

## SUPPLEMENTARY DIGITAL CONTENT

### THE ARISE INVESTIGATORS

The ARISE study was a collaboration of the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG), The Australasian College for Emergency Medicine and the Australian and New Zealand Intensive Care Research Center (ANZIC-RC), Monash University. The trial was endorsed by the Irish Critical care Trials Group and the College of Intensive Care Medicine. The trial was funded by the National Health and Medical Research Council (N<sup>OS</sup> 491075 and 1021165) and co-ordinated by the Australian and New Zealand Intensive Care Research Centre (ANZIC RC), Department of Epidemiology and Preventive Medicine, Monash University, Melbourne. **The ARISE Working Committee:** S. Peake (Chair), A. Delaney, R. Bellomo, P. A. Cameron, A. M. Higgins, A. Holdgate, B.D. Howe, S.A.R. Webb, P. Williams. **The ARISE Management and Steering Committee:** S. Peake (Chair), A. Delaney, R. Bellomo, P. A. Cameron, D. J. Cooper, A. Cross, C. Gomersall, C. Graham, A .M. Higgins, A. Holdgate, B.D. Howe, I. Jacobs, S. Johanson, P. Jones, P. Kruger, C. McArthur, J. Myburgh, A. Nichol, V. Pettilä, D. Rajbhandari, S.A.R. Webb, A. Williams, J. Williams, P. Williams. **The ARISE site investigators:** (alphabetically by institution and all in Australia unless specified to New Zealand, NZ, Finland, FL, or Hong Kong, HK or Ireland, IRE). The Alfred Hospital, Melbourne – V. Bennett, J. Board, P. McCracken, S. McGloughlin, V. Nanjajya, A. Teo. Auckland City Hospital, Auckland, NZ – E. Hill, P. Jones. E. O’Brien, F. Sawtell, K. Schimanski, D. Wilson. Austin Health, Melbourne – R. Bellomo, S. Bolch, G. Eastwood, F. Kerr, L. Peak, H. Young. Bendigo Hospital, Bendigo J. Edington, J. Fletcher, J. Smith. Blacktown Hospital, Blacktown - D. Ghelani, K. Nand, T. Sara. Box Hill Hospital, Melbourne – A. Cross, D. Flemming, M. Grummisch, A. Purdue. Canberra Hospital, Canberra - E. Fulton, K. Grove, A. Harney, K. Milburn, R. Millar, I. Mitchell, H. Rodgers, S. Scanlon. Central Gippsland Health Service, Sale – T. Coles, H. Connor, J. Dennett, A. Van Berkel. Christchurch Hospital, Christchurch, NZ – S. Barrington-Onslow, S. Henderson, J. Mehrtens. Coffs Harbour Base Hospital, Coffs Harbour – J. Dryburgh, A. Tankel. Dandenong Hospital, Melbourne – G. Braitberg, B.O’Bree, K. Shepherd, S. Vij. Frankston Hospital, Melbourne – S. Allsop, D. Haji, K. Haji, J. Vuat. Geelong Hospital, Geelong – A. Bone, T. Elderkin, N. Orford, M. Ragg. Gosford Hospital, Gosford – S. Kelly, D. Stewart, N. Woodward. Helsinki University Hospital, Helsinki, FL – V-P. Harjola, M. Okkonen V. Pettilä, S. Sutinen, E. Wilkman. Hornsby Ku-ring-gai Hospital, Hornsby – J. Fratzia, J. Halkhoree, S. Treloar. Ipswich Hospital, Ipswich – K. Ryan, T. Sandford, J. Walsham. John Hunter Hospital, Newcastle – C. Jenkins, D. Williamson. Joondalup Health Campus, Joondalup – J. Burrows, D. Hawkins, C. Tang. Liverpool Hospital, Liverpool – A. Dimakis, A. Holdgate, S. Micallef, M. Parr. Logan Hospital, Meadowbrook – H, White, L. Morrison, K. Sosnowski. Lyell McEwin Hospital, Elizabeth Vale – R. Ramadoss, N. Soar, J. Wood. Manly Hospital, Manly – M. Franks. Middlemore Hospital, Auckland, NZ – A. Williams, C. Hogan, R. Song, A. Tilsley. Modbury Hospital, Modbury – D. Rainsford, N. Soar, R. Wells, J. Wood. Monash Medical Centre, Clayton – J. Dowling, P. Galt, T. Lamac, D. Lightfoot, C. Walker. Nepean Hospital, Penrith – K. Braid, T. DeVillecourt, H.S. Tan, I. Seppelt. Pamela Youde Nethersole Eastern Hospital, Chai Wan, HK – L.F Chang, W.S Cheung, S.K Fok, P.K Lam, S.M Lam, H.M So, W.W Yan. Port Macquarie Base, Port Macquarie – A. Altea, B. Lancashire. Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, HK – C.D. Gomersall, C.A. Graham, P. Leung. Prince of Wales Hospital, Sydney – S. Arora, F. Bass, Y. Shehabi. Princess Alexandra, Woolloongabba – J. Isoardi, K. Isoardi, D. Powrie, S. Lawrence. Royal

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Supplemental Digital Content 1. Baseline characteristics (cont.)

Characteristic	Isolated Refractory Hypotension	Isolated Hyperlactatemia	p-value†	Standardized Difference*	
Weight Category (kg)	N(%)	N(%)			
<59	139(16.9%)	56(12.0%)	0.04	-14	0.15
60-69	141(17.1%)	73(15.6%)		-4.05	5.4
70-79	193(23.5%)	102(21.8%)		-3.84	-4.7
80-92	200(24.3%)	128(27.4%)		7.09	-6.6
>92	150(18.2%)	108(23.1%)		12.11	7.0
Hemoglobin Category (g/L)					
<95	96(11.5%)	32(6.9%)	<0.001	-16.02	2.1
96-106	93(11.2%)	33(7.1%)		-14.07	-0.51
107-114	101(12.1%)	33(7.1%)		-17.04	4.7
115-121	81(9.7%)	36(7.8%)		-6.93	-1.2
122-127	87(10.5%)	46(9.9%)		-1.72	3.0
128-132	79(9.5%)	40(8.6%)		-2.98	-0.35
133-139	90(10.8%)	55(11.9%)		3.35	-2.0
140-146	85(10.2%)	49(10.6%)		1.2	-3.3
147-154	64(7.7%)	59(12.7%)		16.72	-0.39
>155	56(6.7%)	80(17.3%)		32.86	-1.9
Concurrent medical conditions					
Cardiac arrhythmia	100 (11.7%)	60 (12.6%)	0.65	2.58	0.18
Acute pulmonary edema	16 (1.9%)	13 (2.7%)	0.31	5.65	0.01
Acute coronary syndrome	11 (1.3%)	13 (2.7%)	0.060	10.22	-0.10
Acute cerebrovascular accident	1 (0.1%)	2 (0.4%)	0.27	5.82	2.2
Immediate surgery required	21 (2.5%)	20 (4.2%)	0.080	9.63	0.27
Seizure	4 (0.5%)	10 (2.1%)	0.005	14.47	-4.5

Drug overdose	5(0.6%)	4(0.8%)	0.59	3.0	-0.28
Neutrophil Count Low	26(3.0%)	14(2.9%)	0.91	-0.68	1.9
<b>Glasgow Coma Scale</b>					
GCS 3-8	25(3.2%)	12(2.7%)	0.008	-3.3	2.0
GCS 9-12	23(3.0%)	30(6.7%)		17	-7.0
GCS 13-15	726(93.8%)	406(90.6%)		-12	4.4
<b>Hospital Site</b>					
Victoria	208(24.4%)	92(19.2%)	0.02	-12.38	-0.78
NSW	338(39.6%)	207(43.3%)		7.56	-1.5
South Australia	108(12.6%)	79(16.5%)		11	-0.34
Western Australia	20(2.3%)	19(4.0%)		9.34	-0.88
Queensland	53(6.2%)	24(5.0%)		-5.15	-0.19
New Zealand	71(8.3%)	33(6.9%)		-5.32	7.8
Hong Kong	29(3.4%)	6(1.3%)		-14.23	-3.5
Ireland	2(0.2%)	3(0.6%)		6	-0.69
Finland	25(2.9%)	15(3.1%)		1.23	0.12
<b>Hospital Type</b>					
Metropolitan Tertiary	671(78.6%)	361(75.5%)	0.44	-7.25	1.4
Metropolitan Not Tertiary	136(15.9%)	86(18.0%)		5.5	-1.1
Rural	47(5.5%)	31(6.5%)		4.13	-0.80

\*Standardized difference is a measure of imbalance between baseline values, with values greater than 10% indicating potential confounding.

Reported here as the difference between isolated refractory hypotension and isolated hyperlactatemia groups only. The propensity weighted figure shows residual imbalance after inverse propensity score weighting and is based on the analysis of the 897 participants for whom a propensity score was calculated.

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†p-value is for the comparison between isolated refractory hypotension and isolated hyperlactatemia groups only.

Supplemental Digital Content 2. Logistic regression propensity score model.  
 Outcome variable; Isolated Hyperlactatemia=1, Isolated Refractory Hypotension=0

	Odds Ratio	P-value	95% Confidence Interval	
Age	1.0	0.60	0.99	1.0
Female	1.0	0.83	0.74	1.5
Weight(kg)	1.0	0.84	0.99	1.0
Residential Care	0.96	0.91	0.46	2.0
Charlson Score	1.0	0.91	0.83	1.2
Ventilated at Baseline	1.1	0.65	0.65	1.9
Chronic Cardiovascular Disease	1.2	0.45	0.71	2.2
Chronic Respiratory Disease	0.61	0.11	0.34	1.1
Chronic Endocrine Disease	1.9	0.002	1.3	3.1
Chronic CNS disease	1.6	0.26	0.69	3.9
Chronic Hematological Disease	1.1	0.78	0.54	2.3
Chronic Liver Disease	1.8	0.14	0.84	3.8
Chronic Renal Disease	1.3	0.57	0.55	3.0
Other Chronic Disease	0.78	0.43	0.42	1.4
Immunosuppressive Therapy	0.7	0.20	0.40	1.2
Concurrent Medical Conditions				
Cardiac Arrhythmia	0.98	0.88	0.61	1.6
Acute Coronary Syndrome	1.1	0.83	0.36	3.6
Immediate Surgery Required	2.1	0.13	0.83	5.6
Stroke-minor deficit	0.42	0.12	0.14	1.3
Stroke-hemiplegia	2.2	0.40	0.35	14
Seizure	1.3	0.77	0.26	6.1

Hepatic Failure	13	0.002	2.5	67
Acute Pulmonary Edema	1.7	0.29	0.64	4.5
Drug Overdose	1.6	0.60	0.26	10
Low Neutrophil Count	1.2	0.71	0.46	3.1
Apache 2 Score	1.1	<0.001	1.0	1.1
Albumin(g/L)	1.0	0.008	1.0	1.1
Hemoglobin(g/L)				
<95	Baseline			
96-106	1.3	0.50	0.62	2.7
107-114	1.4	0.40	0.66	2.9
115-121	1.7	0.17	0.80	3.8
122-127	2.4	0.02	1.2	5.0
128-132	1.8	0.13	0.84	3.8
133-139	2.3	0.025	1.1	4.9
140-146	2.3	0.037	1.1	4.9
147-154	3.8	<0.001	1.8	8.1
155-204	4.5	<0.001	2.2	9.4
Location				
Victoria	Baseline			
New South Wales/Australian Capital Territory	1.3	0.3	0.82	1.9
South Australia	1.8	0.03	1.1	3
Western Australia	1.1	0.84	0.44	2.8
Queensland	0.97	0.93	0.48	1.9
New Zealand	0.99	0.99	0.49	2
Hong Kong	0.55	0.29	0.18	1.7
Ireland	2.7	0.46	0.19	37
Finland	2.0	0.52	0.24	17

Hospital Type				
Metropolitan/Tertiary	Baseline			
Metropolitan	1.5	0.07	0.97	2.2
Rural	1.8	0.11	0.87	3.5
Glasgow Coma Scale				
3-8	Baseline			
9-12	2.5	0.15	0.73	8.6
13-15	2.8	0.073	0.92	8.3
Core Temperature (C°)	1.2	0.004	1.0	1.3
Site of Infection				
Blood	Baseline			
Medical Soft Tissue	0.6	0.16	0.3	1.2
Surgical Soft Tissue	0.38	0.11	0.12	1.2
Lungs	0.68	0.19	0.38	1.2
Abdomen	1.1	0.89	0.50	2.2
Urinary	0.65	0.17	0.35	1.2
CNS	17	0.01	1.8	162
Surgical Other	0.44	0.39	0.07	2.8
Medical Other	0.76	0.49	0.35	1.6



Supplemental Digital Content 3. Proportion of missing values for variables used in propensity score model.

Variable	Isolated Refractory Hypotension N(%)	Isolated Hyperlactatemia N(%)
Albumin concentration	100(11.7)	52(10.9)
Hemoglobin concentration	22(2.6)	15(3.1)
Glasgow Coma Scale	80(9.4)	30(6.3)
Core Temperature	88(10.3)	50(10.4)
Weight	31(3.6)	11(2.3)
Infection Site	0(0)	1(0.2)

Supplemental Digital Content 4. Distribution of causative organisms

Type of shock	Isolated Refractory Hypotension	Isolated Hyperlactatemia	p-value
N	854	478	
Gram positive coccus	260 (30.4%)	158 (33.1%)	0.32
Gram positive rod	23 (2.7%)	13 (2.7%)	0.98
Gram negative coccus	34 (4.0%)	27 (5.6%)	0.16
Gram negative rod	227 (26.6%)	110 (23.0%)	0.15
Fungus/yeast	27 (3.2%)	14 (2.9%)	0.81
Parasite	4 (0.5%)	1 (0.2%)	0.46
Virus	42 (4.9%)	13 (2.7%)	0.053

Supplemental table 5. Intervention-free survival outcomes

	Isolated refractory hypotension (n = 854)	Isolated hyperlactatemia (n = 478)	Unweighted		Propensity Weighted	
			Mean difference (95% CI)	P-value	Mean difference (95% CI)	P-value
ICU-free survival (days), mean (SD)	77.9 (25.0)	67.8 (34.0)	10.1 (6.9, 13.3)	<0.001	6.9 (1.8, 11.9)	0.008
Hospital-free survival (days), mean (SD)	66.4 (27.0)	56.1 (33.5)	10.2 (6.9, 13.5)	<0.001	9.0 (3.9, 14.2)	0.001
Ventilator-free survival (days), mean (SD)	80.3 (24.4)	69.8 (34.4)	10.5 (7.0, 13.0)	0.001	7.6 (2.5, 12.7)	0.003
Vasopressor free survival (days), mean (SD)	80.1 (25.0)	70.6 (34.3)	9.5 (6.3, 12.7)	< 0.001	7.1 (2.0, 12.2)	0.006

Survival times are truncated at the end of the 90 day follow-up.

ICU denotes intensive care unit; CI, confidence interval; SD, standard deviation.



Supplemental Digital Content 6. Intravenous fluid administration

IV Fluids	Isolated Refractory Hypotension N=854	Isolated Hyperlactatemia N=478	Propensity weighted risk ratio	p-value
Hr0 to Hr6				
Any fluids given	833(98%)	464(98%)	1.02 (1.0-1.03)	0.11
Amount given, ml Median(IQR)	1400(760 2200)	1600 (940 2600)		
Hr7 to Hr 24				
Any fluids given	818(96%)	438(92%)	0.97 (0.93 1.01)	0.18
Amount given, ml Median(IQR)	1600 (1000 2300)	1600 (1000 2500)		
Hr25 to Hr 72				
Any fluids given	729(85%)	385(81%)	0.92 (0.85 1.0)	0.05
Amount given, ml Median(IQR)	2000 (829 3253)	1975 (631 3482)		
Packed Blood Cells				
Hr0 to Hr6				
Any PBC given	93(11%)	39(8%)	1.2 (0.75 1.9)	0.43
If transfused, amount given, ml Median(IQR)	394(256 531)	470 (269 539)		
Hr7 to Hr24				
Any PBC given	27(3.2%)	31(6.5%)	1.3 (0.67 2.5)	0.42
If transfused amount given, ml Median(IQR)	275 (243 524)	263 (248 489)		
Any PBC given	60(7.0%)	28(5.9%)	1.2( 0.60 2.4)	0.60

If transfused, amount given, ml Median(IQR)	487 (255 669)	431 (290 670)		
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IV fluids-intravenous crystalloid and colloid; Hr- Hour; IQR-Interquartile range; PBC-Packed blood cells

Supplemental Digital Content 7. Ratio of geometric mean intravenous fluid administration for those who received fluid in isolated hyperlactatemia compared to isolated refractory hypotension.

Unweighted	Ratio of Geometric Means*	95%CI	P-value	Constant†
Hr0 to Hr6	1.2	1.1-1.3	<0.001	1200
Hr7 to Hr24	1.0	0.92-1.2	0.50	1200
Hr25 to Hr72	0.83	0.68-1.0	0.07	1200
Weighted	Ratio of Geometric Means*	95%CI	P-value	Constant
Hr0 to Hr6	1.2	1.03-1.3	0.02	1200
Hr7 to Hr24	0.87	0.71-1.1	0.18	1300
Hr25 to Hr72	0.60	0.43-0.82	0.002	1200

\*Isolated refractory hypotension is the reference category

†estimate of median intravenous fluid administration in reference category

Hr – hour; CI – confidence interval





