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SCIENTIFIC SESSIONS 2017

Prevention of Serious Adverse Events Following Angiography (PRESERVE) Trial

VA Cooperative Studies Program Trial # 578

VA | U.S. Department of Veterans Affairs

VA Cooperative CSP Studies Program

Contrast-Associated Acute Kidney Injury (CA-AKI)

- Common post-angiography & associated with death, dialysis, progressive CKD
- Potentially preventable → known timing of renal insult
- Many trials of NaCl v. $NaHCO_3$ and of N-acetylcysteine (NAC)
  - Underpowered with divergent findings
  - Meta-analyses inconclusive
- Persistent equipoise on efficacy of $NaHCO_3$ and NAC despite widespread utilization in clinical practice
- PRESERVE was designed to address this equipoise

PRESERVE trial – hypotheses, design, and endpoints

1) Compared with isotonic IV NaCl, isotonic IV $NaHCO_3$ ↓ serious adverse outcomes following angiography
2) Compared with placebo, oral NAC ↓ serious adverse outcomes following angiography

Beneficial effect mediated by ↓ in CA-AKI

2 x 2 factorial design

1^0 endpoint – death, dialysis, or persistent ↑ SCr ≥ 50% @ 90 days

2^0 endpoints – CA-AKI (↑ SCr ≥ 0.5 mg/dL or ≥25% @ 4 days);

individual components of 1^0 endpoint; hospitalization for HF, stroke, ACS; all-cause hospitalization

Analyses – logistic regression including assessment of interaction fx

PRESERVE trial – pt population

- Pts undergoing coronary or non-coronary angiography
- Baseline eGFR - 45-60 mL/min + DM or 15-45 mL/min ± DM
- Key exclusions – emergent angiography, ongoing AKI, decompensated HF
- Sample size target – 7,680 pts
  - 90% power, p=0.025, relative 25% ↓ 1^0 endpoint for each intervention from 8.7% to 6.5%, 3% loss to f/u
- 53 sites in US, Australia, NZ, Malaysia

PRESERVE trial – study interventions

- **IV fluids ($NaHCO_3$/NaCl)**
  - Pre-angio 1-3 mL/kg/hr over 1-12 hrs → total volume 3-12 mL/kg
  - Intra-angio 1-1.5 mL/kg/hr
  - Post-angio 1-3 mL/kg/hr over 2-12 hrs → total volume 6-12 mL/kg
  - Local providers specified rate, duration, volume w/i these specific parameters

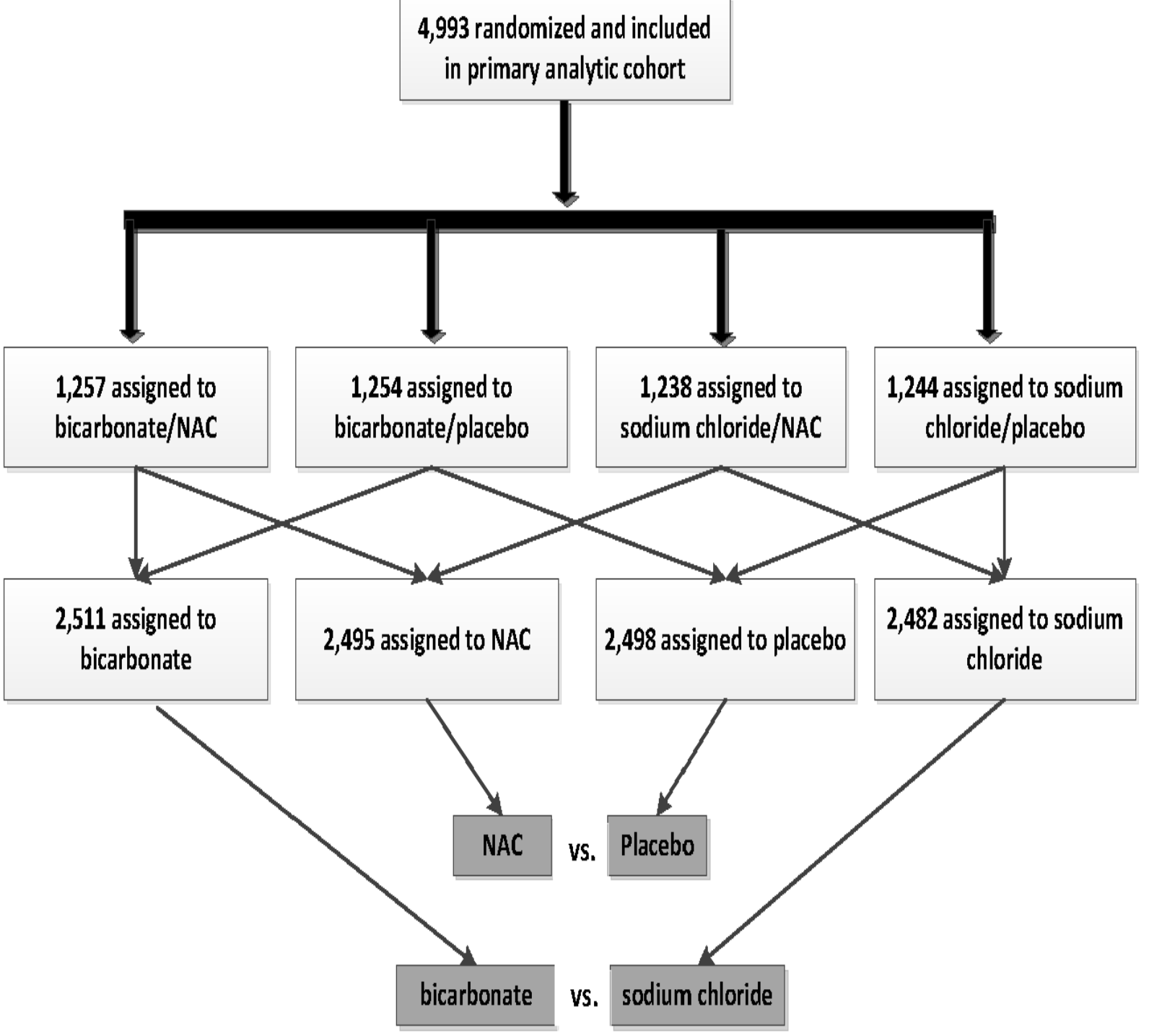
- **NAC/placebo capsules**
  - 1200 mg po bid x 5 days starting ~ 1 hr prior to angiography

Trial stopped by sponsor after 5,177 pts (67%) randomized @ pre-planned interim analysis based on:

- results to date
- conditional power <12% with full enrollment & all future events in control gps

- 4,993 pts in analytic cohort

- $NaHCO_3$*NAC interaction p=0.33



Pt/angio characteristics & study intervention comparisons

Variable	Overall	NaHCO3 (n=2511)	NaCl (n=2482)	NAC (n=2495)	Placebo (n=2498)
Age – (mean yr)	69.8	69.9	69.7	70.0	69.6
Diabetes (%)	80.9	80.4	81.5	80.7	81.3
Baseline SCr (median)	1.5	1			
Baseline eGFR (median)	50.2	5(			
Coronary angio (%)	90.5	9(			
Non-coronary angio (%)	9.5	9			
Intervention (%)	28.5	2			
Contrast volume (median)	85	85	85	85	85
Pre-IV fluid (median)	344	345	342	-	-
Intra-IV fluid (median)	114	114	114	-	-
Post-IV fluid (median)	570	570	569		
Capsule compliance (%)*	81.0	-	-	80.4	81.8

No differences across groups

*denotes % of pts fully compliant with capsules

Primary and secondary endpoint comparisons – $NaHCO_3$ vs. NaCl

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	Sodium bicarbonate (N=2,511)	Sodium chloride (N=2,482)	Odds ratio (95% CI)	p-value
Outcome	**no. of patients (%)**			
Primary end point	110 (4.4)	116 (4.7)	0.93 (0.72 - 1.22)	0.62
Secondary end points				
Contrast-associated acute kidney injury	239 (9.5)	206 (8.3)	1.16 (0.96 - 1.41)	0.13
Death by day 90	60 (2.4)	68 (2.7)	0.87 (0.61 - 1.24)	0.43
Need for dialysis by day 90			1.09 (0.65 - 1.81)	0.73
Persistent renal impairmer			1.10 (0.64 - 1.91)	0.71
Hospitalization with ACS, h stroke at 90 days			1.08 (0.90 - 1.29)	0.40
All-cause hospitalization by day 90	1071 (42.7)	1052 (42.4)	1.01 (0.90 - 1.13)	0.85

No differences in any 2^0 endpoints

Primary and secondary endpoint comparisons – NAC vs. placebo

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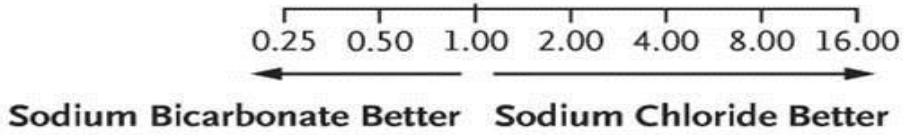
	NAC (N=2,495)	Placebo (N=2,498)	Odds ratio (95% CI)	p-value
Outcome	**no of patients (%)**			
Primary end point*	114 (4.6)	112 (4.5)	1.02 (0.78 - 1.33)	0.88
Secondary end points				
Contrast-associated acute kidney injury†	228 (9.1)	217 (8.7)	1.06 (0.87 - 1.28)	0.58
Death by day 90	67 (2.7)	61 (2.4)	1.10 (0.78 - 1.57)	0.59
Need for dialysis by day 90			0.97 (0.58 - 1.60)	0.90
Persistent renal impairment			0.96 (0.56 - 1.66)	0.89
Hospitalization with ACS, he stroke at 90 days‡			0.86 (0.71 - 1.04)	0.11
All-cause hospitalization by day 90	1069 (42.9)	1054 (42.2)	1.03 (0.91 - 1.15)	0.64

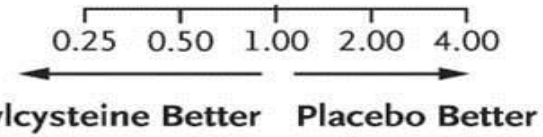
No differences in any 2^0 endpoints

Pre-specified sub-groups – 1º endpoint

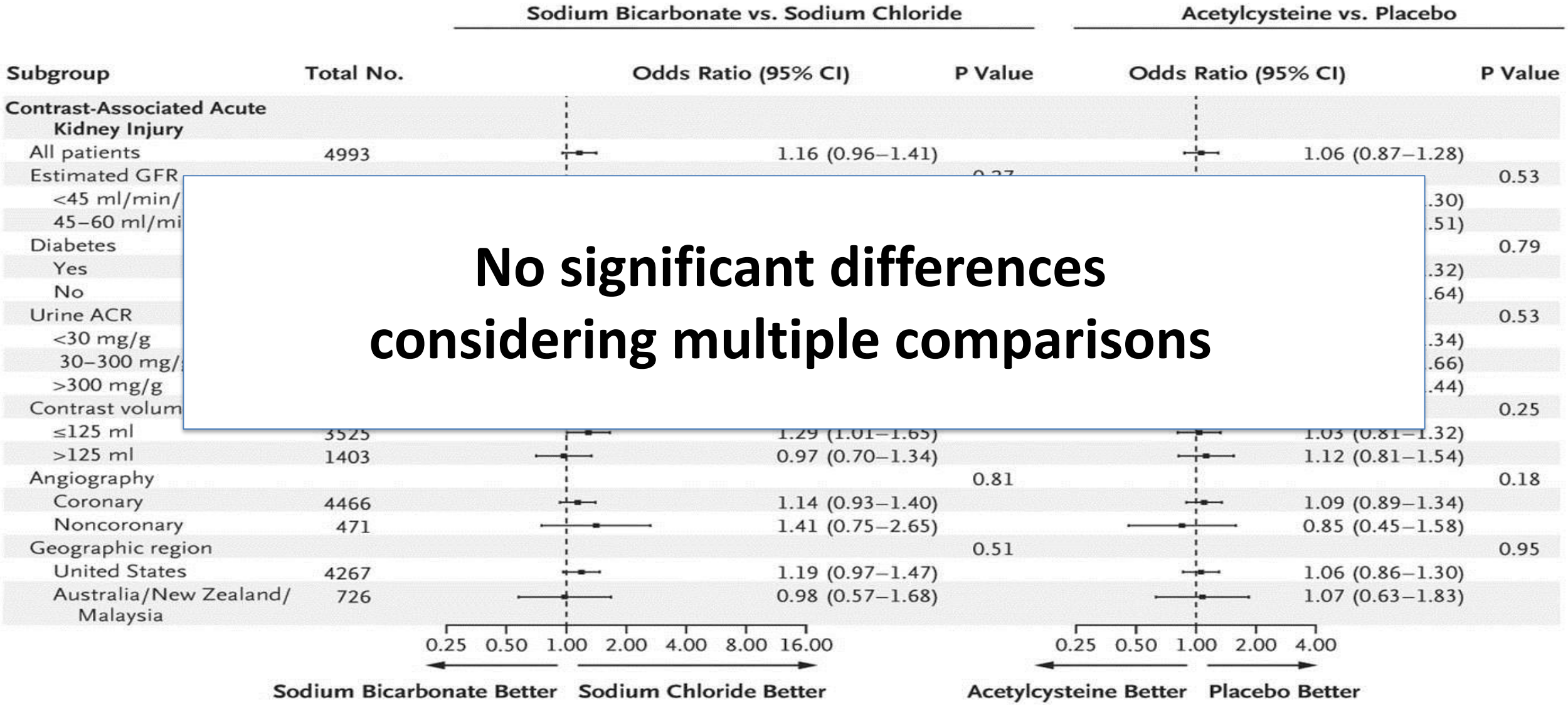
Subgroup	Total No.	Sodium Bicarbonate vs. Sodium Chloride: Odds Ratio (95% CI)	P Value	Acetylcysteine vs. Placebo: Odds Ratio (95% CI)	P Value
Primary End Point					
All patients	4993	0.93 (0.72–1.22)		1.02 (0.78–1.33)	
Estimated GFR			0.79		0.79
<45 ml/min/1.73 m²	2615	0.91 (0.65–1.26)		0.98 (0.71–1.37)	
45–60 ml/mi				.67)	
Diabetes					0.25
Yes				.27)	
No				.48)	
Urine ACR					0.12
≤30 mg/g				.62)	
30–300 mg/g				.66)	
>300 mg/g				.12)	
Contrast volum					0.19
≤125 ml				.26)	
>125 ml		1.01 (0.61–1.67)		1.19 (0.72–1.98)	
Angiography			0.02		0.29
Coronary	4466	0.83 (0.62–1.10)		1.00 (0.75–1.32)	
Noncoronary	471	3.19 (1.03–9.94)		0.91 (0.35–2.41)	
Geographic region			0.73		0.48
United States	4267	0.92 (0.69–1.22)		1.06 (0.79–1.40)	
Australia/New Zealand/ Malaysia	726	1.06 (0.49–2.29)		0.79 (0.36–1.71)	

No significant differences considering multiple comparisons





Pre-specified sub-groups – CA-AKI



No significant differences considering multiple comparisons

PRESERVE trial - summary

- IV $NaHCo_3$ is **not more effective** than IV NaCl for prevention of serious outcomes or AKI following angiography
- NAC is **not effective** for prevention of serious outcomes or AKI following angiography
- Current standard of care for prevention of CA-AKI and associated adverse outcomes should be:
  - IV isotonic NaCl
  - No use of NAC

PRESERVE trial sites

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Department of Veterans Affairs
VA Cooperative Studies program-funded sites

MAVERIC – Boston – DCC
Albuquerque
Ann Arbor
Atlanta
Augusta
Bay Pines
Boston
Buffalo
Charleston
Cincinnati
Cleveland
Dallas
Dayton
Durham
Gainesville
Houston
Indianapolis
Kansas City
Little Rock
Memphis
Minneapolis
New York Harbor
Oklahoma City
Palo Alto
Pittsburgh
Portland
Richmond
St. Louis
Salem
San Antonio
San Francisco
Salt Lake City
Seattle
West Los Angeles
Tucson
Albuquerque CRPCC

George Institute for Global Health
NHMRC of Australia funded-sites

Austin Health
Auckland City Hospital
Concord Hospital
Gosford Hospital
Liverpool Hospital
Nepean Hospital
Royal North Shore Hospital
St. George Hospital
Flinders Medical Centre
Northern Health
Fremantle Hospital
Royal Perth Hospital
Wellington Hospital
University Malaya Medical Centre
Hospital Pulau Pinang
Canberra Hospital
Hospital Serdang
Taranaki Base Hospital

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Outcomes after Angiography with Sodium Bicarbonate and Acetylcysteine

S.D. Weisbord, M. Gallagher, H. Jneid, S. Garcia, A. Cass, S.-S. Thwin, T.A. Conner, G.M. Chertow, D.L. Bhatt, K. Shunk, C.R. Parikh, E.O. McFalls, M. Brophy, R. Ferguson, H. Wu, M. Androsenko, J. Myles, J. Kaufman, and P.M. Palevsky, for the PRESERVE Trial Group*