Fluids, steroids, anti-psychotics

Anders Perner

Billedet kan ikke vises. Computeren har muligvis ikke hukommelse nok til at åbne billedet, eller billedet er muligvis blevet beskadiget. Genstart computeren, og åbn derefter filen igen. Hvis det røde x stadig vises, skal du muligvis slette billedet og indsætte det igen.

Billedet kan ikke vises. Computeren har muligvis ikke hukommelse nok til at åbne billedet, eller billedet er muligvis blevet beskadiget. Genstart computeren, og åbn derefter filen igen. Hvis det røde x stadig vises, skal du muligvis slette billedet og indsætte det igen.

Billedet kan ikke vises. Computeren har muligvis ikke hukommelse nok til at åbne billedet, eller billedet er muligvis blevet beskadiget.

University of Copenhagen

Billedet kan ikke vises. Computeren har muligvis ikke hukommelse nok til at åbne billedet, eller billedet er muligvis blevet beskadiget. Genstart computeren, og åbn derefter filen igen. Hvis det røde x stadig vises, skal du muligvis slette billedet og indsætte det igen.

COIs

Research funds from Ferring Pharmaceuticals

SPECIAL EDITORIAL

The Surviving Sepsis Campaign Bundle: 2018 update

Mitchell M. Levy[1*], Laura E. Evans[2] and Andrew Rhodes[3]

Hour-1 bundle

Bundle element	Grade of recommendation and level of evidence
Measure lactate level. Re-measure if initial lactate is > 2 mmol/L	Weak recommendation, low quality of evidence
Obtain blood cultures prior to administration of antibiotics	Best practice statement
Administer broad-spectrum antibiotics	Strong recommendation, moderate quality of evidence
Rapidly administer 30 ml/kg crystalloid for hypotension or lactate ≥ 4 mmol/L	Strong recommendation, low quality of evidence
Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥ 65 mm Hg	Strong recommendation, moderate quality of evidence

Petition to retire the surviving sepsis campaign guidelines

https://emcrit.org/

No clean IV large fluid RCTs in early resus in adults

Classic

Systematic Review

SPECIAL ARTICLE

Lower vs. higher fluid volumes in sepsis—protocol for a systematic review with meta-analysis

T. S. Meyhoff[1,2], M. H. Møller[1,2], P. B. Hjortrup[1,2], M. Cronhjort[3], A. Perner[1,2] and J. Wetterslev[2,4]

[1]Department of Intensive Care 4131, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark
[2]Centre for Research in Intensive Care (CRIC), Copenhagen, Denmark
[3]Department of Clinical Science and Education, Södersjukhuset, Section of Anaesthesia and Intensive Care, Karolinska Institutet, Stockholm, Sweden
[4]Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

Correspondence
T. S. Meyhoff, Department of Intensive Care 4131, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, DK-2100, Copenhagen, Denmark
E-mail: tine.sylvest.meyhoff@regionh.dk

Background: Intravenous fluid administration with crystalloids is recommended in the initial management of sepsis. However, the quality of evidence supporting the recommendation on fluid volumes is low, and clinical equipoise exists. Potential benefits of restricting fluid volumes has been suggested, but the overall ben-

Methods

- **Population: Adult hospitalized patients with sepsis**

- **Intervention: Separation in fluid volumes or balances during resuscitation**

Results

- **7 trials included**
  - **2 sepsis, 5 septic shock**
  - **High-income countries**
  - **Contemporary trials – 2015 and onwards**
  - **Perceived restrictive intervention vs standard-care**

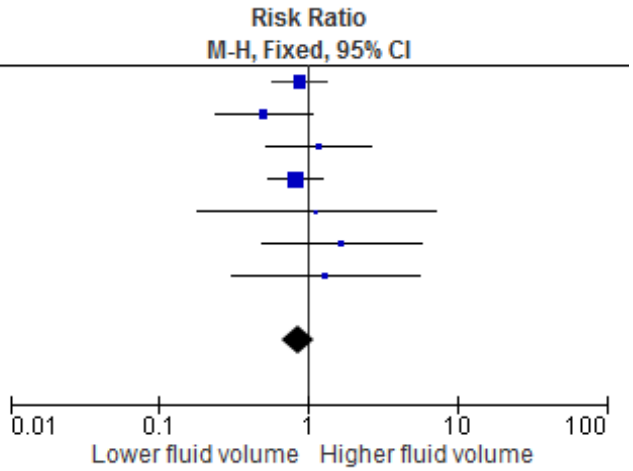
Classic

Mortality with lower vs. higher fluid volume in adults with sepsis

Study or Subgroup	Events	Total	Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Chen and Kollef 2015	20	41	23	41	28.1%	0.87 [0.57, 1.32]	2015
Richard et al. 2015	7	30	14	30	17.1%	0.50 [0.24, 1.06]	2015
Van Genderen et al. 2015	7	15	6	15	7.3%	1.17 [0.51, 2.66]	2015
Hjortrup et al. 2016	25	75	31	76	37.7%	0.82 [0.54, 1.24]	2016
Cronhjort et al. 2017	2	16	2	18	2.3%	1.13 [0.18, 7.09]	2017
Lanspa et al. 2018	5	15	3	15	3.7%	1.67 [0.48, 5.76]	2018
Macdonald et al. 2018	4	48	3	47	3.7%	1.31 [0.31, 5.52]	2018
Total (95% CI)		**240**		**242**	**100.0%**	**0.86 [0.67, 1.10]**	
Total events	70		82				

Heterogeneity: $Chi^2 = 4.08$, $df = 6$ ($P = 0.67$); $I^2 = 0\%$

Test for overall effect: $Z = 1.18$ ($P = 0.24$)



Unpublished

!?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

!?

Restrictive versus Liberal Fluid Therapy for Major Abdominal Surgery

P.S. Myles, R. Bellomo, T. Corcoran, A. Forbes, P. Peyton, D. Story, C. Christophi, K. Leslie, S. McGuinness, R. Parke, J. Serpell, M.T.V. Chan, T. Painter, S. McCluskey, G. Minto, and S. Wallace, for the Australian and New Zealand College of Anaesthetists Clinical Trials Network and the Australian and New Zealand Intensive Care Society Clinical Trials Group*

Table 2. Blood Loss and Administered Intravenous-Fluid Volumes.*

Variable	Restrictive Fluid (N = 1490)	Liberal Fluid (N = 1493)	P Value
At 24 hr after surgery			
Median cumulative total for intravenous fluids (IQR) — ml	3671 (2885 to 4880)	6146 (5000 to 7410)	<0.001
Median fluid balance (IQR) — ml¶	1380 (540 to 2338)	3092 (2010 to 4241)	<0.001†
Median weight gain (IQR) — kg‖	0.3 (−1.0 to 1.9)	1.6 (0.0 to 3.6)	ND

Outcome	Restrictive Fluid (N=1490)	Liberal Fluid (N=1493)	Hazard or Risk Ratio (95% CI)†	P Value
Primary outcome				
Disability-free survival at 1 yr — no. (%)‡	1223 (81.9)	1232 (82.3)	1.05 (0.88–1.24)	0.61
Death or persistent disability — no.	267	261		
Death	95	96		
Persistent disability	172	165		
Secondary outcomes§				
Composite septic outcome or death — no./total no. (%)¶	323/1481 (21.8)	295/1487 (19.8)	1.10 (0.96–1.27)	0.19
Surgical-site infection — no./total no. (%)	245/1481 (16.5)	202/1487 (13.6)	1.22 (1.03–1.45)	0.02
Sepsis — no./total no. (%)	157/1481 (10.6)	129/1487 (8.7)	1.22 (0.98–1.52)	0.08
Anastomotic leak — no./total no. (%)	49/1481 (3.3)	35/1487 (2.4)	1.41 (0.92–2.16)	0.12
Pneumonia — no./total no. (%)	54/1481 (3.6)	57/1487 (3.8)	0.95 (0.66–1.37)	0.79
Acute kidney injury — no./total no. (%)**	124/1443 (8.6)	72/1439 (5.0)	1.71 (1.29–2.27)	<0.001
Renal-replacement therapy — no./total no. (%)	13/1460 (0.9)	4/1462 (0.3)	3.27 (1.01–13.8)	0.048
Pulmonary edema — no./total no. (%)	20/1481 (1.4)	32/1487 (2.2)	0.63 (0.36–1.09)	0.10
Unplanned admission to ICU — no./total no. (%)	161/1487 (10.8)	145/1491 (9.7)	1.11 (0.90–1.38)	0.32
Median peak serum lactate level (IQR) — mmol per liter††	1.6 (1.1–2.5)	1.6 (1.1–2.4)	NA	NA
Median C-reactive protein level on day 3 (IQR) — mg per liter‡‡	136 (82–198)	133 (80–200)	NA	0.66
Median duration of mechanical ventilation (IQR) — hr§§	17 (5–65)	14 (3–31)	NA	0.07
Median score on quality-of-recovery scale (IQR)¶¶	106 (89–121)	107 (90–122)	NA	0.31
Median duration of stay in HDU or ICU (IQR) — days‖‖	1.8 (1.0–3.1)	1.4 (0.9–2.9)	NA	0.13
Median duration of hospital stay (IQR) — days	6.4 (3.6–10.6)	5.6 (3.6–10.5)	NA	0.26
Death — no. (%)‡				
At 90 days	31 (2.1)	18 (1.2)	1.73 (0.97–3.10)	0.06
At 12 mo	95 (6.5)	96 (6.6)	1.03 (0.78–1.36)	0.86

Funded by NNF…

Effects of Restricting Intravenous Fluids in Patients with Septic Shock on Patient-important Outcomes

1554 patient randomized trial

50 ICUs in

DK, S, FIN, N, NL, F, CH, UK, I, Cz, Esp

1st pt enrolled 27th November 2018


50 bags of chips= 1 liter 0.9% NaCl
Lay's
Classic
0.9%
SODIUM CHLORIDE
INJECTION, USP
(Sean Bagshaw)

which crystalloid?

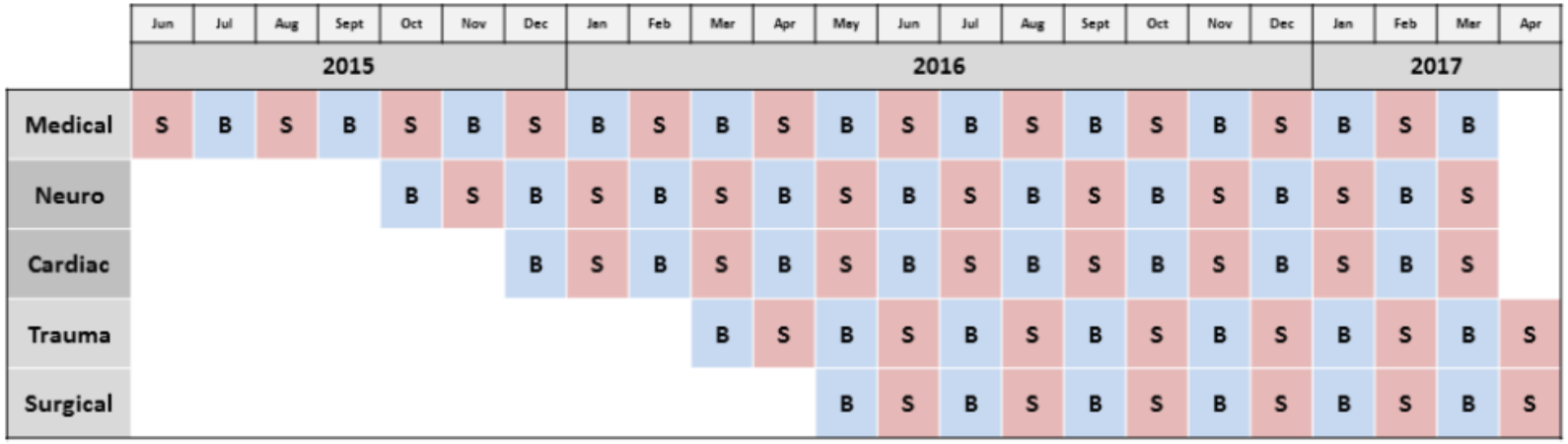
- No IV fluids match plasma
- Unphysiologic load of chloride 154 mmol/l
- Unphysiologic load of…
  - Acetate 25 mmol/l
  - Lactate 25 mmol/l
  - Acetate 25 mmol/l + Gluconate 25 mmol/l

ORIGINAL ARTICLE

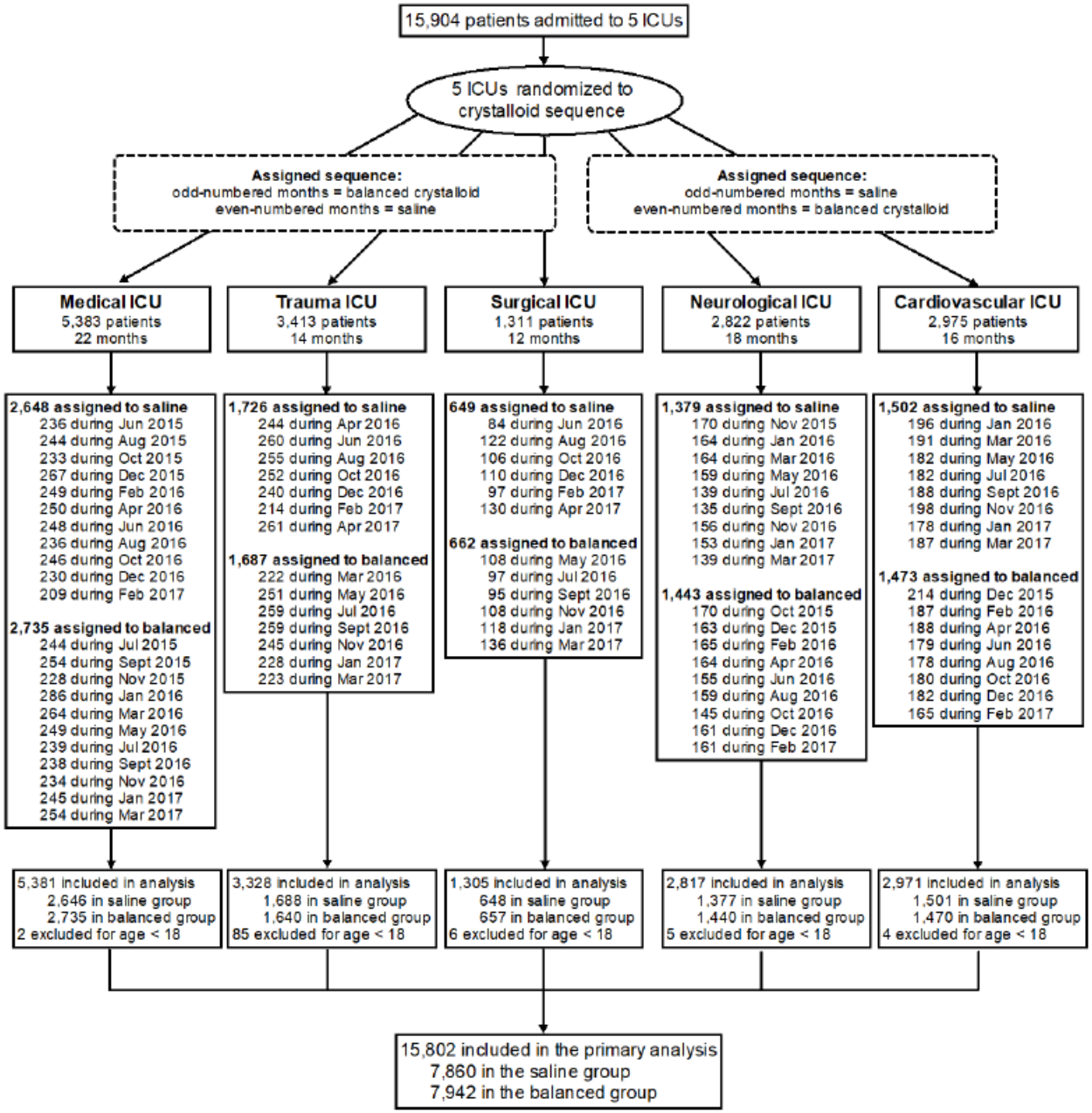
Balanced Crystalloids versus Saline in Critically Ill Adults

Matthew W. Semler, M.D., Wesley H. Self, M.D., M.P.H., Jonathan P. Wanderer, M.D., Jesse M. Ehrenfeld, M.D., M.P.H., Li Wang, M.S., Daniel W. Byrne, M.S., Joanna L. Stollings, Pharm.D., Avinash B. Kumar, M.D., Christopher G. Hughes, M.D., Antonio Hernandez, M.D., Oscar D. Guillamondegui, M.D., M.P.H., Addison K. May, M.D., Liza Weavind, M.B., B.Ch., Jonathan D. Casey, M.D., Edward D. Siew, M.D., Andrew D. Shaw, M.B., Gordon R. Bernard, M.D., and Todd W. Rice, M.D., for the SMART Investigators and the Pragmatic Critical Care Research Group*

Allocation to saline vs. balanced solutions

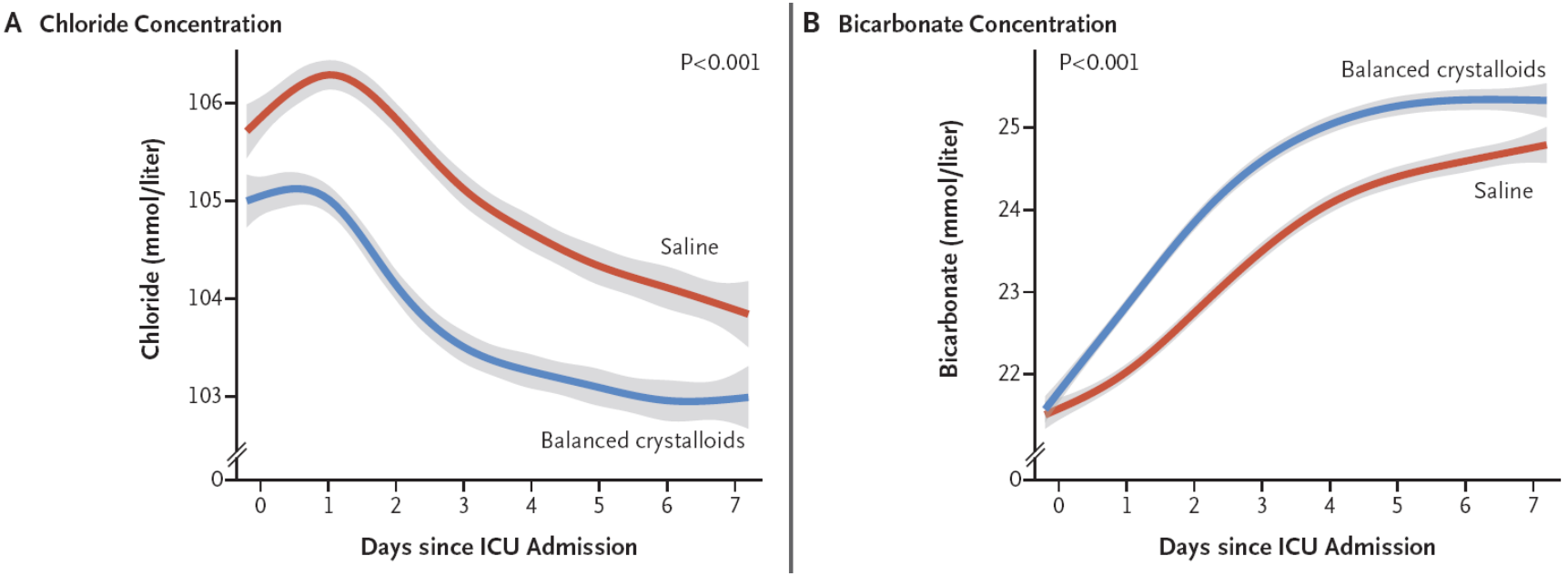


	Jun	Jul	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	Apr
	2015							2016												2017			
Medical	S	B	S	B	S	B	S	B	S	B	S	B	S	B	S	B	S	B	S	B	S	B	
Neuro					B	S	B	S	B	S	B	S	B	S	B	S	B	S	B	S	B	S	
Cardiac							B	S	B	S	B	S	B	S	B	S	B	S	B	S	B	S	
Trauma										B	S	B	S	B	S	B	S	B	S	B	S	B	S
Surgical												B	S	B	S	B	S	B	S	B	S	B	S


15,904 patients admitted to 5 ICUs
5 ICUs randomized to crystalloid sequence
Assigned sequence:
odd-numbered months = balanced crystalloid
even-numbered months = saline
Assigned sequence:
odd-numbered months = saline
even-numbered months = balanced crystalloid
Medical ICU
5,383 patients
22 months
Trauma ICU
3,413 patients
14 months
Surgical ICU
1,311 patients
12 months
Neurological ICU
2,822 patients
18 months
Cardiovascular ICU
2,975 patients
16 months
2,648 assigned to saline
236 during Jun 2015
244 during Aug 2015
233 during Oct 2015
267 during Dec 2015
249 during Feb 2016
250 during Apr 2016
248 during Jun 2016
236 during Aug 2016
246 during Oct 2016
230 during Dec 2016
209 during Feb 2017
2,735 assigned to balanced
244 during Jul 2015
254 during Sept 2015
228 during Nov 2015
286 during Jan 2016
264 during Mar 2016
249 during May 2016
239 during Jul 2016
238 during Sept 2016
234 during Nov 2016
245 during Jan 2017
254 during Mar 2017
1,726 assigned to saline
244 during Apr 2016
260 during Jun 2016
255 during Aug 2016
252 during Oct 2016
240 during Dec 2016
214 during Feb 2017
261 during Apr 2017
1,687 assigned to balanced
222 during Mar 2016
251 during May 2016
259 during Jul 2016
259 during Sept 2016
245 during Nov 2016
228 during Jan 2017
223 during Mar 2017
649 assigned to saline
84 during Jun 2016
122 during Aug 2016
106 during Oct 2016
110 during Dec 2016
97 during Feb 2017
130 during Apr 2017
662 assigned to balanced
108 during May 2016
97 during Jul 2016
95 during Sept 2016
108 during Nov 2016
118 during Jan 2017
136 during Mar 2017
1,379 assigned to saline
170 during Nov 2015
164 during Jan 2016
164 during Mar 2016
159 during May 2016
139 during Jul 2016
135 during Sept 2016
156 during Nov 2016
153 during Jan 2017
139 during Mar 2017
1,443 assigned to balanced
170 during Oct 2015
163 during Dec 2015
165 during Feb 2016
164 during Apr 2016
155 during Jun 2016
159 during Aug 2016
145 during Oct 2016
161 during Dec 2016
161 during Feb 2017
1,502 assigned to saline
196 during Jan 2016
191 during Mar 2016
182 during May 2016
182 during Jul 2016
188 during Sept 2016
198 during Nov 2016
178 during Jan 2017
187 during Mar 2017
1,473 assigned to balanced
214 during Dec 2015
187 during Feb 2016
188 during Apr 2016
179 during Jun 2016
178 during Aug 2016
180 during Oct 2016
182 during Dec 2016
165 during Feb 2017
5,381 included in analysis
2,646 in saline group
2,735 in balanced group
2 excluded for age < 18
3,328 included in analysis
1,688 in saline group
1,640 in balanced group
85 excluded for age < 18
1,305 included in analysis
648 in saline group
657 in balanced group
6 excluded for age < 18
2,817 included in analysis
1,377 in saline group
1,440 in balanced group
5 excluded for age < 18
2,971 included in analysis
1,501 in saline group
1,470 in balanced group
4 excluded for age < 18
15,802 included in the primary analysis
7,860 in the saline group
7,942 in the balanced group

Chloride

Bicarbonate



Primary outcome

Outcome	Balanced Crystalloids (N=7942)	Saline (N=7860)	Adjusted Odds Ratio (95% CI)†	P Value†
Primary outcome				
Major adverse kidney event within 30 days — no. (%)‡	1139 (14.3)	1211 (15.4)	0.90 (0.82 to 0.99)	0.04
Components of primary outcome				
In-hospital death before 30 days — no. (%)	818 (10.3)	875 (11.1)	0.90 (0.80 to 1.01)	0.06
Receipt of new renal-replacement therapy — no./total no. (%)§	189/7558 (2.5)	220/7458 (2.9)	0.84 (0.68 to 1.02)	0.08
Among survivors	106/6787 (1.6)	117/6657 (1.8)		
Final creatinine level ≥200% of baseline — no./total no. (%)§	487/7558 (6.4)	494/7458 (6.6)	0.96 (0.84 to 1.11)	0.60

NNT 100

Alternative explanations: Cluster trial, bias

Individual patient RCT

BASICs trial – 13.000 pts

PLUS trial – 8500 pts

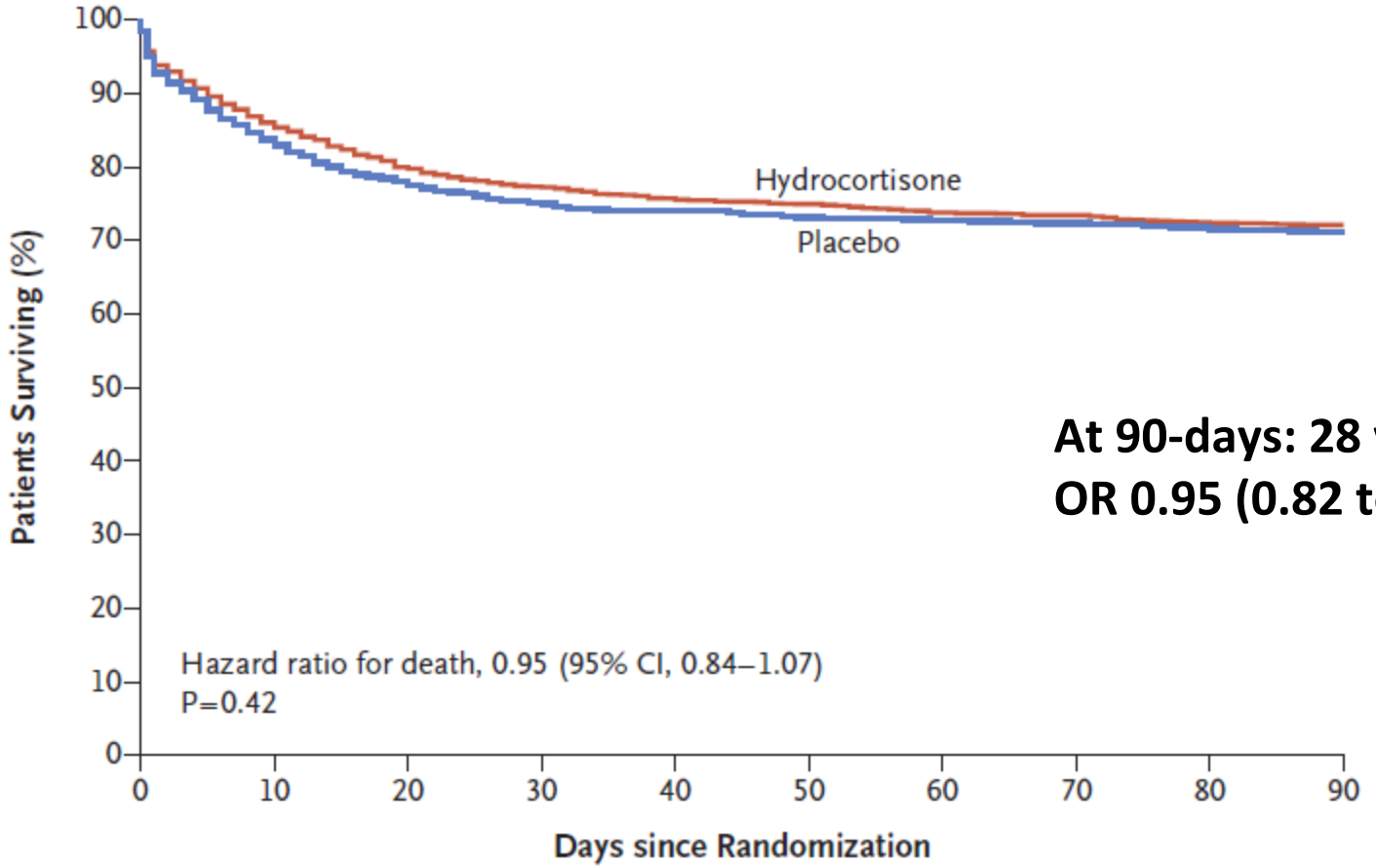
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

B. Venkatesh, S. Finfer, J. Cohen, D. Rajbhandari, Y. Arabi, R. Bellomo, L. Billot, M. Correa, P. Glass, M. Harward, C. Joyce, Q. Li, C. McArthur, A. Perner, A. Rhodes, K. Thompson, S. Webb, and J. Myburgh, for the ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group*

Mortality



At 90-days: 28 vs 29%
OR 0.95 (0.82 to 1.10)

No. at Risk

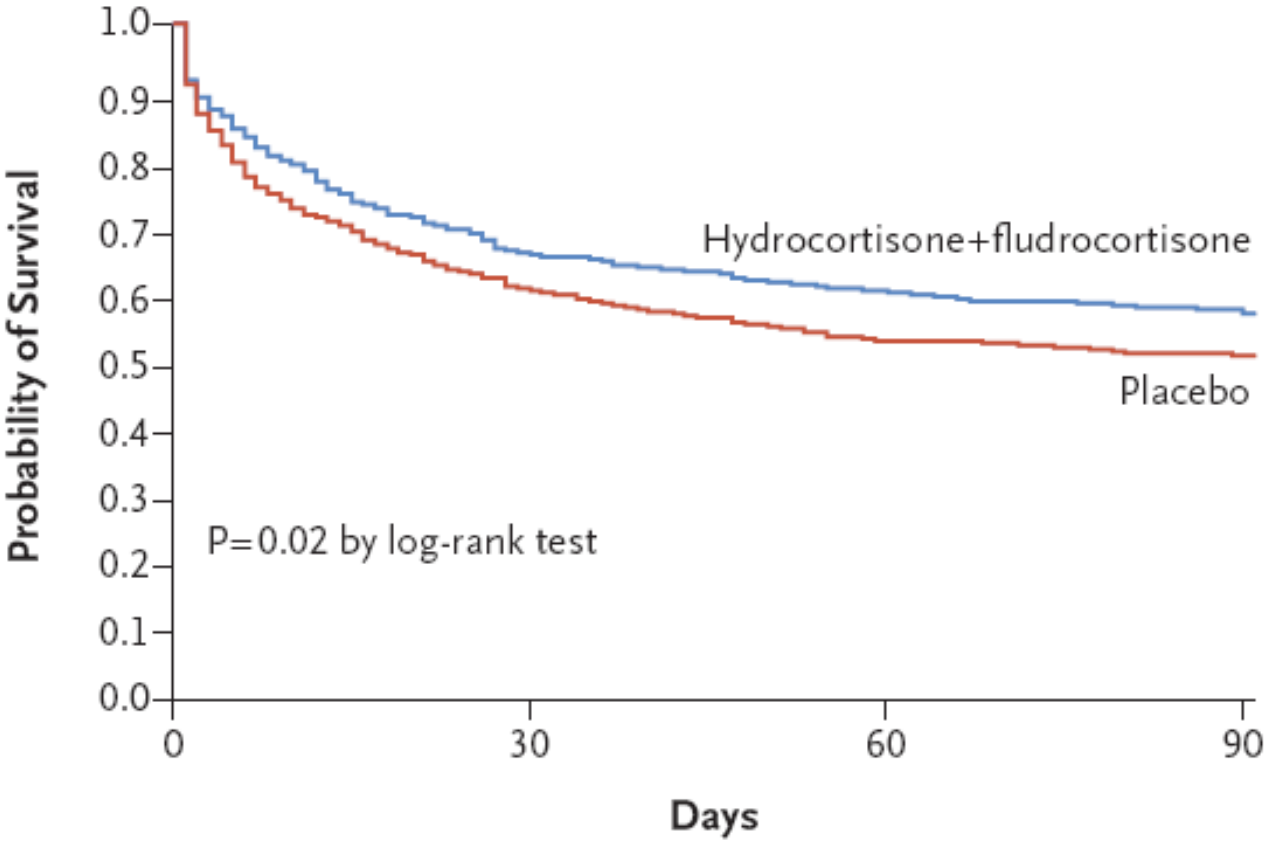
Hydrocortisone	1832	1591	1481	1418	1388	1374	1356	1348	1328	1321
Placebo	1826	1546	1433	1376	1354	1337	1330	1322	1312	1300

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hydrocortisone plus Fludrocortisone for Adults with Septic Shock

D. Annane, A. Renault, C. Brun-Buisson, B. Megarbane, J.-P. Quenot, S. Siami, A. Cariou, X. Forceville, C. Schwebel, C. Martin, J.-F. Timsit, B. Misset, M. Ali Benali, G. Colin, B. Souweine, K. Asehnoune, E. Mercier, L. Chimot, C. Charpentier, B. François, T. Boulain, F. Petitpas, J.-M. Constantin, G. Dhonneur, F. Baudin, A. Combes, J. Bohé, J.-F. Loriferne, R. Amathieu, F. Cook, M. Slama, O. Leroy, G. Capellier, A. Dargent, T. Hissem, V. Maxime, and E. Bellissant, for the CRICS-TRIGGERSEP Network*


Probability of Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
30
60
90
Days
Hydrocortisone+fludrocortisone
Placebo
P=0.02 by log-rank test

Intensive Care Med (2018) 44:1003–1016
https://doi.org/10.1007/s00134-018-5197-6

SEVEN-DAY PROFILE PUBLICATION

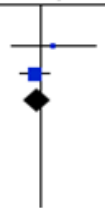
Low-dose corticosteroids for adult patients with septic shock: a systematic review with meta-analysis and trial sequential analysis

Sofie Louise Rygård[1], Ethan Butler[2], Anders Granholm[1], Morten Hylander Møller[1,3], Jeremy Cohen[4,5], Simon Finfer[6,9], Anders Perner[1,3], John Myburgh[2,6,7], Balasubramanian Venkatesh[5,8] and Anthony Delaney[9,10*]

Study or Subgroup	Corticosteroids Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
1.6.1 Trials adjudicated as overall low risk of bias							
Gordon 2016	66	201	62	207	4.5%	1.10 [0.82, 1.46]	2016
Venkatesh 2018	511	1832	526	1826	39.2%	0.97 [0.87, 1.07]	2018
Subtotal (95% CI)		**2033**		**2033**	**43.7%**	**0.98 [0.89, 1.08]**	
Total events	577		588				

Heterogeneity: $Chi^2 = 0.64$, df = 1 (P = 0.43); $I^2 = 0\%$

Test for overall effect: Z = 0.38 (P = 0.71)

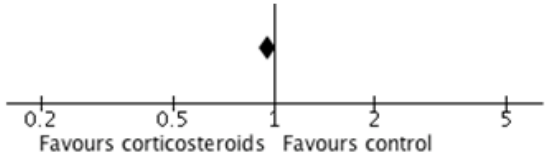


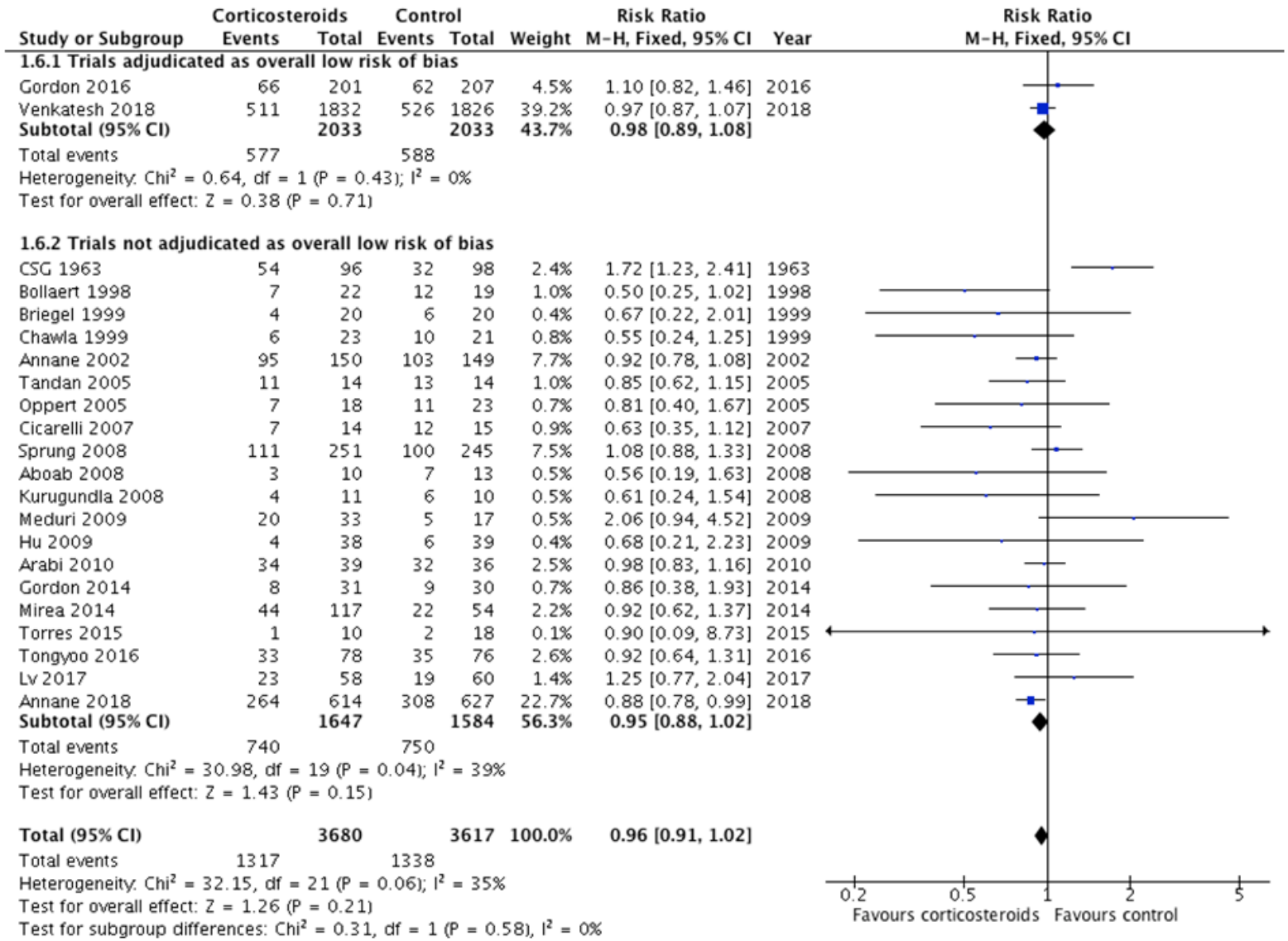
Total (95% CI)	**3680**		**3617**	**100.0%**	**0.96 [0.91, 1.02]**	
Total events	1317		1338			

Heterogeneity: $Chi^2 = 32.15$, df = 21 (P = 0.06); $I^2 = 35\%$

Test for overall effect: Z = 1.26 (P = 0.21)

Test for subgroup differences: $Chi^2 = 0.31$, df = 1 (P = 0.58), $I^2 = 0\%$




Corticosteroids
Control
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Fixed, 95% CI
Year
M-H, Fixed, 95% CI
1.6.1 Trials adjudicated as overall low risk of bias
Gordon 2016 66 201 62 207 4.5% 1.10 [0.82, 1.46] 2016
Venkatesh 2018 511 1832 526 1826 39.2% 0.97 [0.87, 1.07] 2018
Subtotal (95% CI) 2033 2033 43.7% 0.98 [0.89, 1.08]
Total events 577 588
Heterogeneity: Chi² = 0.64, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.38 (P = 0.71)
1.6.2 Trials not adjudicated as overall low risk of bias
CSG 1963 54 96 32 98 2.4% 1.72 [1.23, 2.41] 1963
Bollaert 1998 7 22 12 19 1.0% 0.50 [0.25, 1.02] 1998
Briegel 1999 4 20 6 20 0.4% 0.67 [0.22, 2.01] 1999
Chawla 1999 6 23 10 21 0.8% 0.55 [0.24, 1.25] 1999
Annane 2002 95 150 103 149 7.7% 0.92 [0.78, 1.08] 2002
Tandan 2005 11 14 13 14 1.0% 0.85 [0.62, 1.15] 2005
Oppert 2005 7 18 11 23 0.7% 0.81 [0.40, 1.67] 2005
Cicarelli 2007 7 14 12 15 0.9% 0.63 [0.35, 1.12] 2007
Sprung 2008 111 251 100 245 7.5% 1.08 [0.88, 1.33] 2008
Aboab 2008 3 10 7 13 0.5% 0.56 [0.19, 1.63] 2008
Kurugundla 2008 4 11 6 10 0.5% 0.61 [0.24, 1.54] 2008
Meduri 2009 20 33 5 17 0.5% 2.06 [0.94, 4.52] 2009
Hu 2009 4 38 6 39 0.4% 0.68 [0.21, 2.23] 2009
Arabi 2010 34 39 32 36 2.5% 0.98 [0.83, 1.16] 2010
Gordon 2014 8 31 9 30 0.7% 0.86 [0.38, 1.93] 2014
Mirea 2014 44 117 22 54 2.2% 0.92 [0.62, 1.37] 2014
Torres 2015 1 10 2 18 0.1% 0.90 [0.09, 8.73] 2015
Tongyoo 2016 33 78 35 76 2.6% 0.92 [0.64, 1.31] 2016
Lv 2017 23 58 19 60 1.4% 1.25 [0.77, 2.04] 2017
Annane 2018 264 614 308 627 22.7% 0.88 [0.78, 0.99] 2018
Subtotal (95% CI) 1647 1584 56.3% 0.95 [0.88, 1.02]
Total events 740 750
Heterogeneity: Chi² = 30.98, df = 19 (P = 0.04); I² = 39%
Test for overall effect: Z = 1.43 (P = 0.15)
Total (95% CI) 3680 3617 100.0% 0.96 [0.91, 1.02]
Total events 1317 1338
Heterogeneity: Chi² = 32.15, df = 21 (P = 0.06); I² = 35%
Test for overall effect: Z = 1.26 (P = 0.21)
Test for subgroup differences: Chi² = 0.31, df = 1 (P = 0.58), I² = 0%
0.2
0.5
1
2
5
Favours corticosteroids
Favours control

Low - moderate - high quality evidence

- **Low dose hydrocortison appears to cause**
  - **No effect on mortality**

Low - moderate - high quality evidence

- **Low dose hydrocortison appears to cause**
  - **No effect on mortality**
  - **Faster shock reversal**
  - **Reduced time ventilated**
  - **Reduced ICU length of stay**

Low - moderate - high quality evidence

- **Low dose hydrocortison appears to cause**
  - **No effect on mortality**
  - **Faster shock reversal**
  - **Reduced time ventilated**
  - **Reduced ICU length of stay**
  - **More adverse effects**
  - **Recovery?**
  - **HRQoL?**

Use of low-dose steroid in septic shock…

- **Give steroids to all if you favor reducing time on**
  - **Vasopressor**
  - **MV**
  - **ICU**

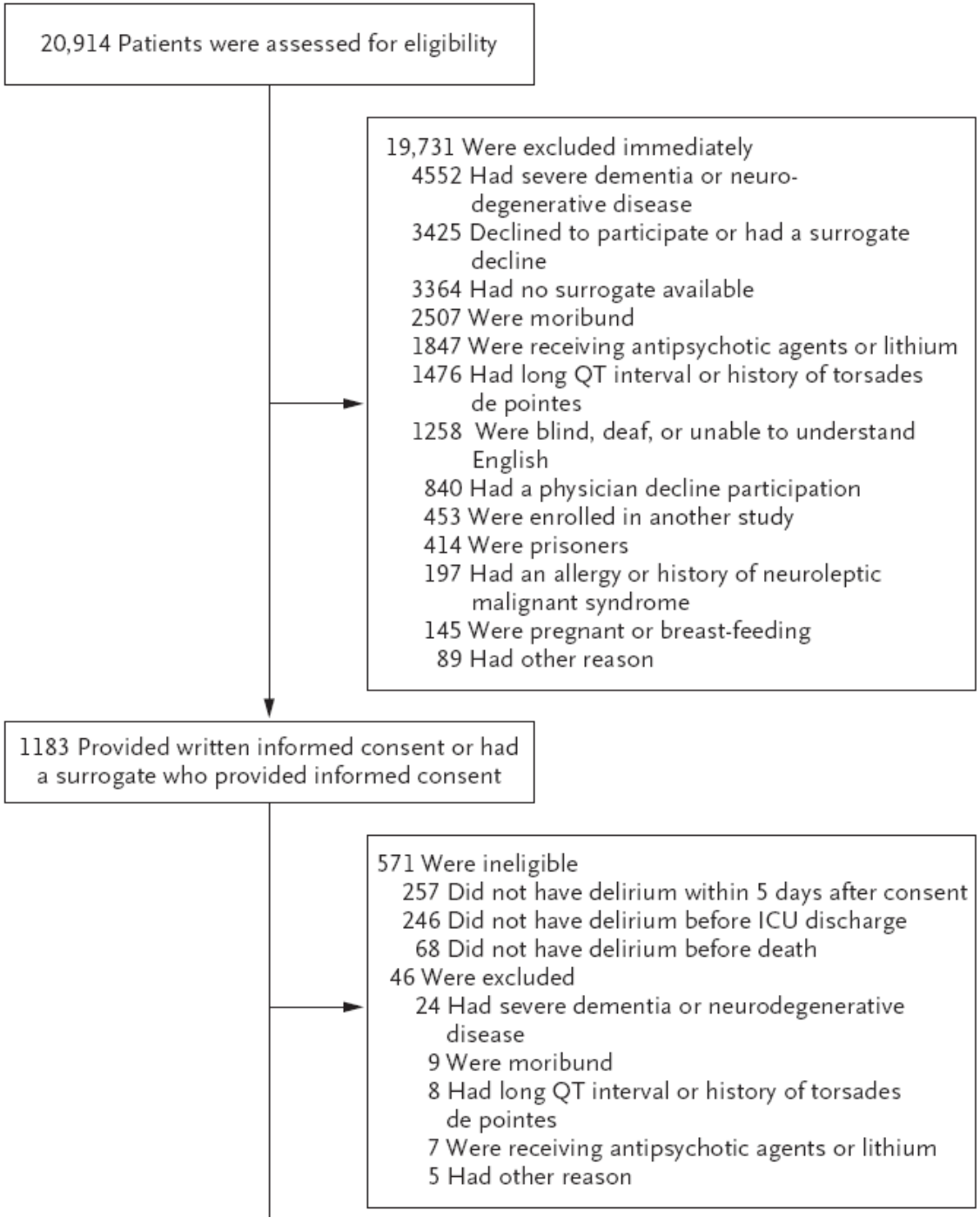
- **Don’t if you are concerned about**
  - **Side-effects – hypernatremia, hyperglycemia**
  - **Recovery**
  - **QoL**

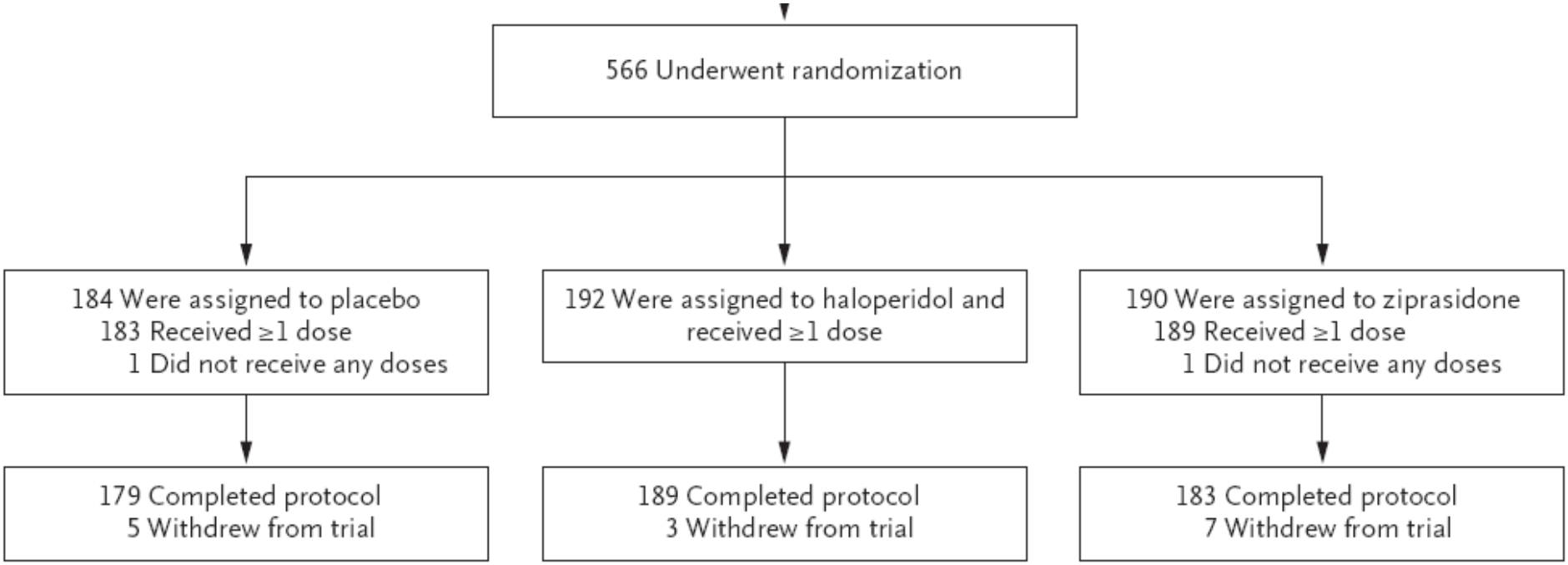
The NEW ENGLAND JOURNAL of MEDICINE

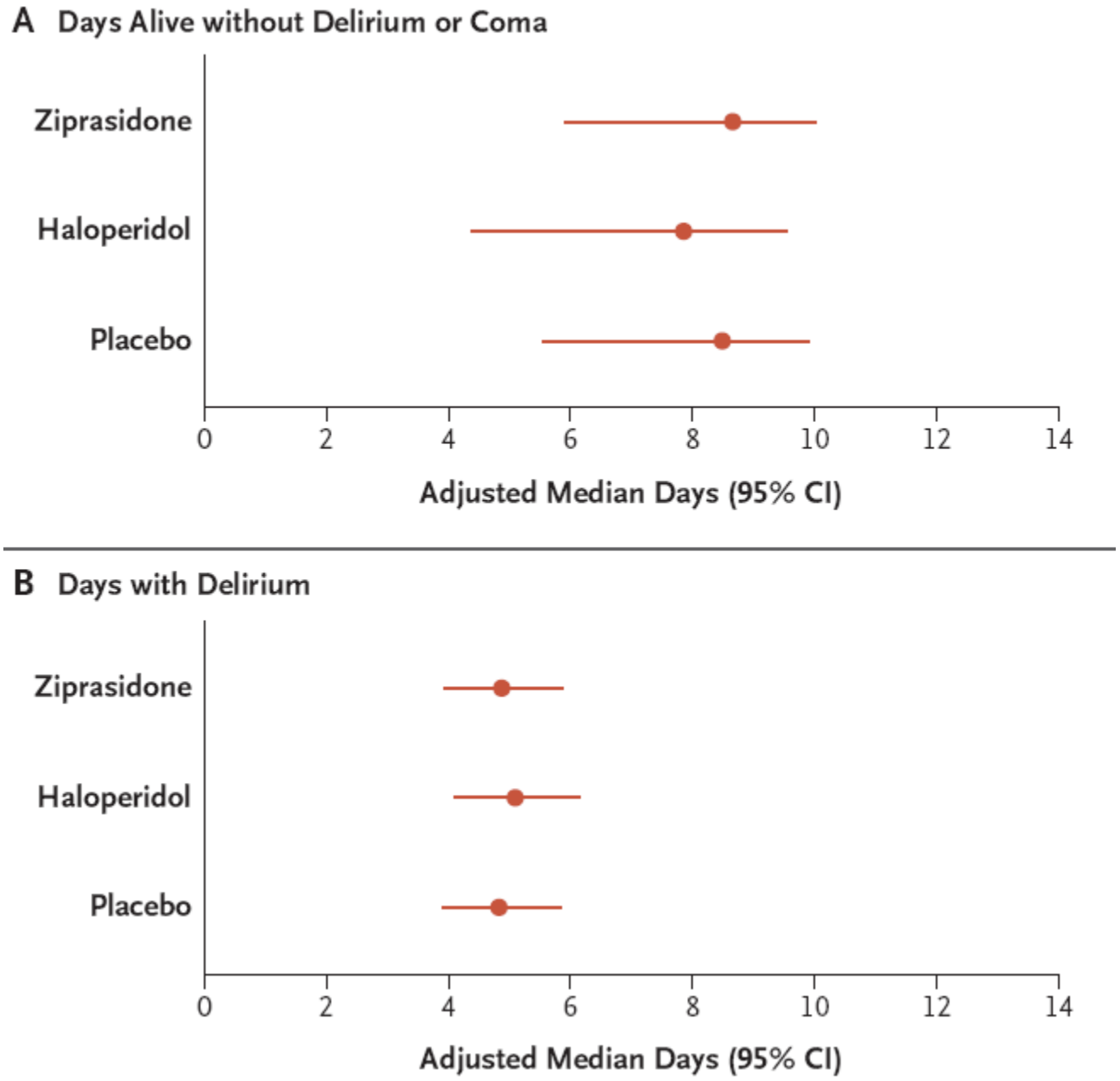
ORIGINAL ARTICLE

Haloperidol and Ziprasidone for Treatment of Delirium in Critical Illness

T.D. Girard, M.C. Exline, S.S. Carson, C.L. Hough, P. Rock, M.N. Gong, I.S. Douglas, A. Malhotra, R.L. Owens, D.J. Feinstein, B. Khan, M.A. Pisani, R.C. Hyzy, G.A. Schmidt, W.D. Schweickert, R.D. Hite, D.L. Bowton, A.L. Masica, J.L. Thompson, R. Chandrasekhar, B.T. Pun, C. Strength, L.M. Boehm, J.C. Jackson, P.P. Pandharipande, N.E. Brummel, C.G. Hughes, M.B. Patel, J.L. Stollings, G.R. Bernard, R.S. Dittus, and E.W. Ely, for the MIND-USA Investigators*


20,914 Patients were assessed for eligibility
19,731 Were excluded immediately
4552 Had severe dementia or neuro-degenerative disease
3425 Declined to participate or had a surrogate decline
3364 Had no surrogate available
2507 Were moribund
1847 Were receiving antipsychotic agents or lithium
1476 Had long QT interval or history of torsades de pointes
1258 Were blind, deaf, or unable to understand English
840 Had a physician decline participation
453 Were enrolled in another study
414 Were prisoners
197 Had an allergy or history of neuroleptic malignant syndrome
145 Were pregnant or breast-feeding
89 Had other reason
1183 Provided written informed consent or had a surrogate who provided informed consent
571 Were ineligible
257 Did not have delirium within 5 days after consent
246 Did not have delirium before ICU discharge
68 Did not have delirium before death
46 Were excluded
24 Had severe dementia or neurodegenerative disease
9 Were moribund
8 Had long QT interval or history of torsades de pointes
7 Were receiving antipsychotic agents or lithium
5 Had other reason


566 Underwent randomization
184 Were assigned to placebo
183 Received ≥1 dose
1 Did not receive any doses
192 Were assigned to haloperidol and received ≥1 dose
190 Were assigned to ziprasidone
189 Received ≥1 dose
1 Did not receive any doses
179 Completed protocol
5 Withdrew from trial
189 Completed protocol
3 Withdrew from trial
183 Completed protocol
7 Withdrew from trial


A Days Alive without Delirium or Coma
Ziprasidone
Haloperidol
Placebo
0
2
4
6
8
10
12
14
Adjusted Median Days (95% CI)
B Days with Delirium
Ziprasidone
Haloperidol
Placebo
0
2
4
6
8
10
12
14
Adjusted Median Days (95% CI)

Should we stop using haloperidol?

- **Patients**
  - 3 x 200 in MIND
  - In all RCTs, 600 pts randomized
  - Selected, very sick group
  - 90% hypoactive at randomization

- **Protocol**
  - 20% cross over
  - QoL & cognitive function?

Classic

8 AID-ICU

HOT-ICU