofiltration*)
  - ❑ Exactly matching i.v. hydration to urine output to avoid hypovolemia (*RenalGuard*)

# Conclusions

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- ❑ CIN represents a frequent complication of PCI, associated with increased morbidity and mortality.
- ❑ Patients with severe renal insufficiency, multiple risk factors, and those undergoing emergency/urgent PCI, have a “*very high risk*” of CIN
- ❑ Prophylactic measures should be routinely taken to avoid CIN in all patients
- ❑ New strategies should be developed in very high-risk patients, in order to prevent CIN and to reduce associated morbidity and mortality.