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Contrast and AKI

An Unsolved Dogma

Iranian Society of Nephrology
Tabriz, Iran
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Disclosures

- I have no conflict of interest with this activity

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Outlines

- Definition
- Origins of Dogma
- Management
- Final thoughts

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Definition and pathophysiology

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CA-AKI

Nomenclature and definition

- Nomenclature
  - Contrast-induced nephropathy (CIN)
  - Contrast-induced acute kidney injury (CI-AKI)
  - Contrast-associated acute kidney injury (CA-AKI)
  - Post-arteriogram acute kidney injury (PA-AKI)
  - Post-contrast acute kidney injury (PC-AKI)

- Definition
  - Increase in SCr within 48-72 hours post-contrast.
    - Relative increase (25%,50%) or absolute increase (0.3 mg/dL, 0.5 mg/dL).
  - Usually non-oliguric.
  - SCr typically returns to baseline by 7-10 days

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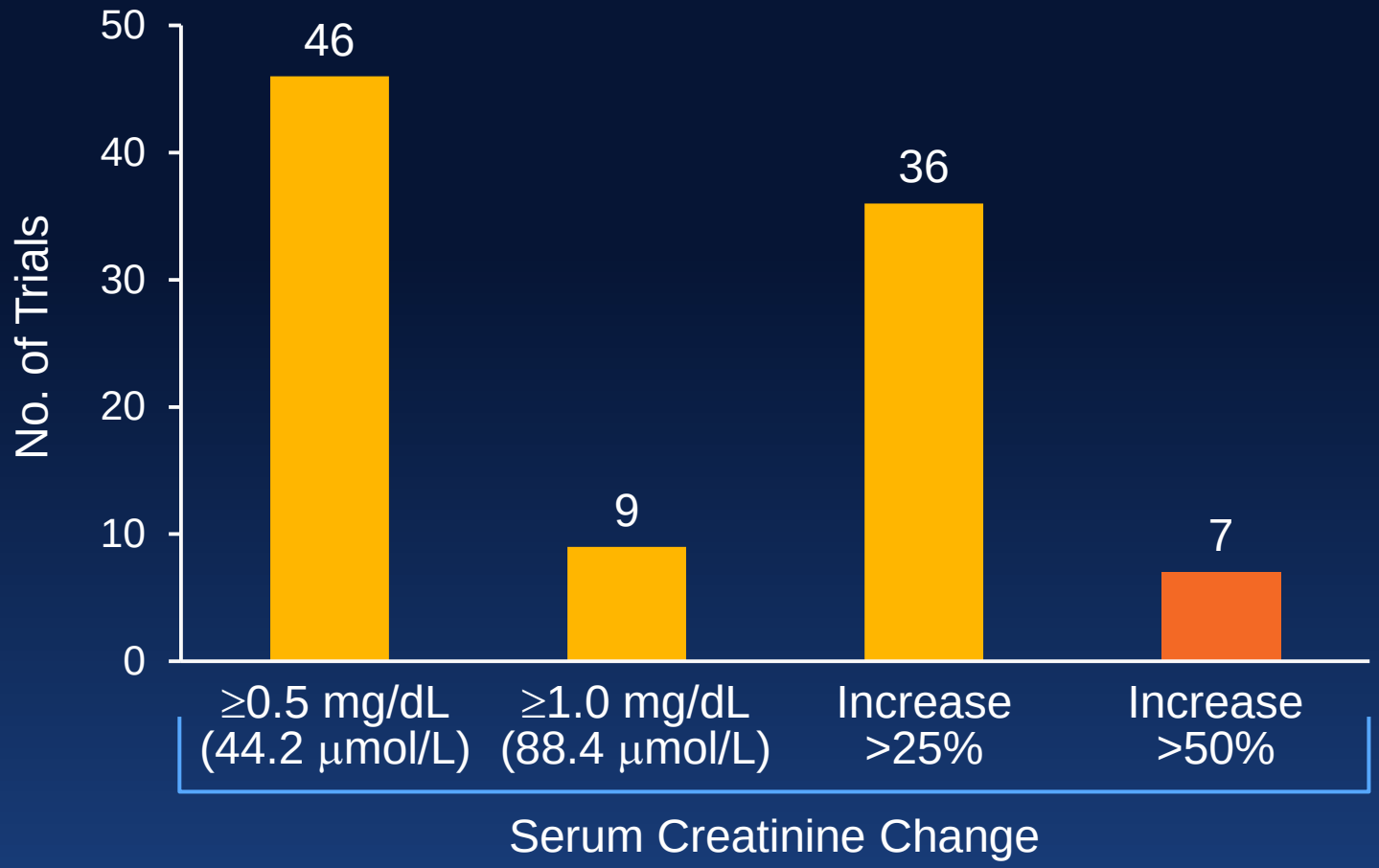
CA-AKI

Definition in Clinical Trials



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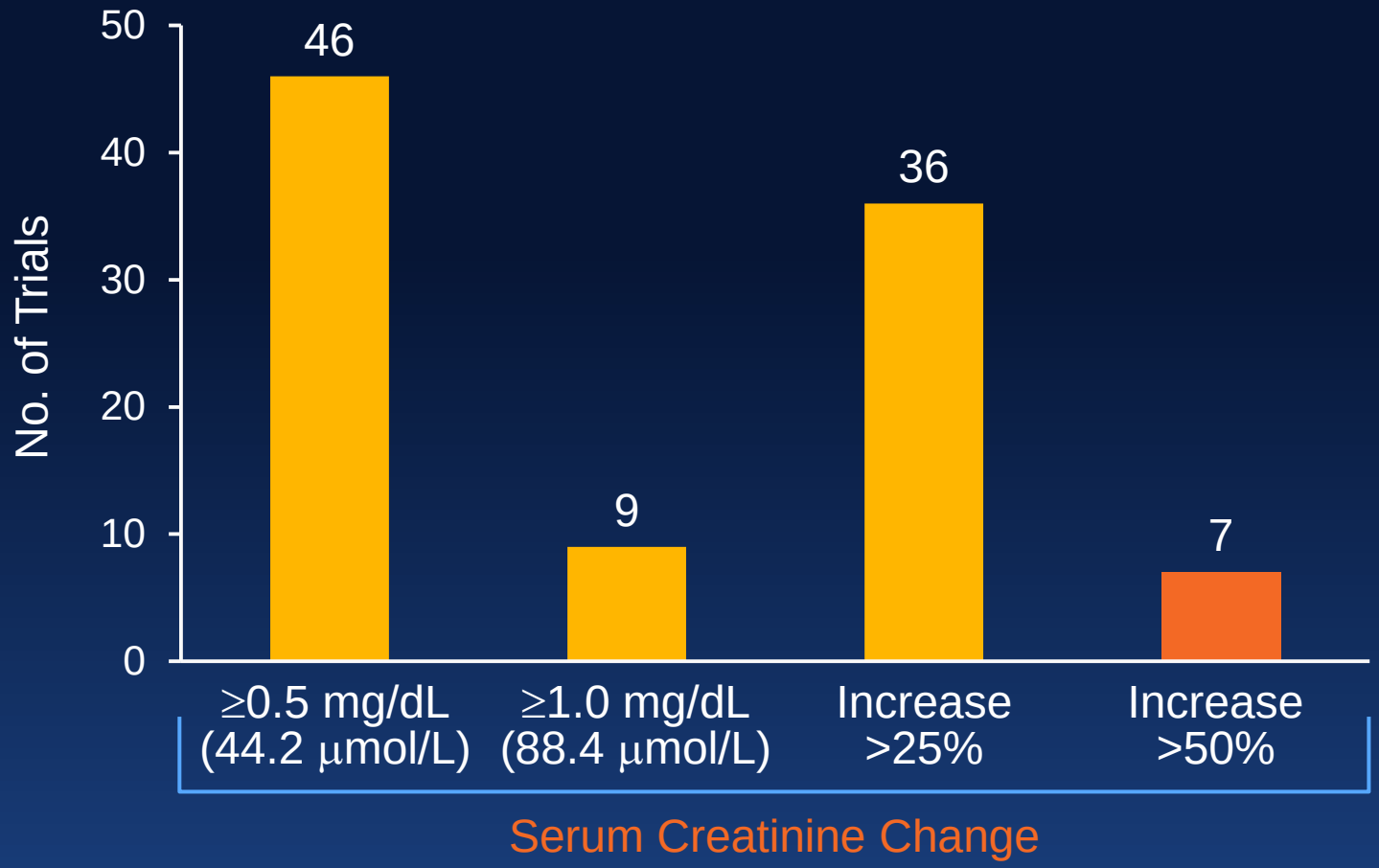
CA-AKI

Definition in Clinical Trials



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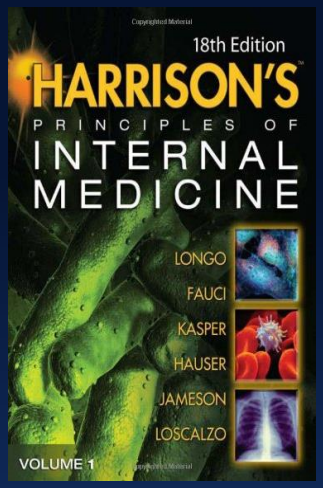
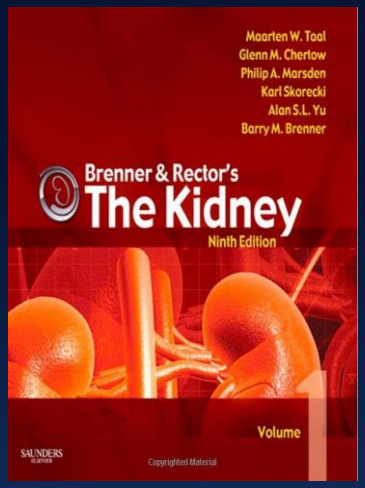
CA-AKI

Conventional wisdom

CA-AKI Incidence

- 2-7% in the general population (Harrisons)
- 50% with moderate-advanced CKD (Brenner)
- "CIN is the third most common cause of acute renal failure in the hospital patient."
  Hou SH et al. Am J Med 74 243-8, 1983 (732 citations!)





CA-AKI Consequences

- Dialysis in 0.5 to 1.0% of pts (Brenner)
- 5x increase in-hospital mortality (Brenner)

"THOU SHALT NOT ADMINISTER CONTRAST TO PATIENTS WITH RENAL DYSFUNCTION!"

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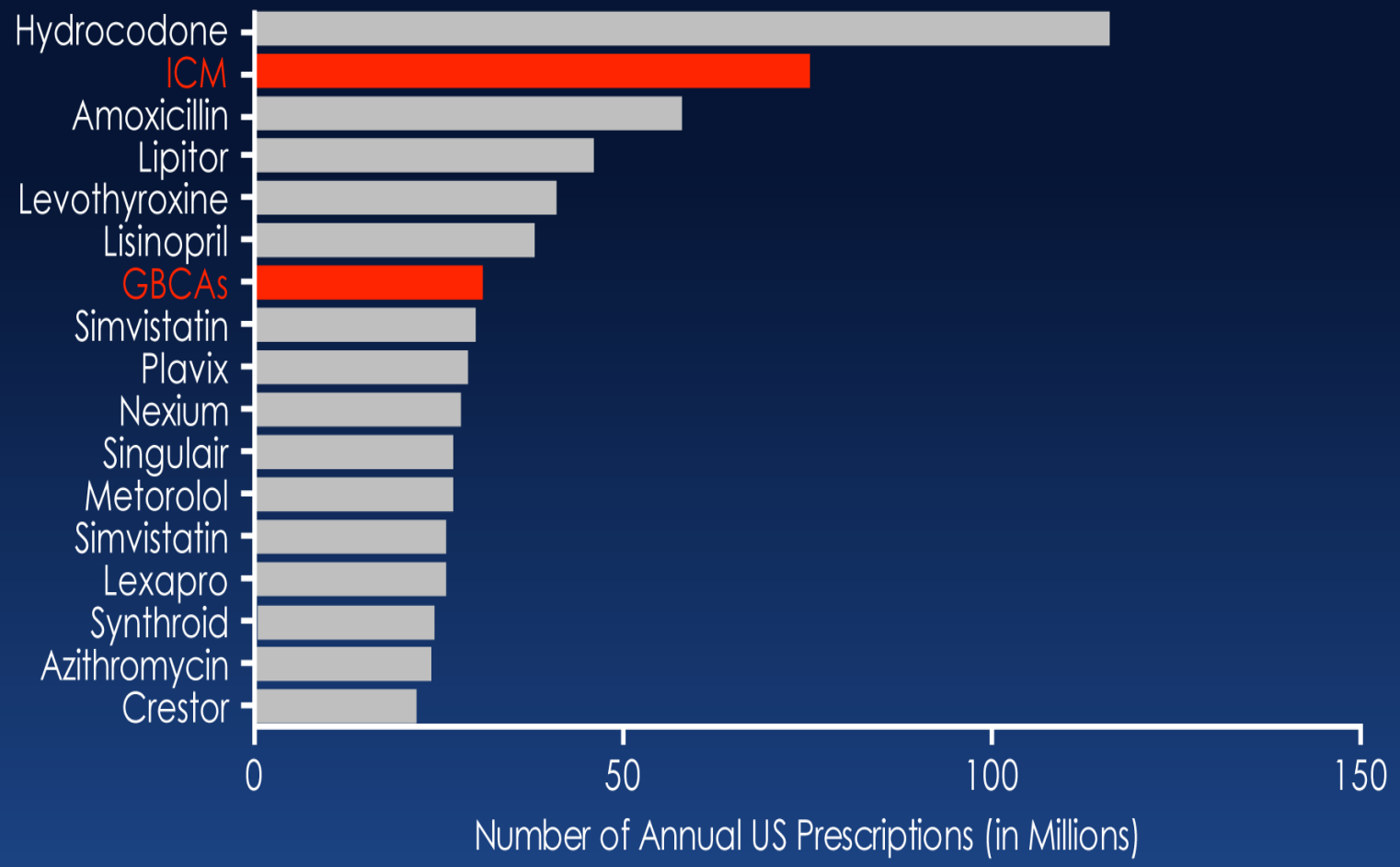
Adapted from Jeff Newhouse M.D.

CA-AKI

Iodinated contrast material usage



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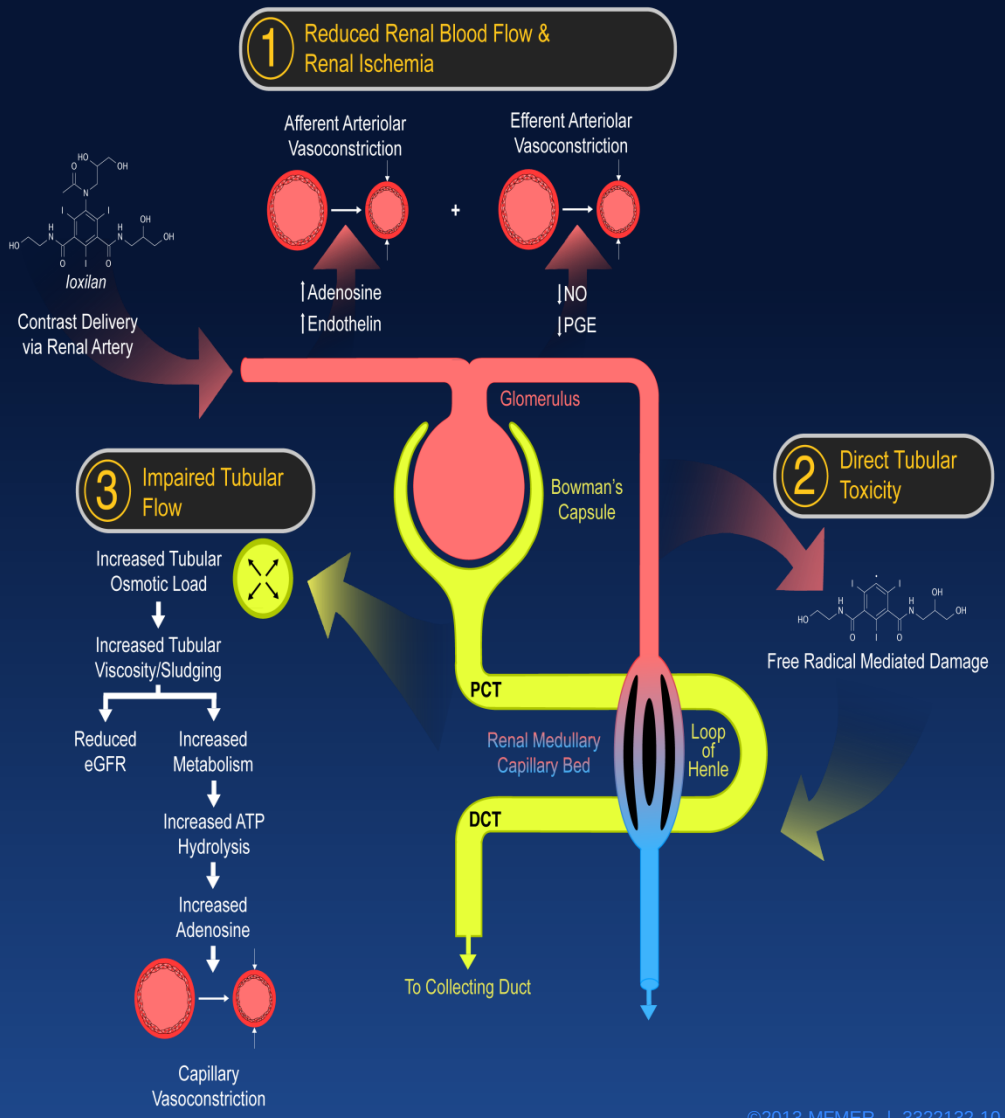
CA-AKI

Proposed mechanism(s)

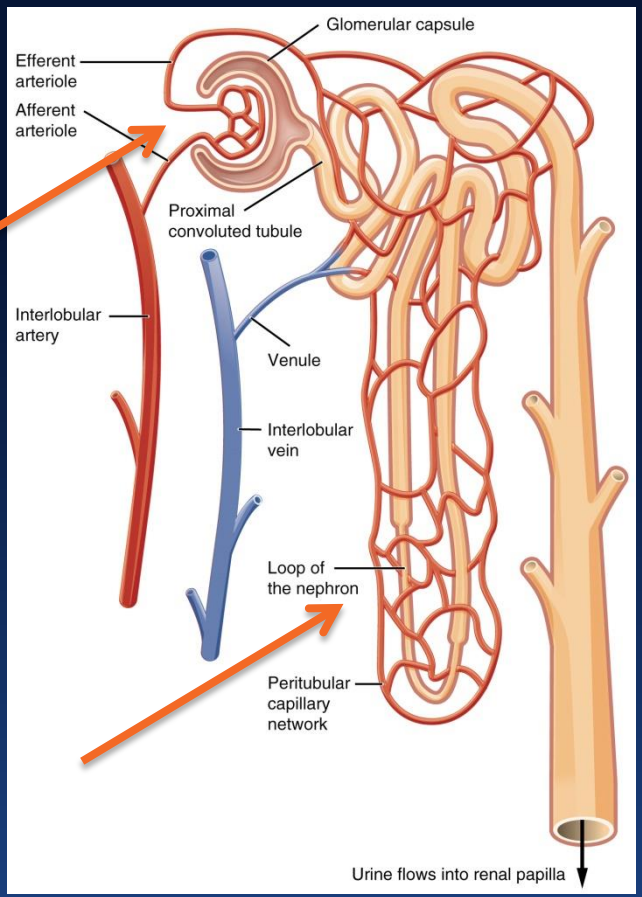
1. ↓ RBF → ischemia
2. Direct toxicity to tubular cells
3. Impaired tubular flow → ischemia

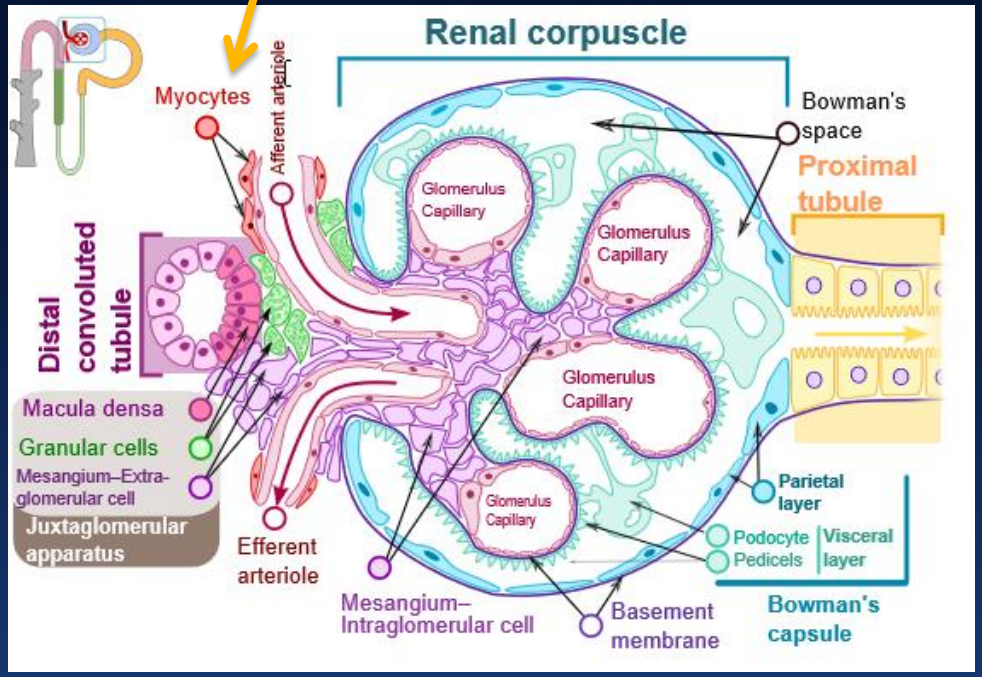


Nephron Blood supply

Sepsis
Liver failure
Hypovolemia
NSAIDs
Contrast

Cardiorenal
Hyperchloremia
Ampho B
Carboplatin
Etc.





OpenStax College - Anatomy & Physiology, Connexions Web site
https://commons.wikimedia.org/w/index.php?curid=76356955

Harm of not using contrast

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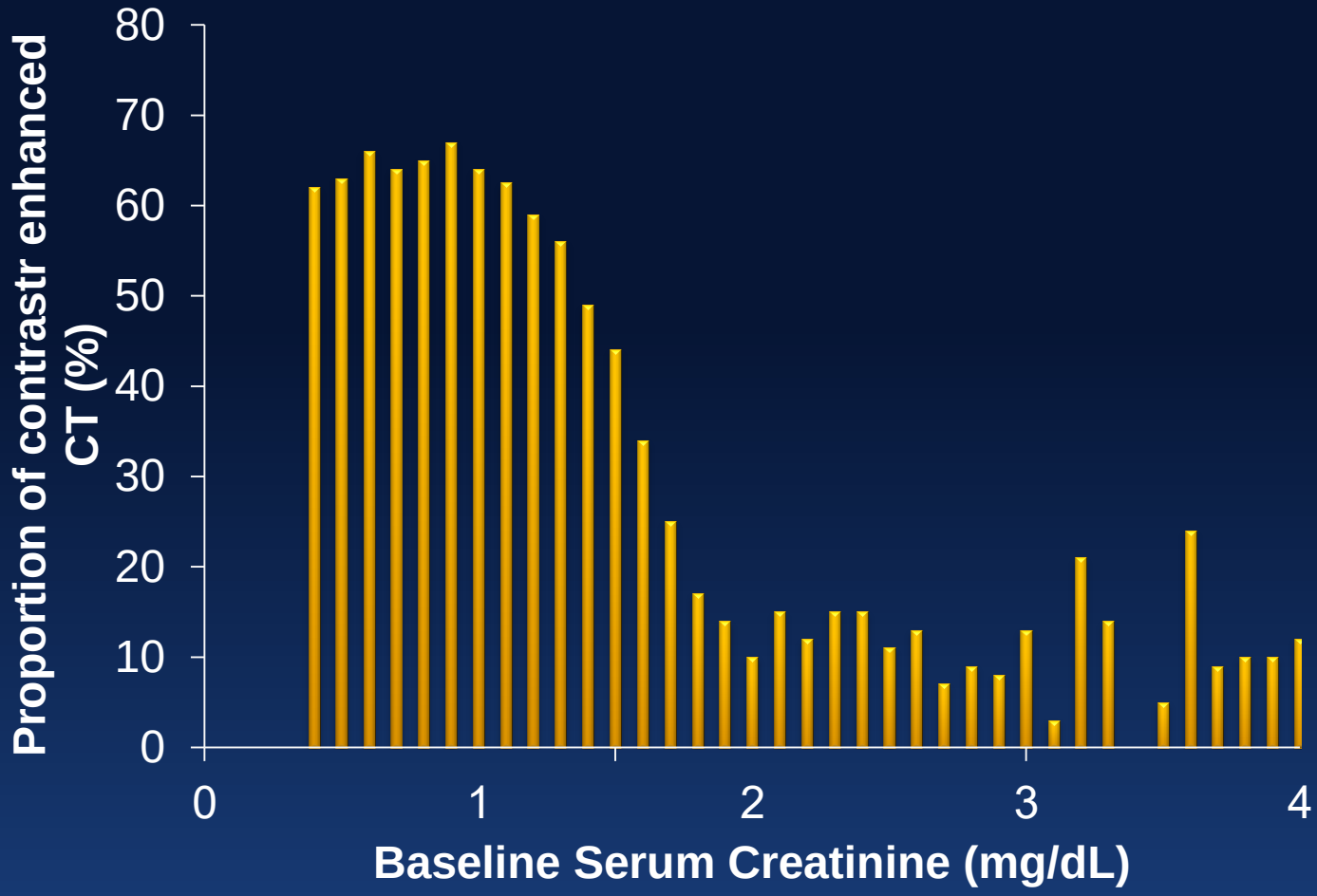
CA-AKI Background

"Renalism" – Avoiding contrast in high-risk patients



Avoiding contrast exams and procedures delays diagnosis and treatment, ultimately harming patients.

Hinson et al. Ann Emerg Med 2017

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Resolution of CA-AKI dilemma

1- RCTs

2- Contrast specific biomarker or biopsy sign

- Does not exist

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(Dis)proving the existence of CA-AKI

RCT challenges

- Ethical concerns
- No clinical equipoise
  - If equipoise, clinicians would not use it
- Need for large sample size needed

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Origins of Dogma

Animal and uncontrolled studies

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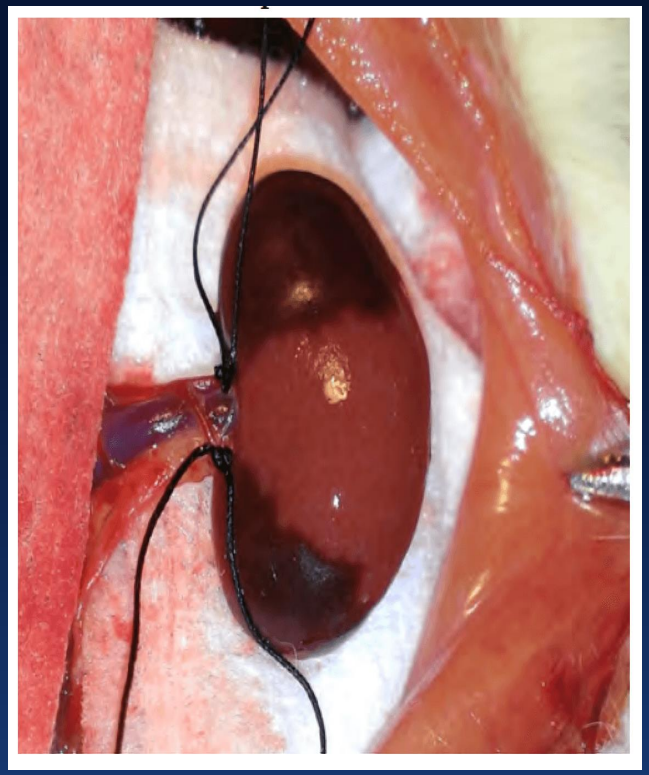
Translatability of preclinical studies

Animal models extrapolation to humans

- Models receive several severe renal insults.
- ICM dose above clinically used doses
- Early animal studies used HOCMs



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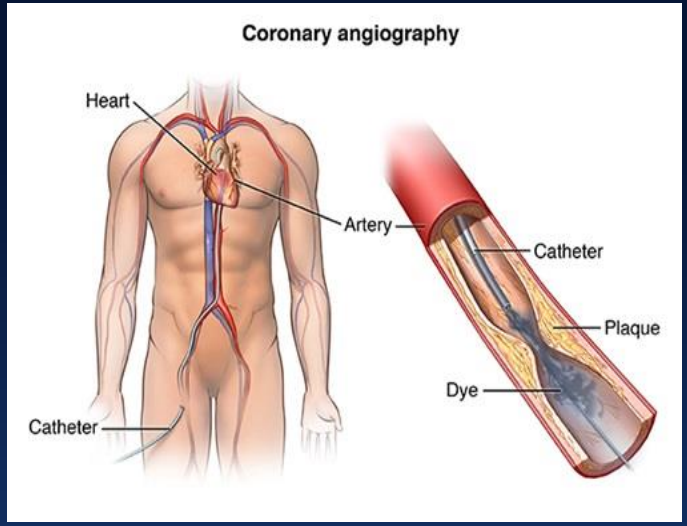
Equating IA and IV ICM administration

Risks of IA extrapolated to IV contrast

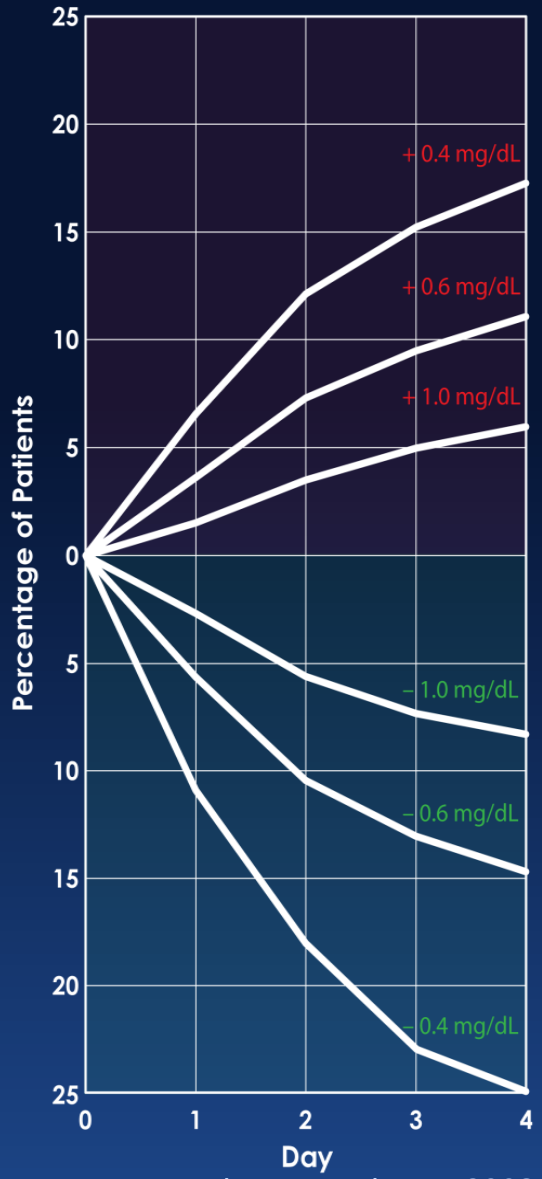
- IA → ↑ Kidney exposure
- IA Procedures → more invasive
  - Atheroemboli
- No unexposed control group available for comparison



Predominance of uncontrolled studies

Uncontrolled studies do not account for contrast-independent causes of AKI

- Any post-contrast ↑ in SCr assumed to be CA-AKI.
- Inpatients not exposed to ICM have similar fluctuations in SCr
- No way to discriminate between CA-AKI and other-cause AKI



Newhouse et al, AJR 2008

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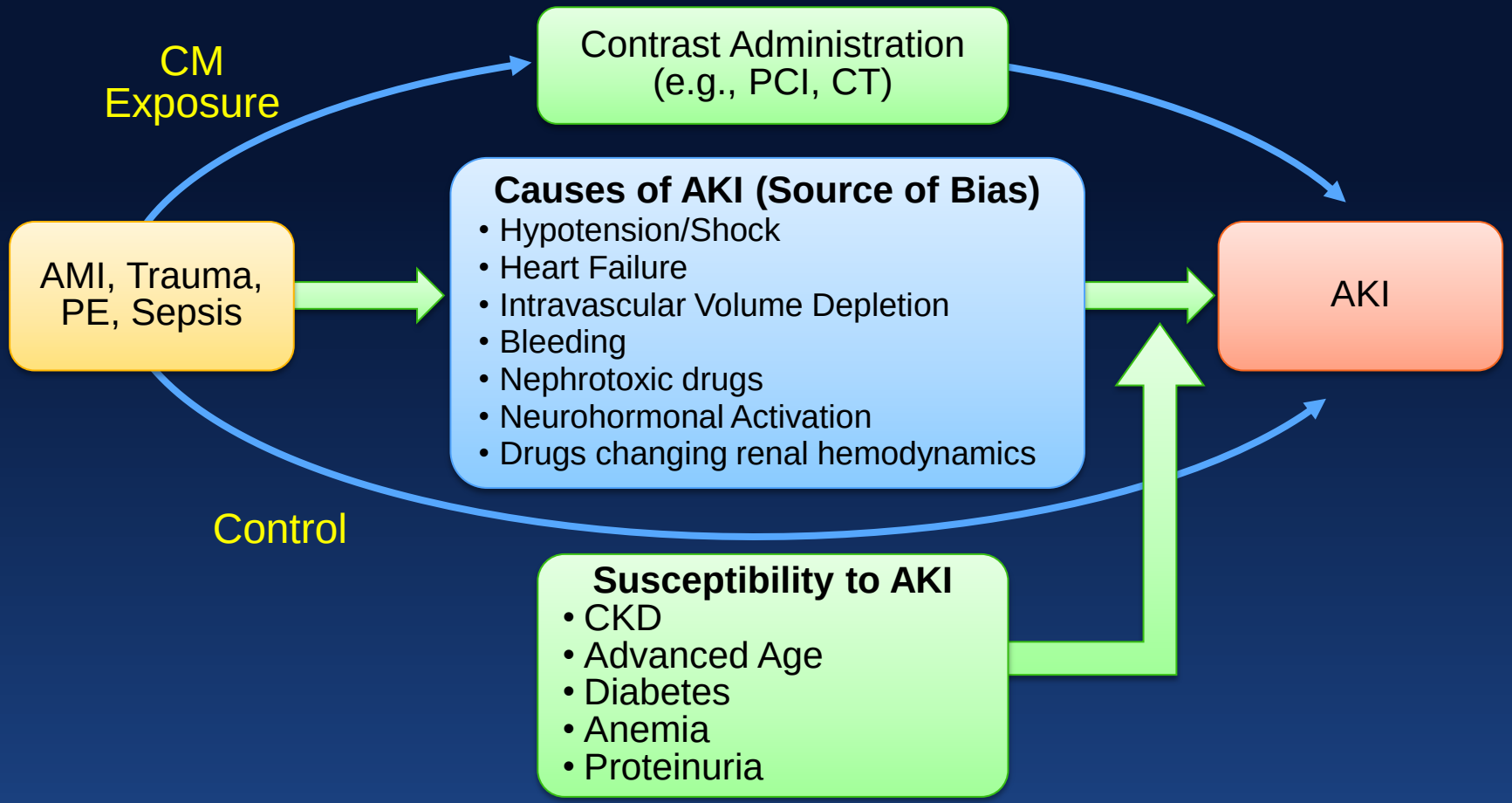
Predominance of uncontrolled studies

Diagnosis bias



Ehrmann et al: Intensive Care Medicine; 44(1):10, 2018

Origins of Dogma

Controlled studies

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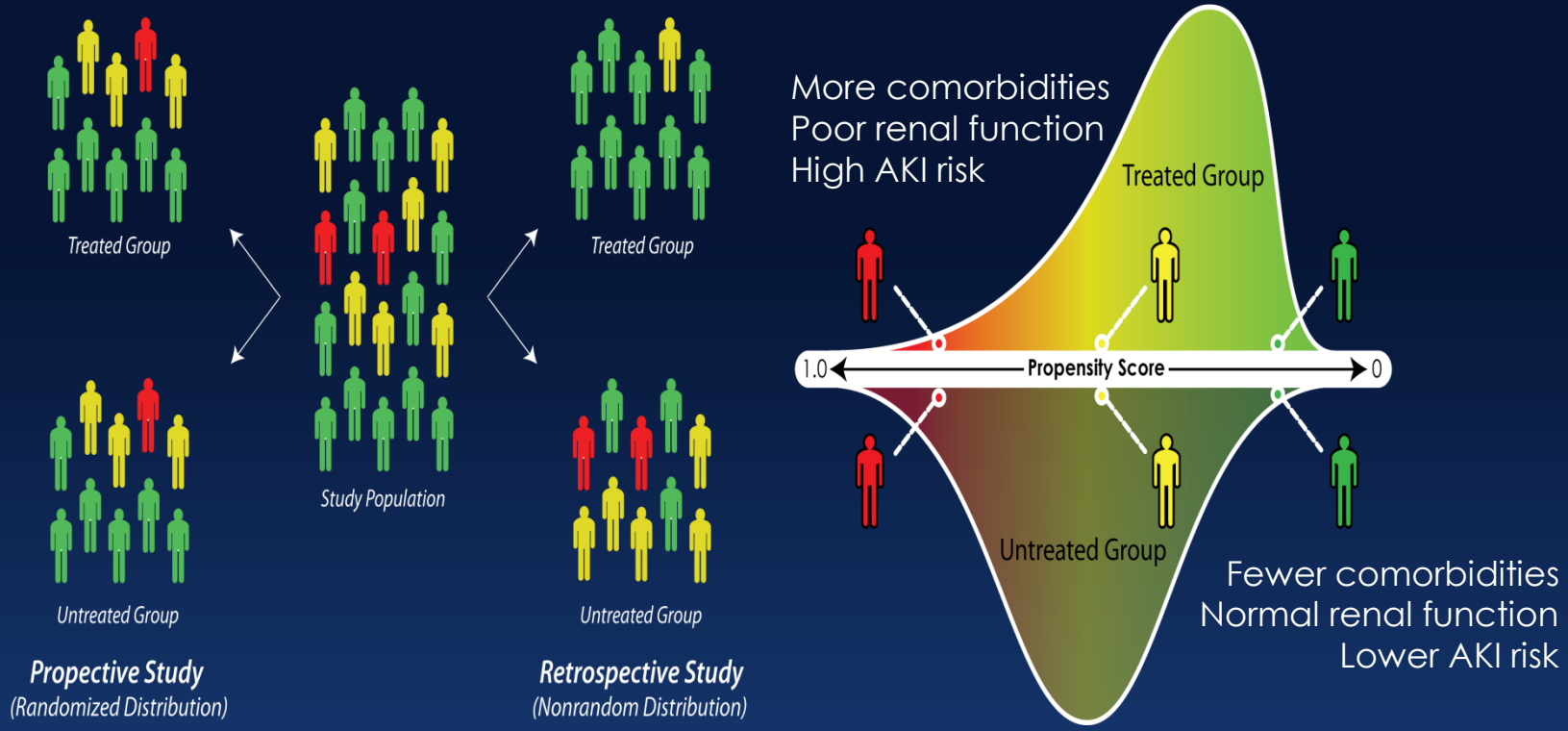
Propensity score matching



Propensity score matching mimics the randomization process of a randomized controlled trial.

McDonald et al, Radiology 2013
McDonald et al, Radiology 2014
McDonald et al, NEJM JW 2014
McDonald et al, Radiology 2015

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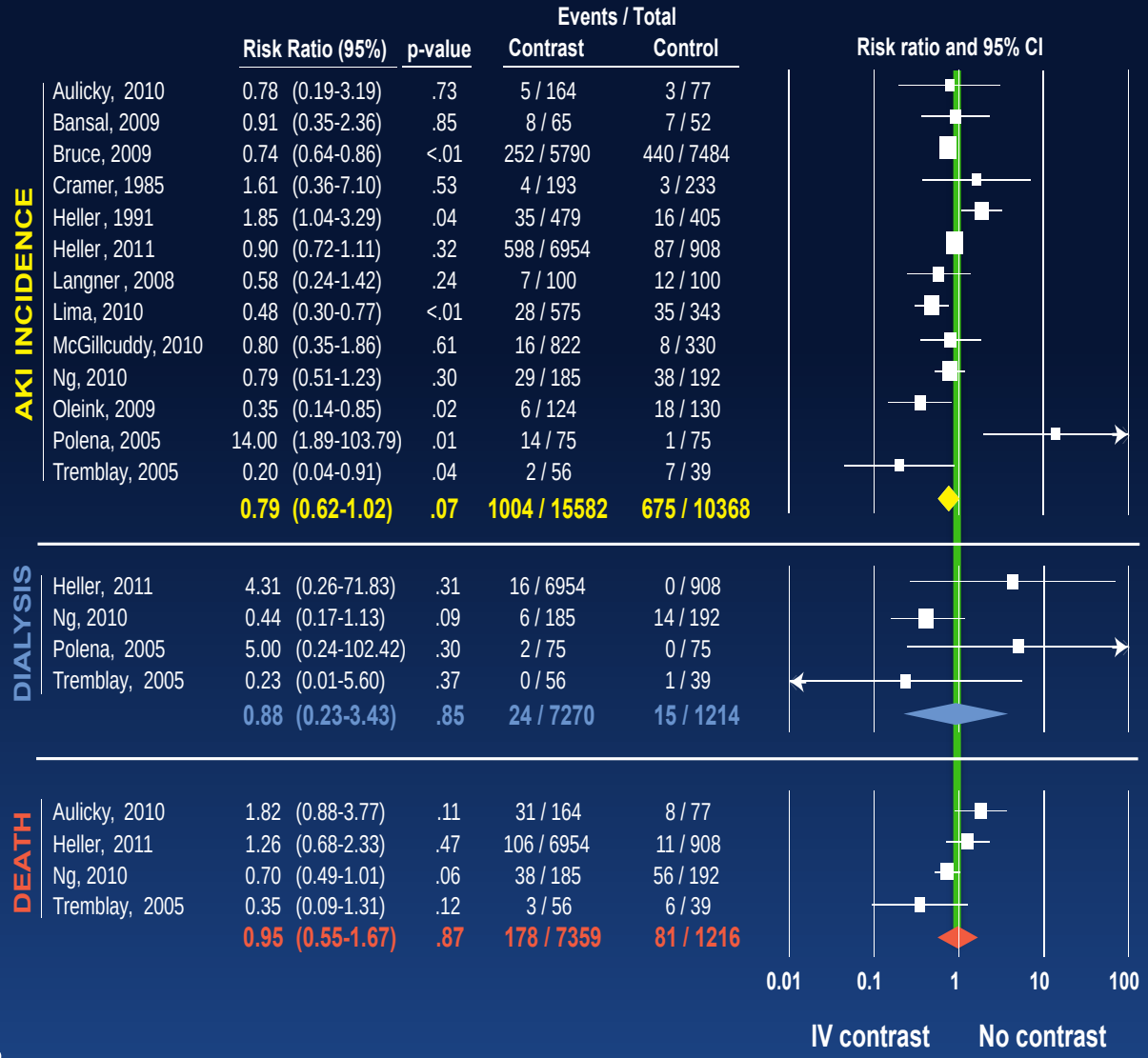
Meta-analysis of controlled studies



In unexposed vs contrast exposed ↔ incidence of:

- AKI
- Dialysis
- Mortality

McDonald et al, Radiology 2013

Retrospective study using informatics

SEARCH RESULTS

1,029,899 Thoracic, Abdominal, & Pelvic CT scans (2000-2010)
251,728 unique MRNs
21,422,489 associated SCr lab values within 14 days of scan

FINAL STUDY POPULATION

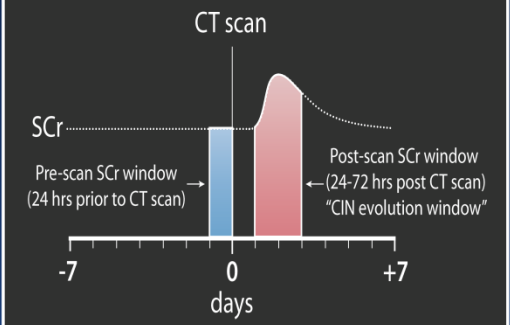
157,140 (**116,694** Contrast: **40,446** Noncontrast) CT Scans
53,439 unique MRNs
1,510,001 Associated SCr values

Patients sorted by contrast exposure AND presumed CIN Risk:
Low risk – SCr < 1.5 mg/dL
Medium risk – SCr 1.5 - 2.0 mg/dL
High risk – SCr > 2.0 mg/dL

Demographics, Comorbidities (ARF, CRF, CHF, DM), Charlson Score, Inpatient status collected for all patients

EXCLUSION CRITERIA

957,025 scan records lacking ≥1 pre and 1 post scan SCr value in each time window as shown below:



24,876 scan records associated with dialysis

47,998 scan records associated with > 1 contrast dose within 14 days of initial CT scan

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Propensity score-adjusted results

	Group		Statistics	
	Contrast	Non-contrast	O.R. (95% CI)	p value
Low Risk Group	N = 7273	N = 7273		
AKI	210 (3%)	226 (3%)	0.93 (0.76-1.13)	.47
30-Day Dialysis	7 (0.1%)	8 (0.1%)	0.88 (0.32-2.41)	.79
30-Day Mortality	417 (5.7%)	426 (5.9%)	0.95 (0.83-1.09)	.44
Medium Risk Group	N = 2442	N = 2442		
AKI	209 (9%)	215 (9%)	0.97 (0.81-1.16)	.76
30-Day Dialysis	7 (0.3%)	7 (0.3%)	1.00 (0.35-2.86)	.79
30-Day Mortality	303 (12.4%)	314 (12.9%)	0.97 (0.83-1.14)	.64
High Risk Group	N = 958	N = 958		
AKI	96 (10%)	103 (11%)	0.91 (0.66-1.24)	.58
30-Day Dialysis	11 (1.1%)	12 (1.3%)	0.92 (0.40-2.09)	.84
30-Day Mortality	130 (13.6%)	135 (14.1%)	0.93 (0.73-1.18)	.56

McDonald et al, Radiology 2013 & 2014

McDonald et al, NEJM JW 2014

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Other high-risk groups

	Group		Statistics	
	Contrast	Noncontrast	O.R. (95% CI)	p value
DM Subset	N = 1974	N = 1974		
AKI	133 (6.7%)	133 (7.0%)	0.96 (0.75-1.23)	.75
30-Day Dialysis	10 (0.5%)	11 (0.6%)	0.91 (0.39-2.14)	.83
30-Day Mortality	173 (8.8%)	162 (8.2%)	1.07 (0.84-1.33)	.54
AKI Subset	N = 2040	N = 2040		
AKI	257 (13%)	237 (12%)	1.10 (0.91-1.32)	.36
30-Day Dialysis	19 (0.9%)	13 (0.6%)	1.47 (0.72-2.98)	.38
30-Day Mortality	273 (13%)	263 (13%)	1.02 (0.86-1.21)	.82
CKD Subset	N = 975	N = 975		
AKI	93 (9.5%)	94 (9.6%)	0.99 (0.73-1.34)	.94
30-Day Dialysis	8 (0.8%)	6 (0.6%)	1.34 (0.46-3.87)	.79
30-Day Mortality	117 (12%)	107 (11%)	1.06 (0.82-1.36)	.65
CHF Subset	N = 1487	N = 1487		
AKI	147 (9.9%)	126 (8.5%)	1.18 (0.92-1.52)	.18
30-Day Dialysis	9 (0.6%)	4 (0.3%)	2.26 (0.69-7.35)	.27
30-Day Mortality	208 (14%)	214 (14%)	0.96 (0.79-1.16)	.67

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McDonald et al, Radiology 2013 & 2014

Other high-risk groups

- Unilateral nephrectomy patients
- ICU patients
- Pediatric patients
- CKD patients (eGFR 30-59) and more propensity score variables (>30)
  - Included IV fluids, nephrotoxic medications, baseline SCr stability.

McDonald et al, Radiology 2016
McDonald et al, Intensive Care Med 2017
McDonald et al, Am J Kidney Dis 2018
McDonald et al, Mayo Clin Proc 2015

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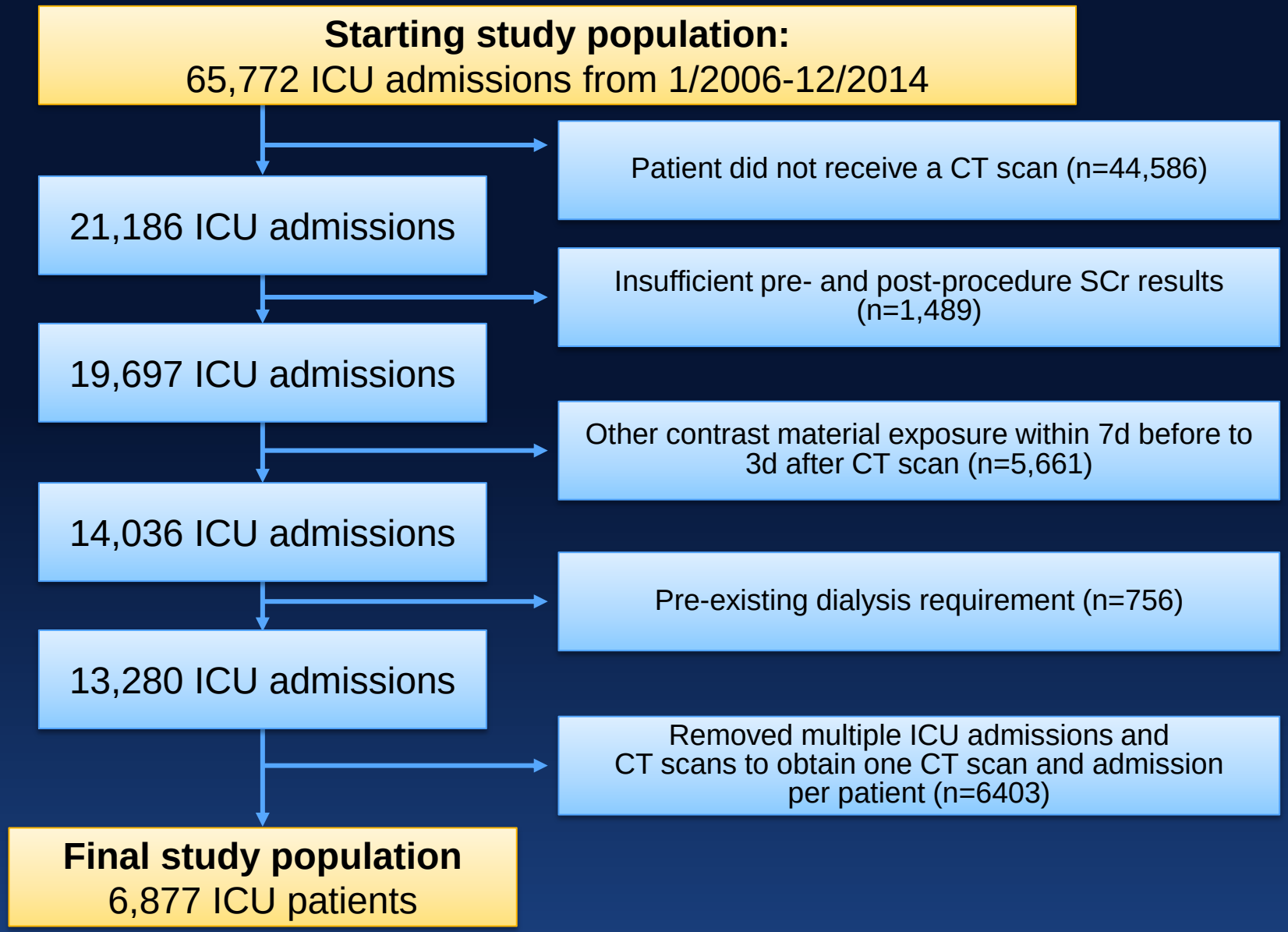

McDonald, Kashani et al: Intensive Care Med 43:774, 2017

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GFR<45

	Contrast Group	Noncontrast Group	Odds ratio (95% CI)*	P
W				
Unadjusted	356	1,260		

Dialysis within 7 days post-scan

Unadjusted	23 (6.5%)	111 (8.8%)	0.71 (0.45-1.14)	0.16
Stratified	–	–	1.94 (1.09-3.45)	**0.0411**
1:1 Matched	19 (6.7%)	7 (2.5%)	2.72 (1.14-6.46)	**0.0240**
1:1 Matched	7 (2.5%)	3 (1.1%)	2.33 (0.60-9.03)	0.22

Following Propensity 1:1 matching there was no other significant differences between the groups

ICU LOS (days)				
Unadjusted	2 (1-4)	2 (1-4)	–	0.12
1:1 Matched	2 (1-4)	2 (1-3)	–	0.12
Total hospitalization LOS (days)				
Unadjusted	8 (5-13)	9 (5-15)	–	**0.0028**
1:1 Matched	8 (5-13)	8 (5-13)	–	0.89

McDonald et al: Intensive Care Med 43:774, 2017

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GFR>45

	Contrast Group	Noncontrast Group	Odds ratio (95% CI)*	P
W				
Unadjusted	3,995	1,266		
Stratified**	3,995	1,266		
1:1 Matched	1,223	1,223		
All post-CT-AKI (SCr and UOP criteria)				
Unadjusted	1265 (32%)	441 (35%)	0.87 (0.76-0.99)	**0.0358**
Stratified**	–	–	0.94 (0.82-1.09)	0.44
1:1 Matched	383 (31%)	417 (34%)	0.88 (0.75-1.05)	0.15
All post-CT-AKI (SCr criteria)				
Unadjusted	444 (11%)	183 (14%)	0.74 (0.61-0.89)	**0.0014**
Stratified	–	–	0.99 (0.82-1.21)	0.98
Dialysis within 7 days post-scan				
Unadjusted	40 (1.0%)	25 (2.0%)	0.50 (0.30-0.83)	**0.0063**
Stratified	–	–	1.03 (0.62-1.74)	0.90
1:1 Matched	25 (2.0%)	21 (1.7%)	1.20 (0.66-2.17)	0.55
Mortality within 30 days post-scan				
Unadjusted	416 (10%)	173 (14%)	0.73 (0.61-0.89)	**0.0014**
Stratified	–	–	0.86 (0.70-1.05)	0.90
1:1 Matched	147 (12%)	167 (14%)	0.87 (0.69-1.10)	0.23
ICU LOS (days)				
Unadjusted	2 (1-3)	2 (1-4)	–	**0.0227**
1:1 Matched	2 (1-3)	2 (1-4)	–	0.80
Total hospitalization LOS (days)				
Unadjusted	8 (5-14)	9 (5-16)	–	**<0.0001**
1:1 Matched	9 (5-16)	9 (5-15)	–	0.70

Following Propensity 1:1 matching there was no significant differences between the groups

McDonald, Kashani et al: Intensive Care Med 43:774, 2017

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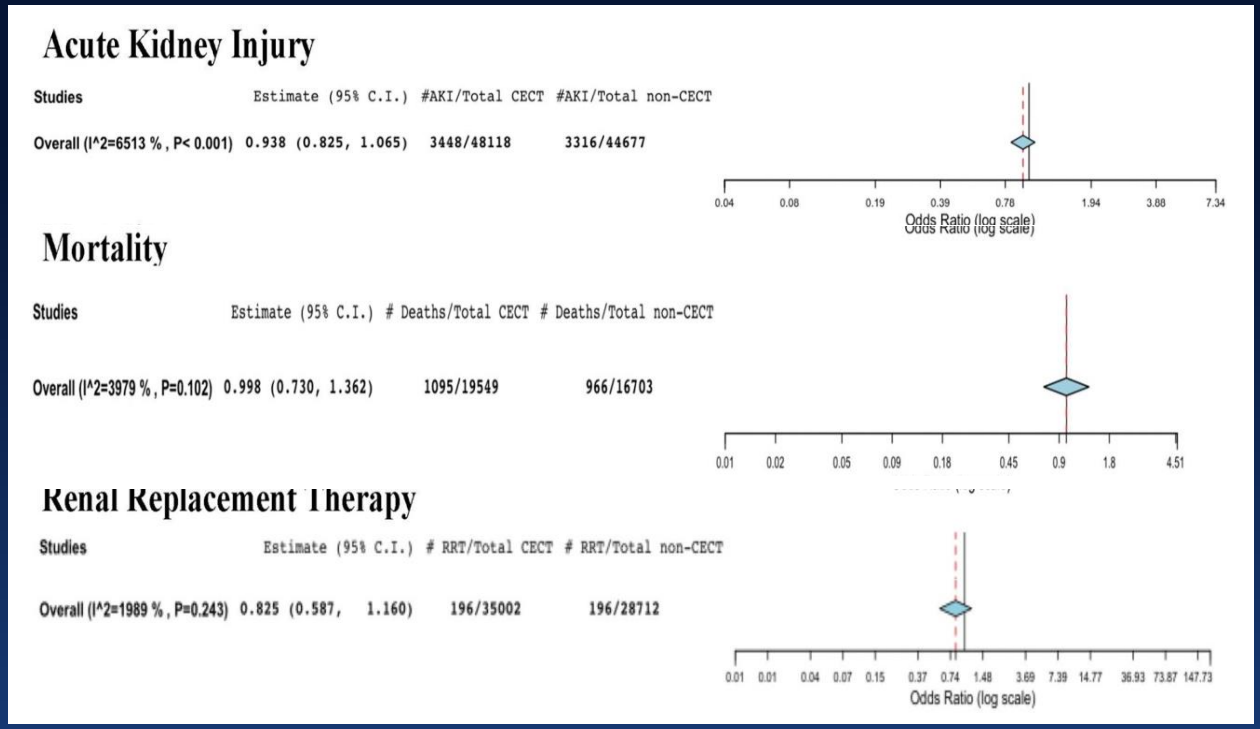
Meta-analysis of controlled studies

Recent reiteration - 2018

Recent meta-analysis of controlled studies (n=28, >100,000 patients) found no association between ICM administration and AKI.



Aycock et al, Ann Emer Med 2018

Origins of Dogma

Prevention bias

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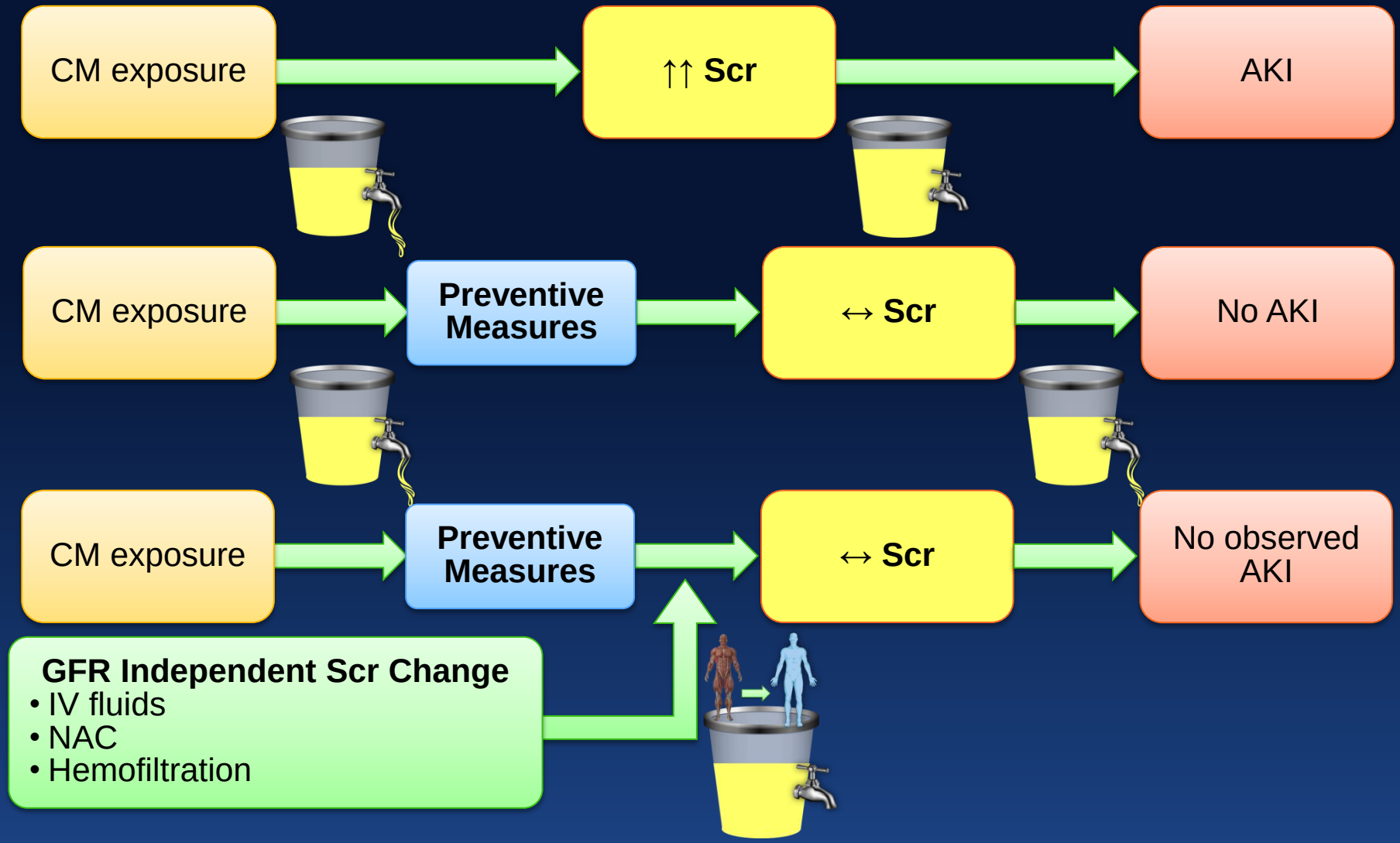
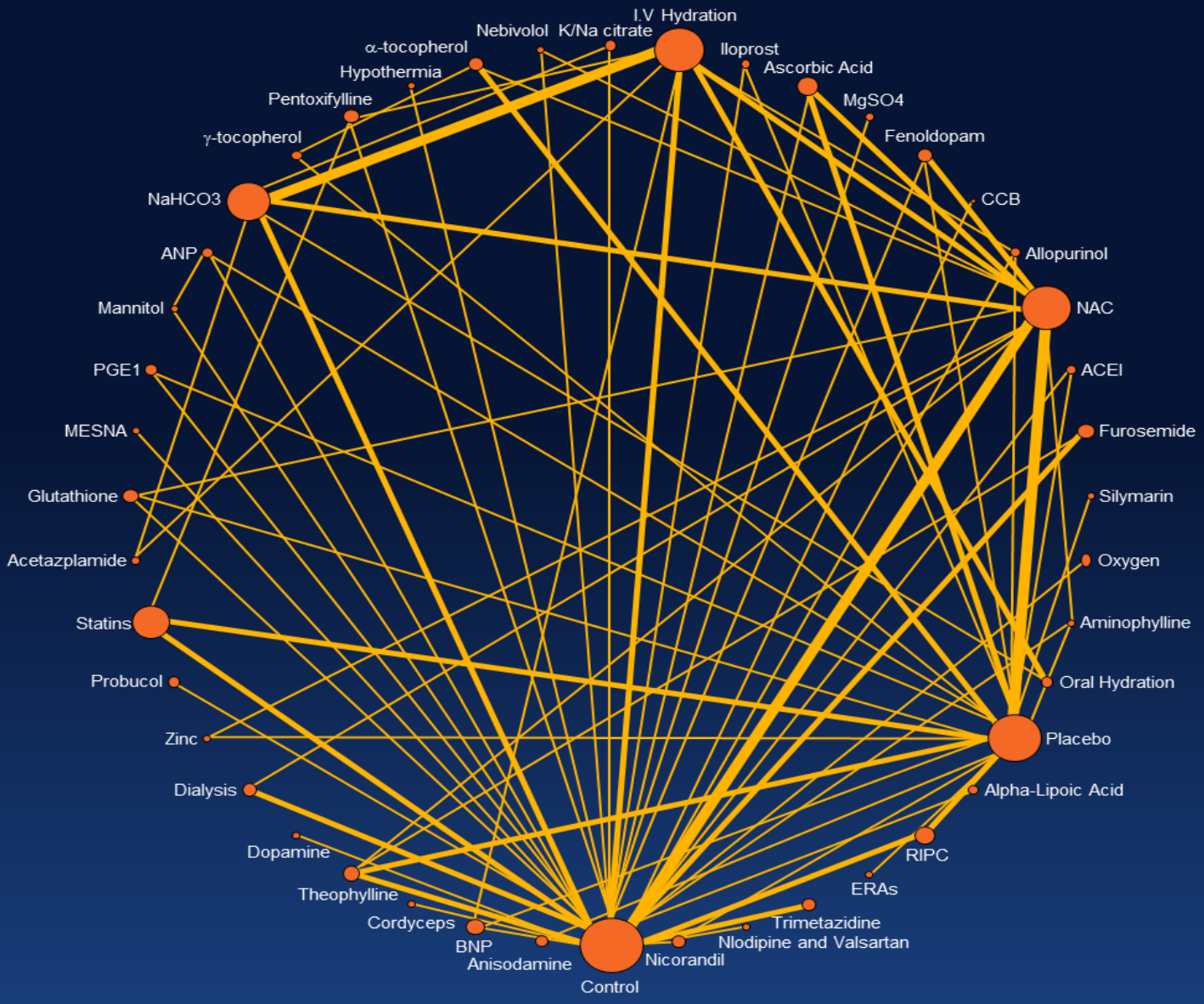
Prevention Bias





Ahmed et al: BMC Nephrology (2018) 19:323

Volume: Hydration

- Careful evaluation for volume status
  - IV fluids to avoid hypovolemia
    - 0.9%NS > 0.45%NS
- IV fluids
  - → Creatinine dilution
  - → Osmolar load
    - → ↑ GFR
      - → ↓ Scr
        - → Interpreted as CA-AKI prevention

Rudnick. Prevention of Contrast-induced Nephropathy, 2013

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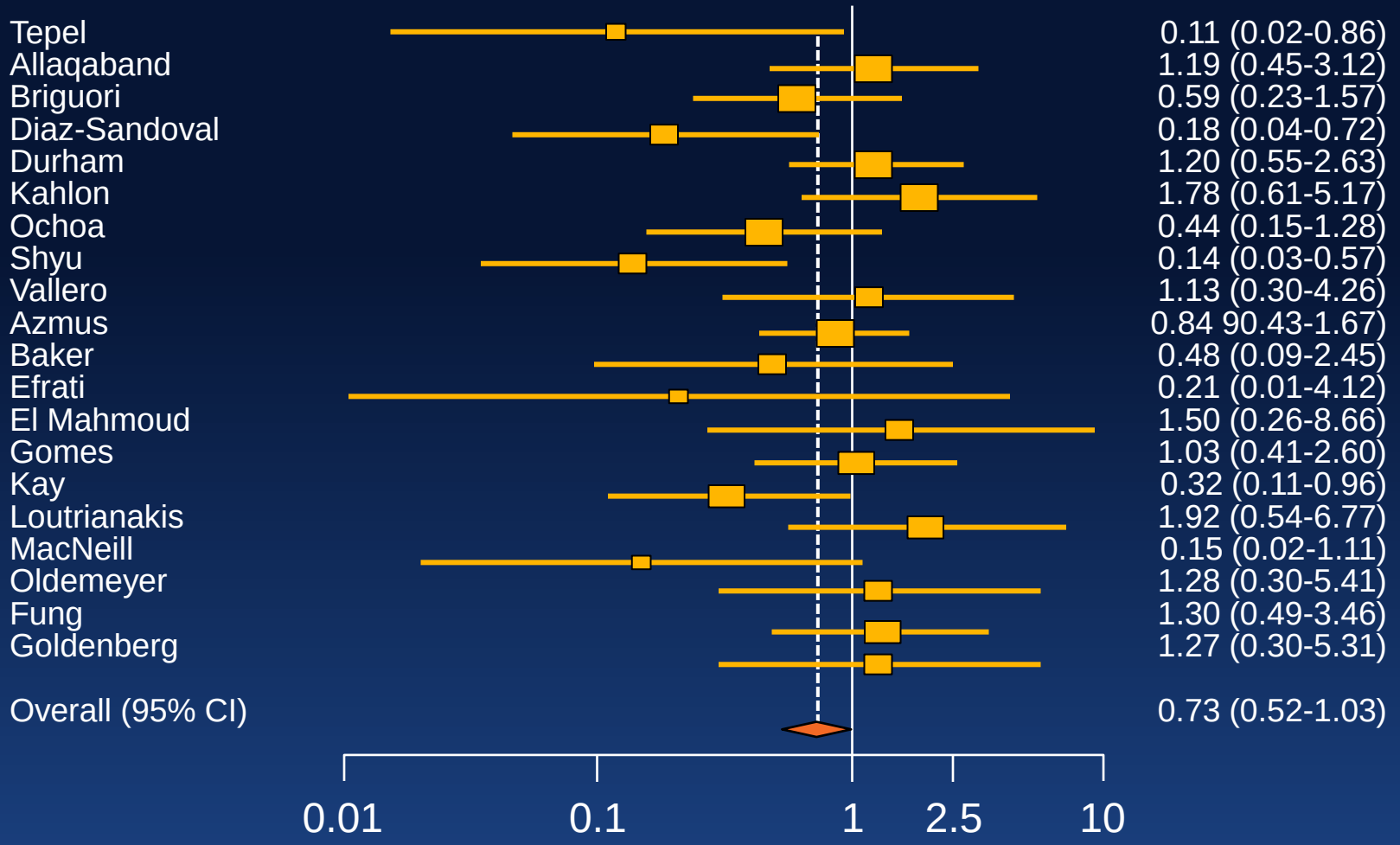
N-acetylcysteine

A Meta-Analysis of 20 RCT; n=2195



Nallamothu BK et al: Am J Med.; 117:938-47, 2004

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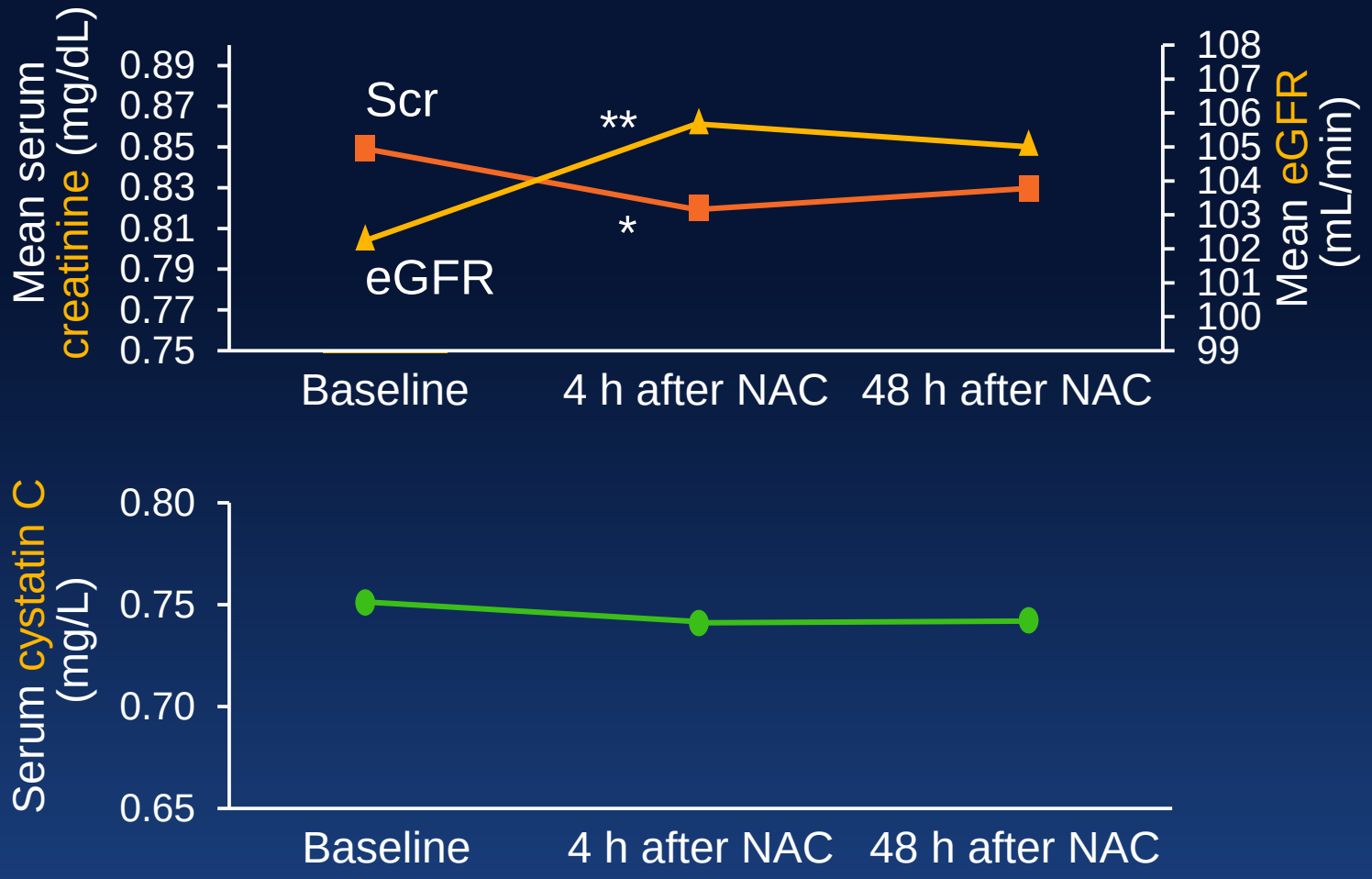
N-Acetylcysteine & Creatinine Production

N=50 healthy volunteers took 600mg NAC bid X four doses



Hoffmann et al: J Am Soc Nephrol 15: 407-410, 2004

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Origins of Dogma

CA-AKI management

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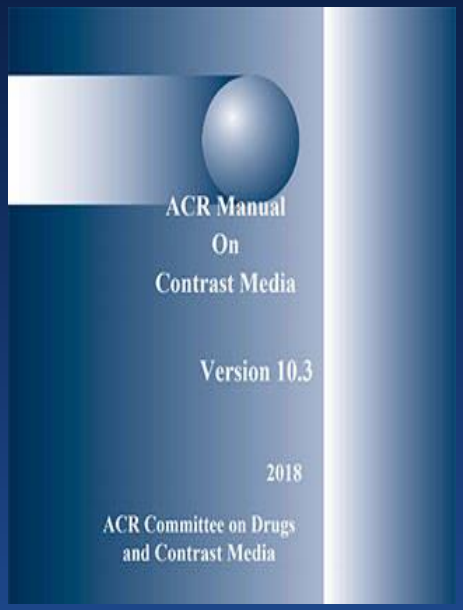
Guidelines for CA-AKI prevention

2018 ACR recommendations

"At the current time, it is the position of ACR Committee on Drugs and Contrast Media that CA-AKI is a real, albeit rare, entity"

1. Suggested Screening
   - Age > 60
   - Renal disease (Dialysis, transplant, uninephrectomy, RCC, HTN, DM)

2. Suggested Prevention
   - If applying a threshold, recommend eGFR <30.
   - Alternative imaging modality.
   - Use lowest effective dose.
   - Use LOCM instead of HOCM
     - IOCM utility is unclear
   - Volume expansion may be of use (IV > oral).



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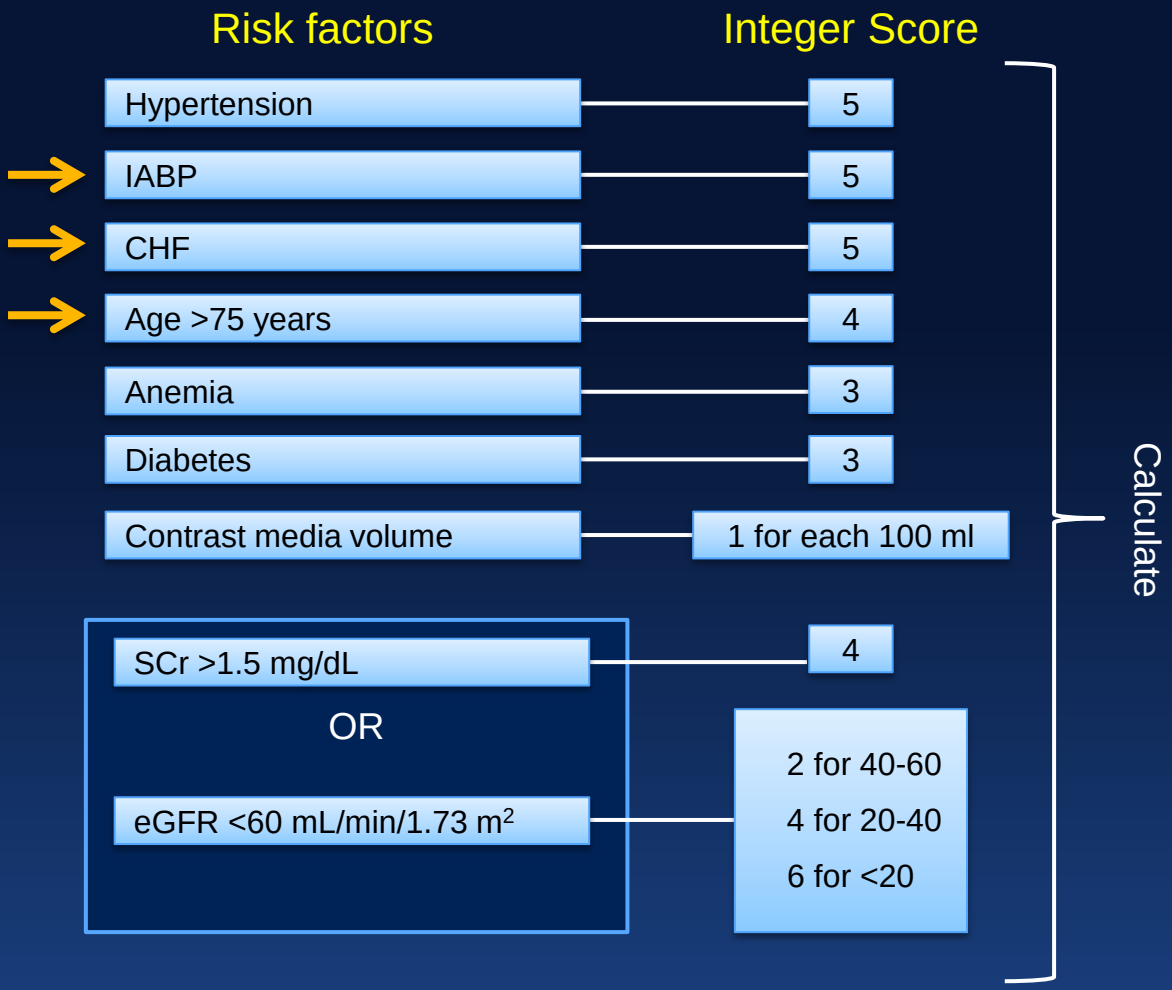
CIN Prediction Model



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

AUC 0.67

AKI **risk score** and **Incidence** were the same regardless of contrast exposure

Petek et al. (2016) Ann Emerg Med **67**(4): 469-476 e461

Mehran et al: JACC Vol 44 (7), 2004

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Consensus Panel for CIN prevention

All patients receive contrast media

- Evaluation for the risk of contrast-induced nephropathy
- Optimized volume status at the time of exposure to contrast
- Low osmolality CM
- Low Volume CM (GFR < 60 ml/min/BSA)

High-Risk Patients

- Pharmacologic prophylaxis (EBM)
- Drugs that adversely affect renal function should be withheld
- Follow-up Scr in 24-72 h following contrast exposure

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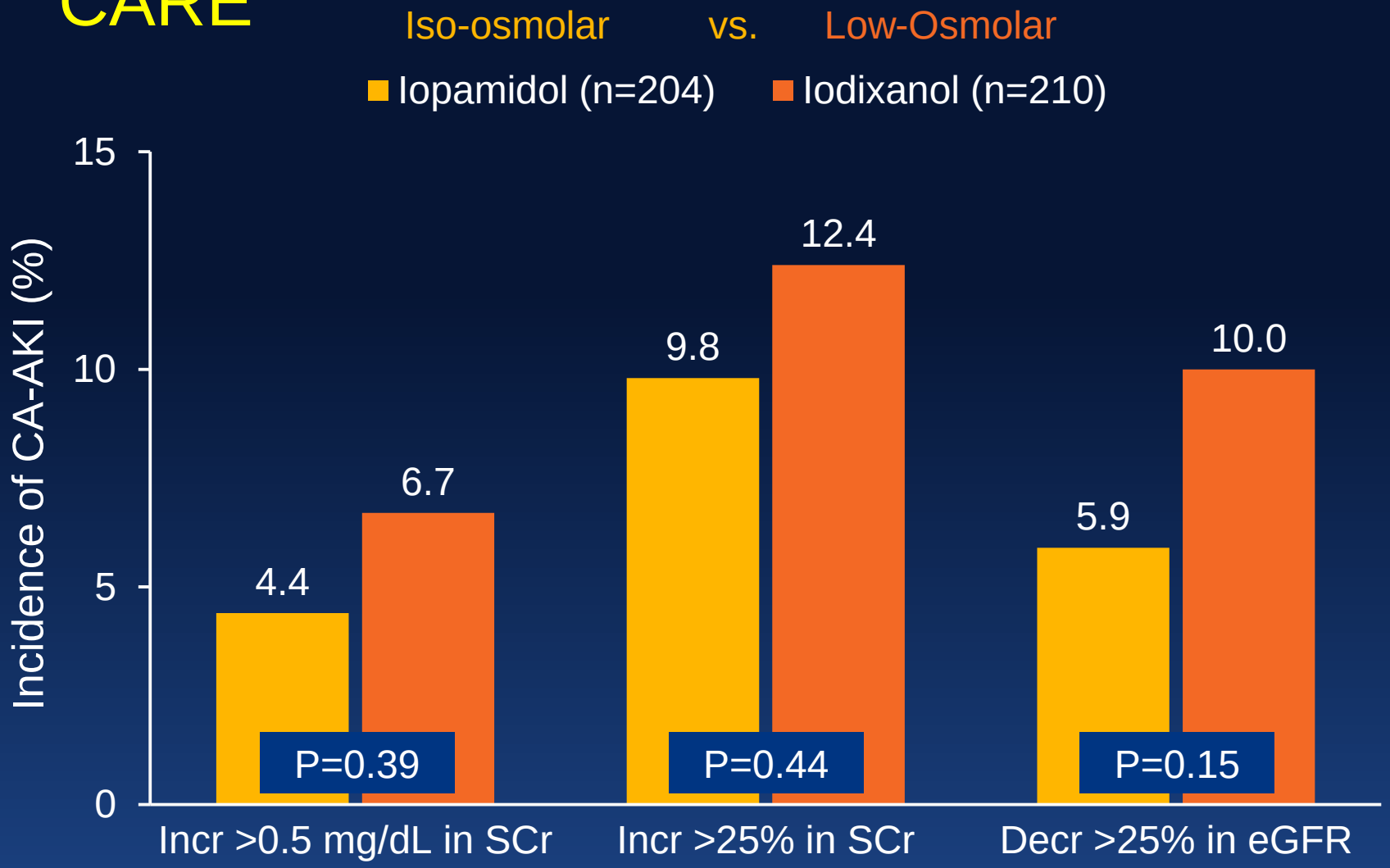
Solomon et al; Kidney International (2006) 69, S51–S53

CARE



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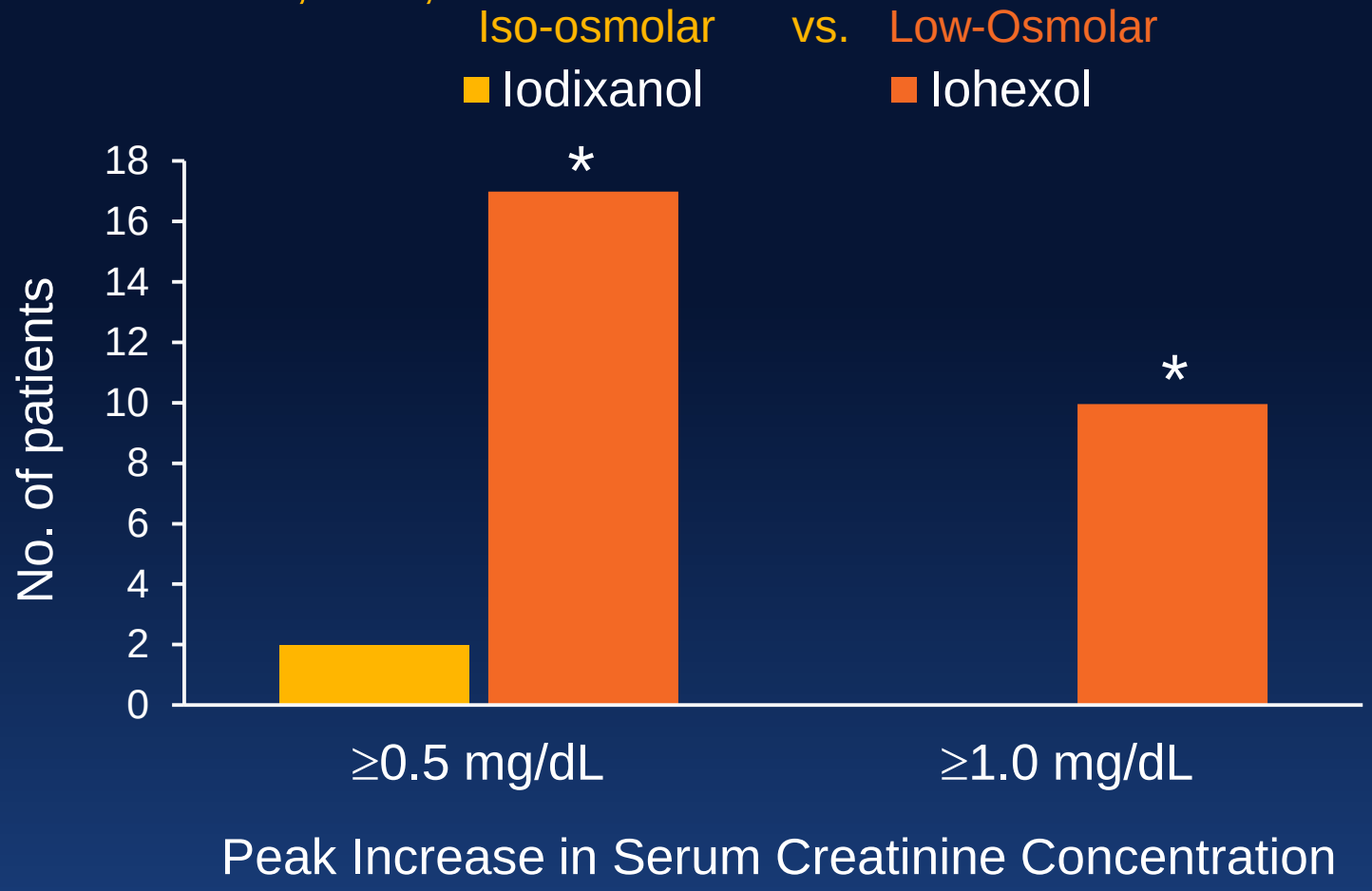
Contrast Type

NEPHRIC Trial, RCT, n=129



Aspeline et al: N Engl J Med; 348:491, 2003

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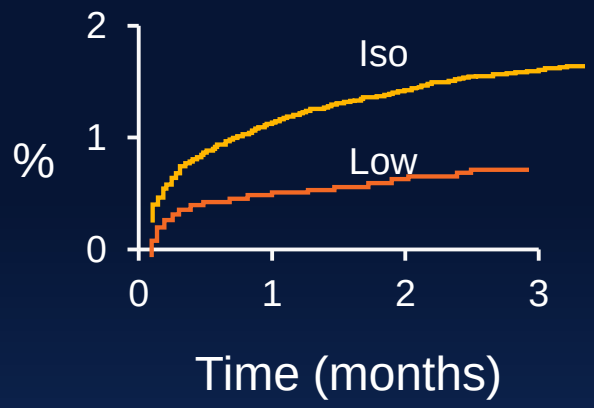
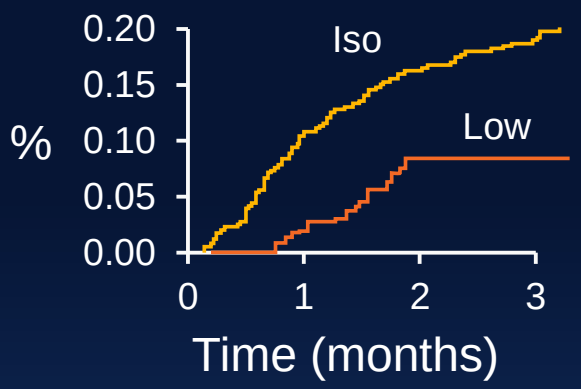
Contrast Type

Swedish Registry; n=52,925; DM/CKD s/p PCI; 1999-2003

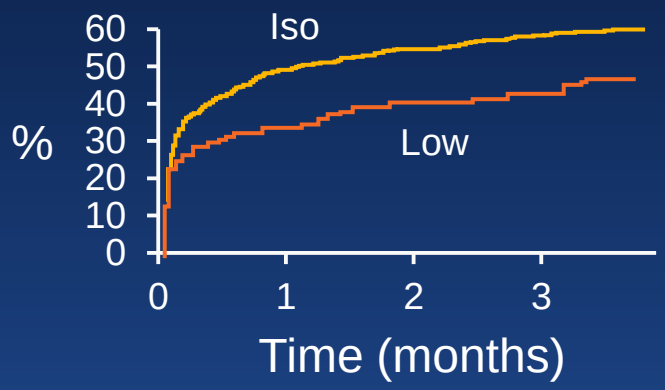
AKI



Dialysis



Reoccurrence of AKI



Liss et al: Kidney International 70, 1811-1817, 2006

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CA-AKI prevention
Contrast Type

- Preference:
  - Low- or Iso-osmolar > high-osmolar contrast
  - Iso-osmolar > low-osmolar contrast
    - Not consistently observed

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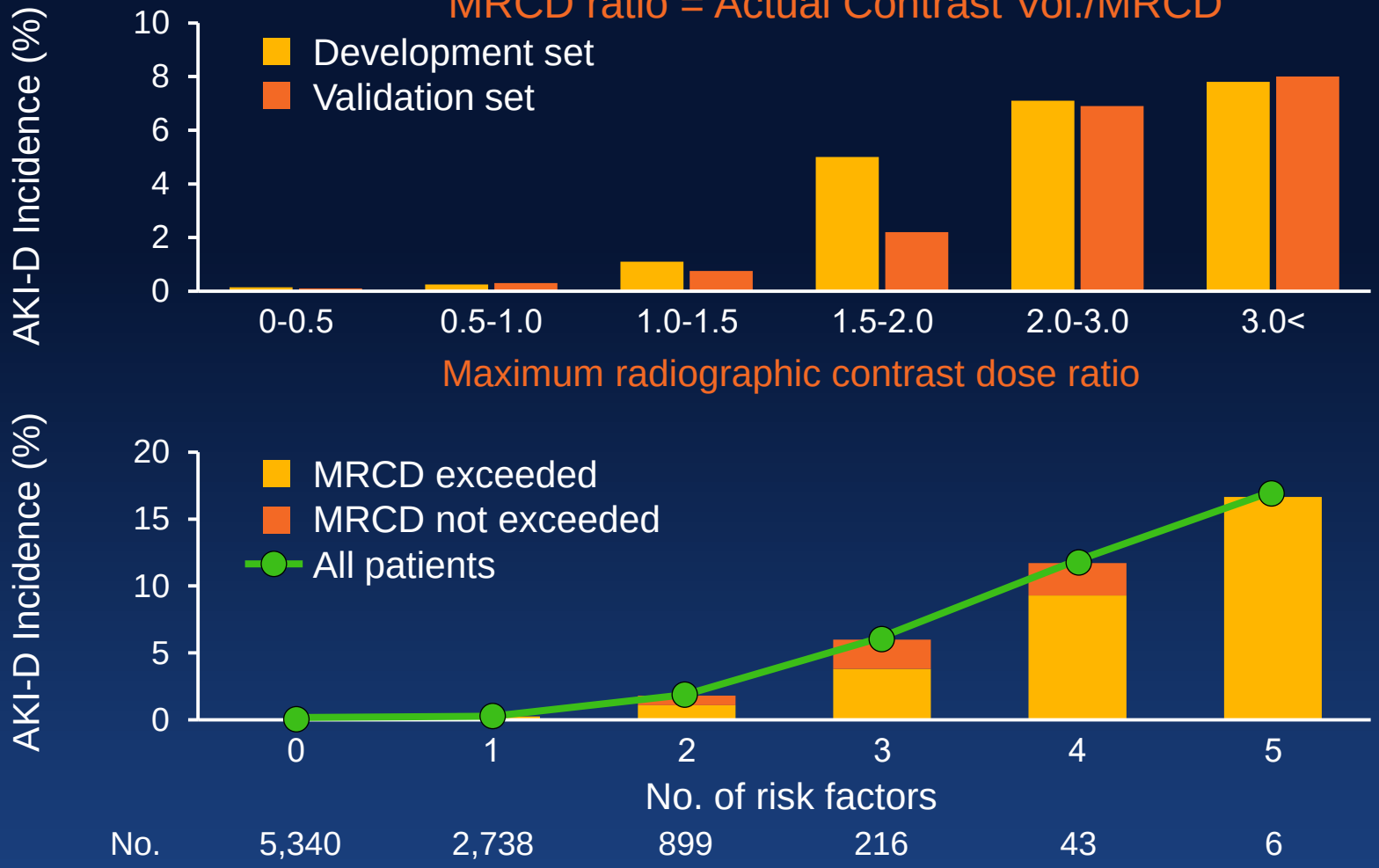
Contrast Dose

N= 16,592 PCI

MRCD: Max Radiographic Contrast Dose = [(5 X kg BW)] / Scr (mg/dL)

MRCD ratio = Actual Contrast Vol./MRCD



Freeman et al: AJC; 90 (10):1068, 2002

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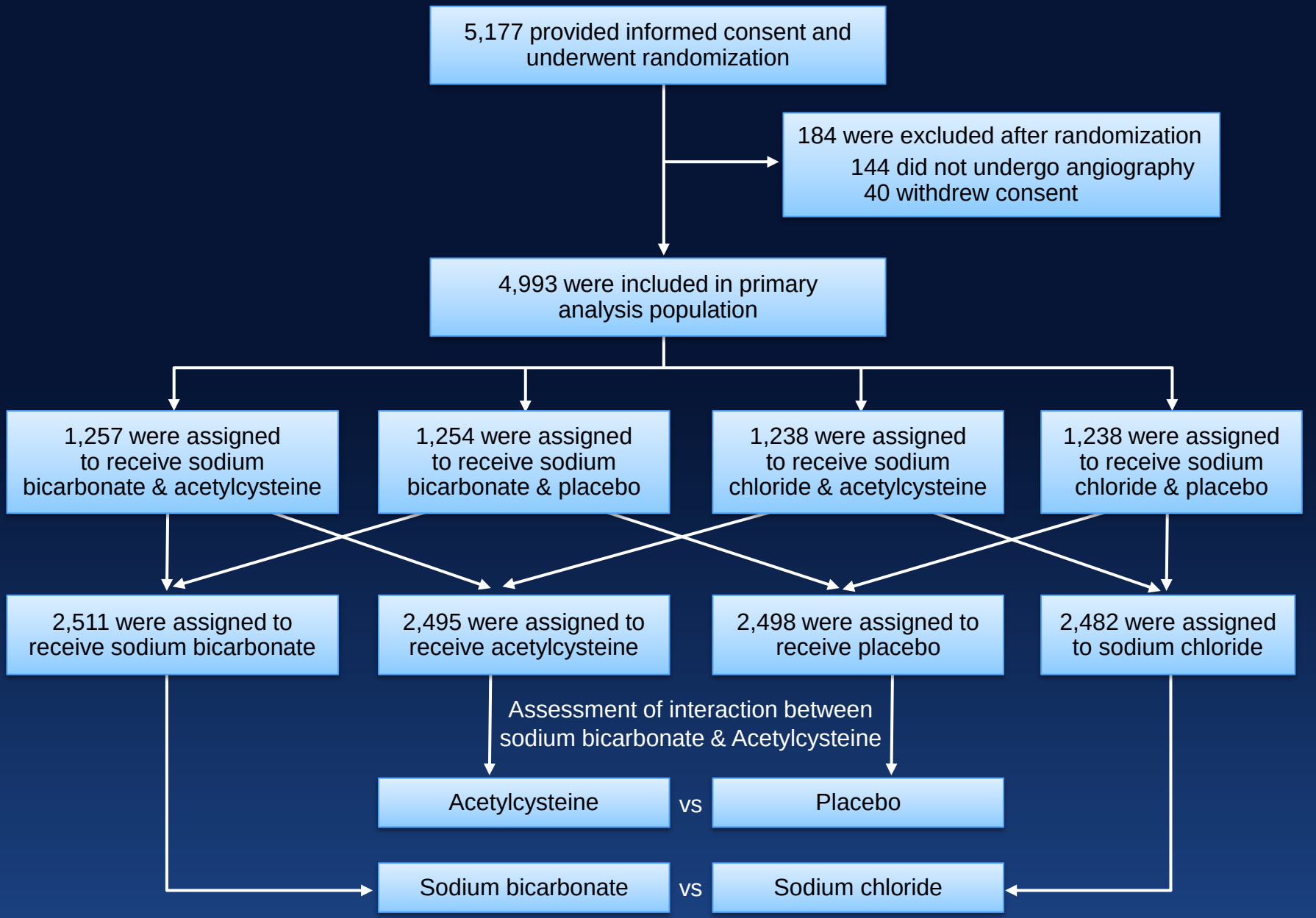

Weisbord et al: NEJM 378:603-614, 20108

PRESERVE Trial

N=5177; Primary outcome MAKE90

	Sodium Bicarbonate (n=2511)		Sodium Chloride (n=2482)		Odds ratio		Acetylcysteine (n=2495)		Placebo (n=2498)		Odds ratio	
Outcome	No.	%	No.	%	95% CI	P	No.	%	No.	%	95% CI	P
1° endpoint MAKE$_{90}$	110	4.4	116	4.7	0.93 (0.72-1.22)	0.62	114	4.6	112	4.5	1.02 (0.78-1.33)	0.88
2° endpoint												
Contrast-associated AKI	239	9.5	206	8.3	1.16 (0.96-1.41)	0.13	228	9.1	217	8.7	1.06 (0.87-1.28)	0.58
Death 90-days	60	2.4	68	2.7	0.87 (0.61-1.24)	0.43	67	2.7	61	2.4	1.10 (0.78-1.57)	0.59
RRT 90-days	32	1.3	29	1.2	1.09 (0.65-1.81)	0.73	30	1.2	31	1.2	0.97 (0.58-1.60)	0.90
CKD 90-days	28	1.1	25	1.0	1.10 (0.64-1.91)	0.71	26	1.0	27	1.1	0.96 (0.56-1.66)	0.89
ACS, HF, or stroke 90-day	272	10.8	251	10.1	1.08 (0.90-1.29)	0.40	244	9.8	279	11.2	0.86 (0.71-1.04)	0.11
All-cause hosp death 90-day	1071	42.7	1052	42.4	1.01 (0.90-1.13)	0.85	1069	42.8	1054	42.2	1.03 (0.91-1.15)	0.64

Weisbord et al: NEJM 378:603-614, 2018

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Take Home Points

- Uncontrolled studies are biased
- Controlled studies → CA-AKI unlikely
  - RCT is not possible
- Withholding contrast may harm patients
- ? Liberalization of contrast in patients with eGFR >30

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Take Home Points

- Contrast in presence of other risks may contribute in AKI
- Prevention
  - Low/iso-osmolar contrast
  - Lower dose
  - General AKI prevention

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Final message

Risk stratify (Other reason/s for Afferent Arteriolar Vasoconstriction)	
High risk	Low risk

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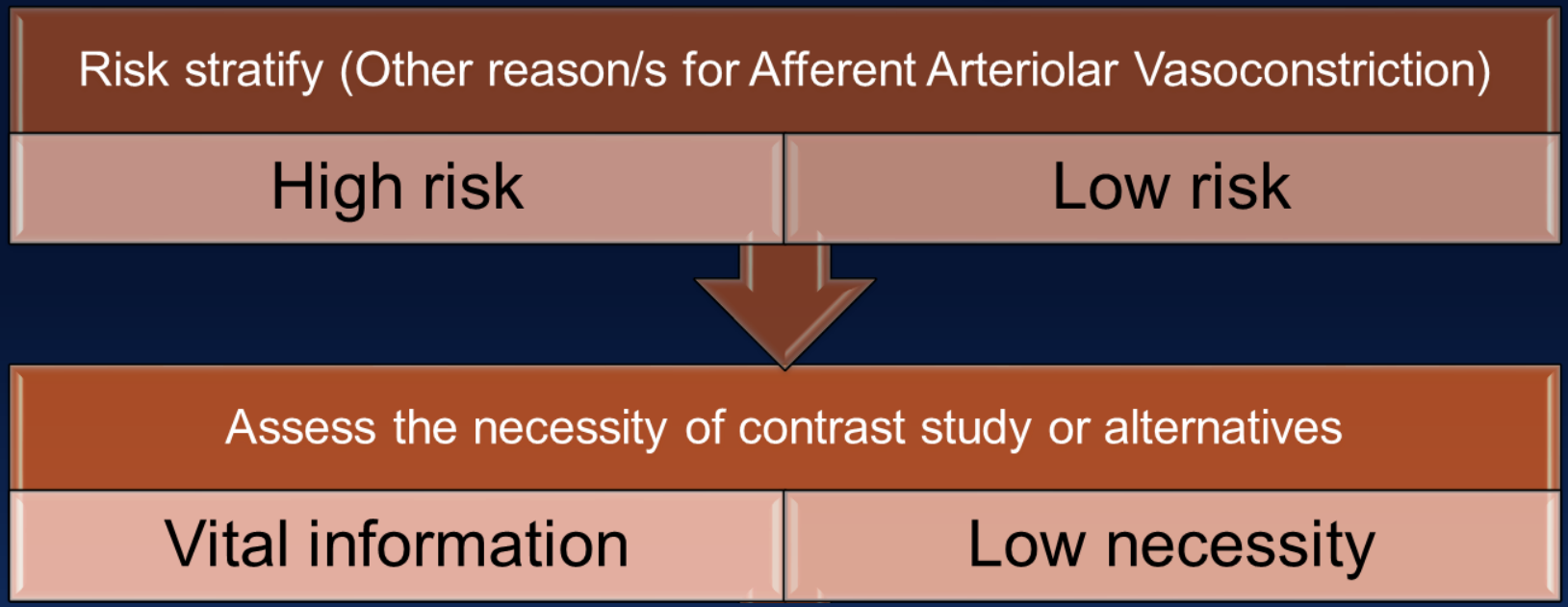
Final message



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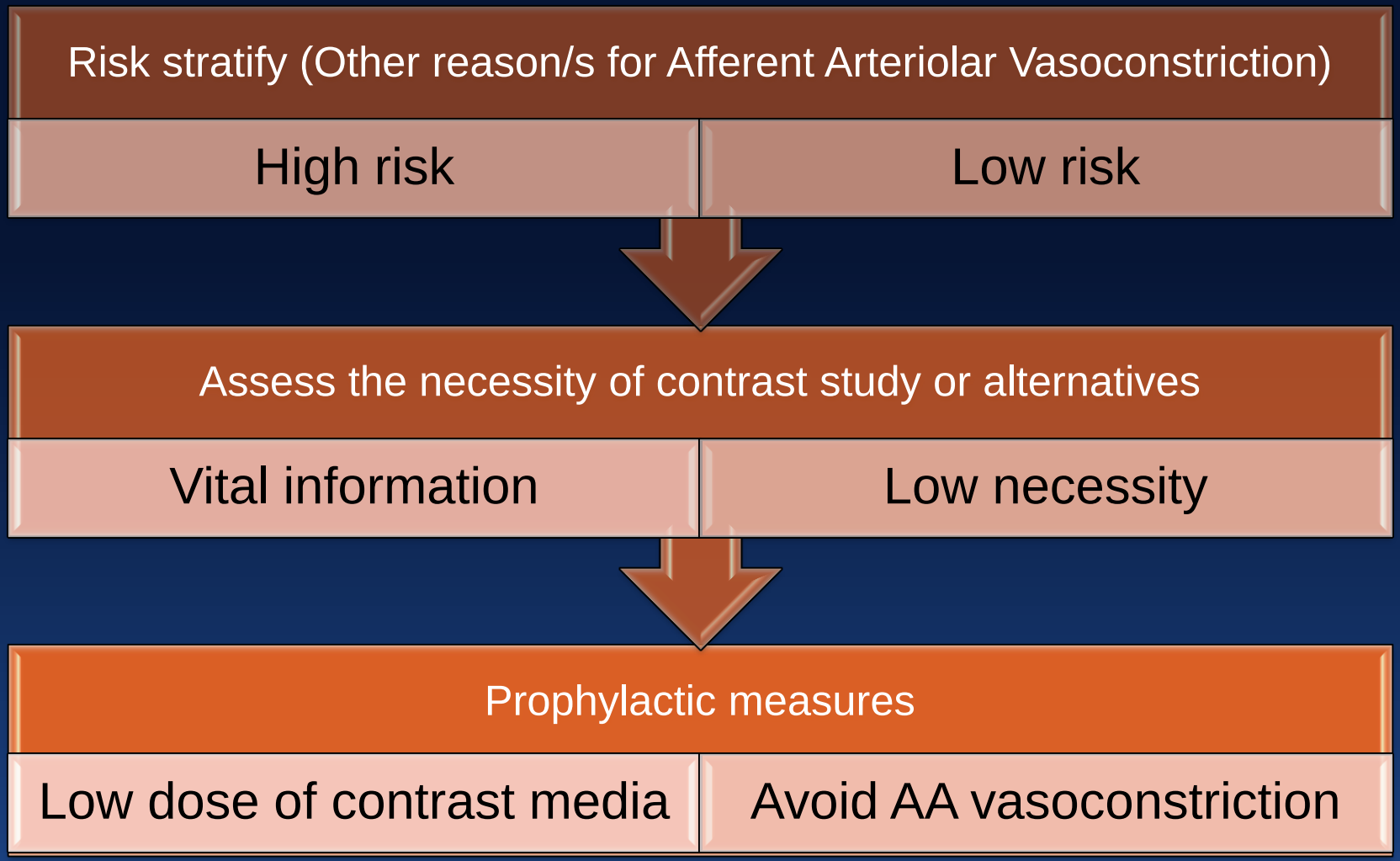
Final message



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THANK YOU FOR YOUR ATTENTION

از توجه شما بسیار متشکرم