‘Learning how to do less better: the key to quality care of the ICU patient?’

Tim Walsh
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EDINBURGH CRITICAL CARE RESEARCH GROUP

Some fundamentals of ICU care

- Maintain oxygenation
  - Supplemental oxygen
- Maintain oxygen delivery to tissues
  - Cardiac output; blood oxygen content (haemoglobin)
- Maintain patient comfort
  - Sedation and analgesia

What is your target oxygen saturation when adjusting FiO_2?

- >88%
- >92%
- >94%
- >98%

Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis

Derek K Chu*†, Lisa H-Y Kim*†, Paul J Young, Nima Zamiri, Saleh A Almenawer, Roman Jaeschke, Wojciech Szczeklik, Holger J Schünemann, John D Neary, Waleed Alhazzani

Lancet 2018; 391: 1693–705

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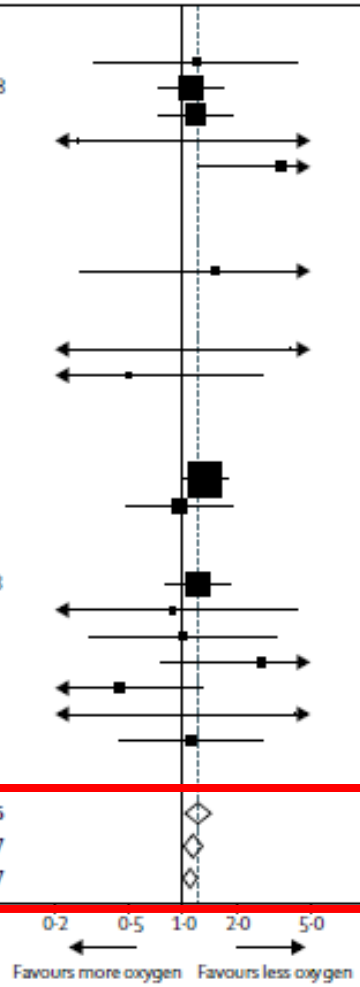
	Setting	Liberal (n/N)	Conservative (n/N)	RR (95% CI)	% weight
Neurological (stroke-traumatic brain injury)					
Ali et al (2014)[64,66]	Stroke	5/155	4/146	1·18 (0·32–4·30)	1·6
Roffe et al (2017)[53]	Stroke	50/2668	45/2668	1·11 (0·75–1·66)	16·6
Ronning et al (1999)[56]	Stroke	36/292	27/258	1·18 (0·74–1·89)	11·9
Singhal et al (2005)[58]	Stroke (ischaemic)	0/9	1/7	0·27 (0·01–5·70)	0·3
NCT00414726	Stroke (ischaemic)	14/43	4/42	3·42 (1·22–9·54)	2·5
Shi et al (2017)[65]	Stroke (ischaemic)	0/9	0/9	(Excluded)	0
Sepsis					
NCT02378545 (2015)	Sepsis	3/25	2/25	1·50 (0·27–8·22)	0·9
Emergency surgery					
Butler et al (1987)[46]	Limb ischaemia	1/17	0/22	3·83 (0·17–88·62)	0·3
Schietroma et al (2016)[57]	Perforated peptic ulcer	2/119	4/120	0·50 (0·09–2·70)	0·9
NCT02687217	Acute appendicitis	0/30	0/30	(Excluded)	0
Critical care (mixed medical-surgical)					
Girardis et al (2016)[47]	Critical illness	80/243	58/235	1·33 (1·00–1·78)	32·1
Panwar et al (2016)[53]	Critical illness	12/51	13/53	0·96 (0·48–1·90)	5·6
Cardiac (myocardial infarction–cardiac arrest)					
Hofmann et al (2017)[48]	Myocardial infarction	53/3311	44/3318	1·21 (0·81–1·80)	16·8
Khoshnood et al (2015)[49]	Myocardial infarction (STEMI)	3/85	3/75	0·88 (0·18–4·24)	1·1
Kuisma et al (2006)[50]	Cardiac arrest	4/14	4/14	1·00 (0·31–3·23)	1·9
Rawles et al (1976)[55]	Myocardial infarction	9/105	3/95	2·71 (0·76–9·73)	1·6
Stub et al (2012)[60]	Myocardial infarction (STEMI)	5/312	11/312	0·45 (0·16–1·29)	2·4
Ukholkina et al (2005)[61]	Myocardial infarction	1/58	0/79	4·07 (0·17–98·10)	0·6
Young et al (2014)[62]	Cardiac arrest	5/9	4/8	1·11 (0·45–2·75)	3·2
p [illegible] =0·07					
In-hospital mortality, overall (I^2=0%, p=0·020)		**283/7555**	**227/7516**	**1·21 (1·03–1·43)**	**100**
30-day mortality, overall (I^2=0%, p=0·033)		**484/7546**	**422/7507**	**1·14 (1·01–1·28)**	**100**
Mortality at longest follow-up, overall (I^2=0%, p=0·044)		**828/7897**	**749/7857**	**1·10 (1·00–1·20)**	**100**



Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis

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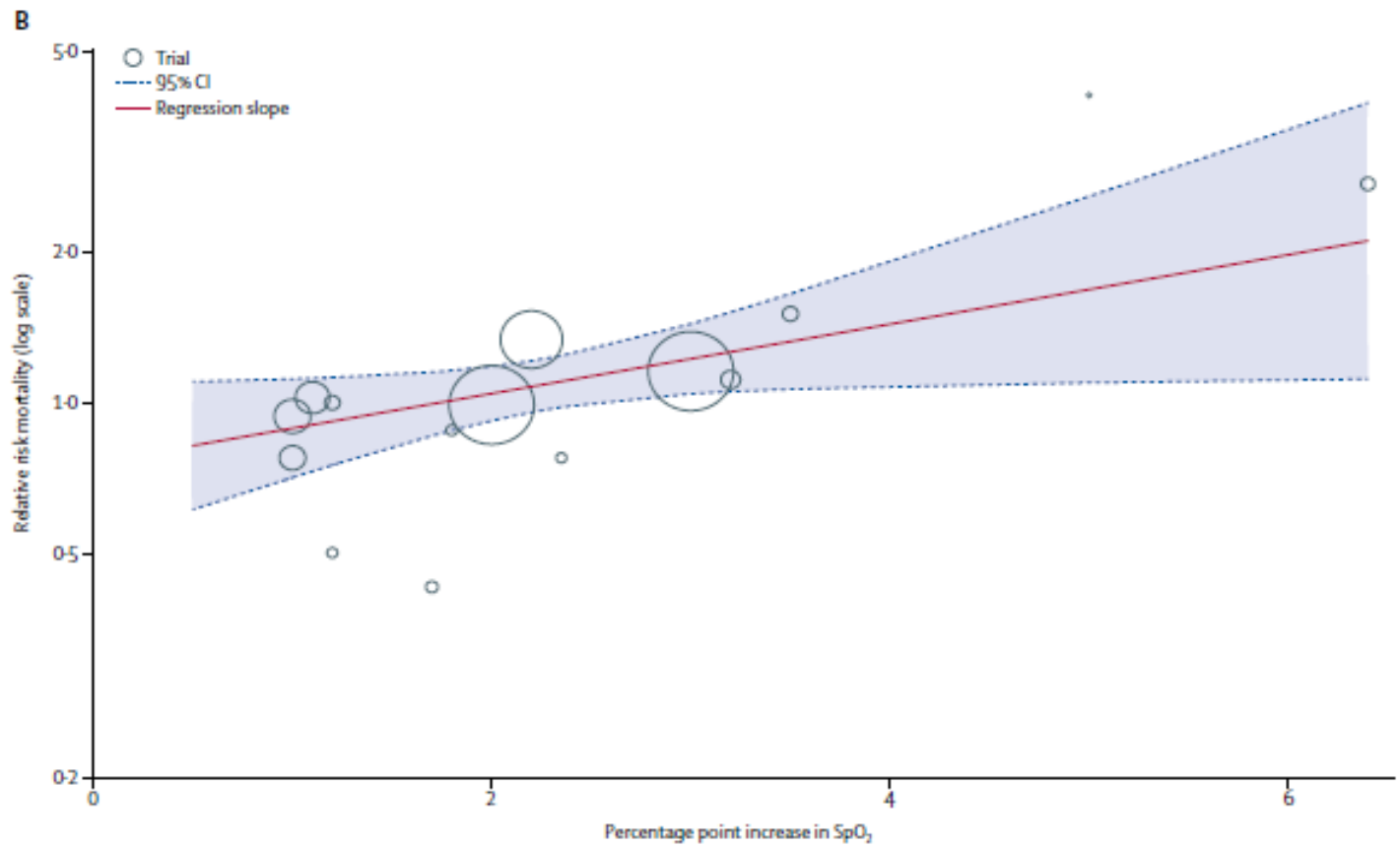


Supplemental oxygen may be harmful if given above an SpO_2 of 94-96%

Why might more oxygen cause harm?

- Lung atelectasis/collapse (washes the nitrogen out)
- Vasoconstriction and ischaemia (vital organ damage)
- ‘Oxidative stress’ (generation of oxygen fee radicals)

Oxygen delivery

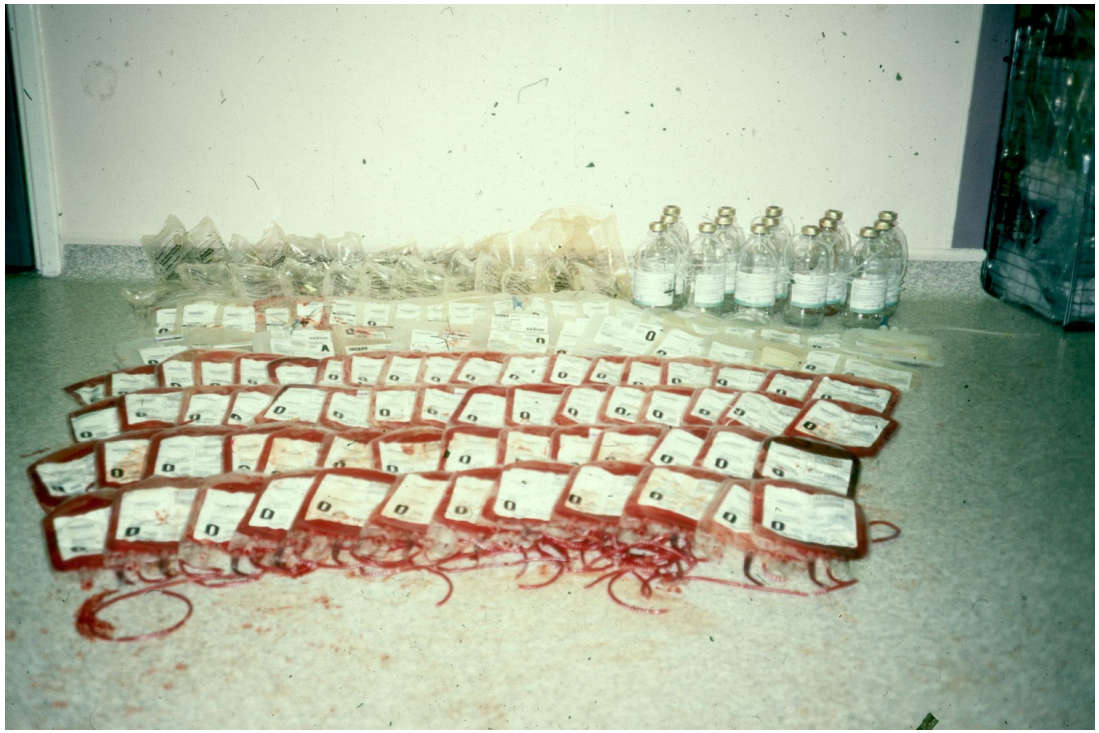
- Cardiac output x arterial oxygen content (>98% carried by haemoglobin in RBCs)

- High oxygen delivery was previously thought to be critical to preventing organ failures

What haemoglobin concentration do you think your patient needs as a minimum in the ICU?

- >60g/L
- >70g/L
- >80g/L
- >90g/L
- >100g/L

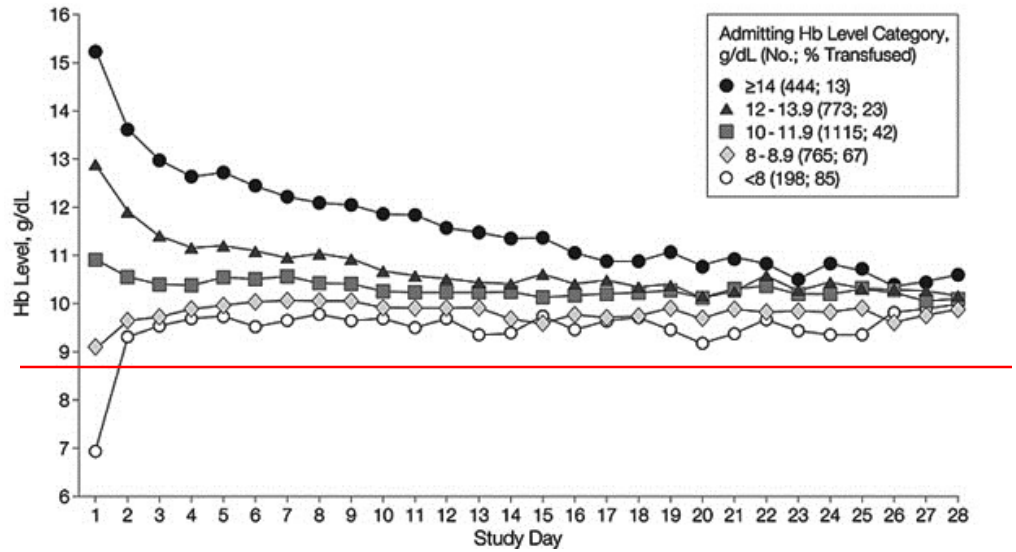
The decision to transfuse…..



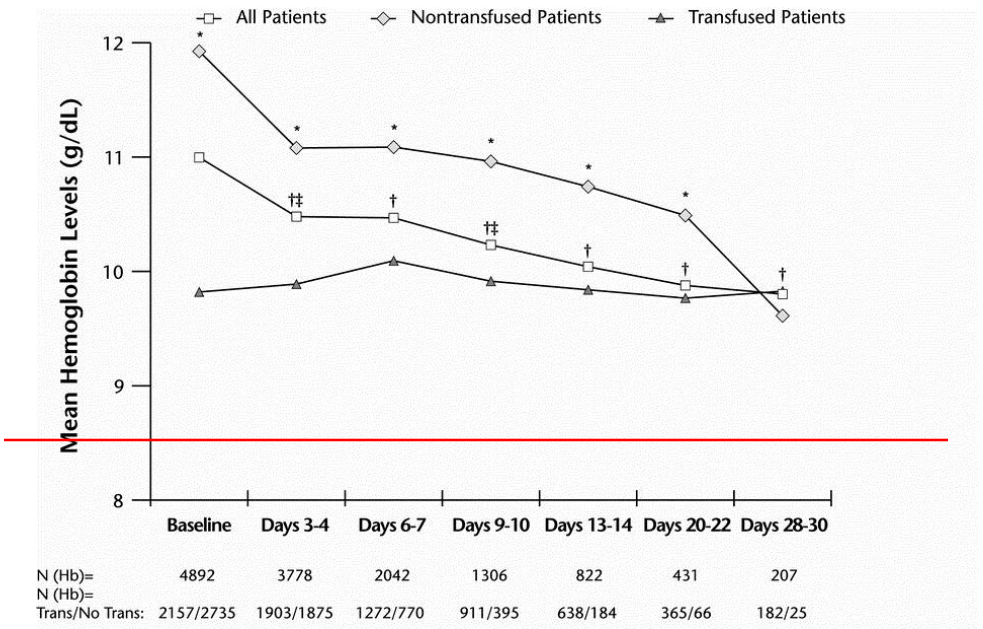
"No question!"

"Not sure"

Anaemia during intensive care



ABC study (Europe)
Vincent et al. *JAMA* 2002;**288**:1499-507



*The difference across groups (transfused vs. nontransfused) is significant at $p<0.007$ (using Bonferonni adjustment).
†The difference is significant at $p<.0045$ (using ANOVA and Bonferonni adjustment) compared with baseline (all patients sample).
‡The difference is significant at $p<.0045$ (using ANOVA and Bonferonni adjustment) compared with previous period (all patients sample).

CRIT study (US)
Corwin et al. *Crit Care Med* 2004;**32**:39-52

Causes of anaemia during critical illness

Pre-existing anaemia

Acquired anaemia

Haemodilution

Blood loss

- Blood sampling
- Haemorrhage

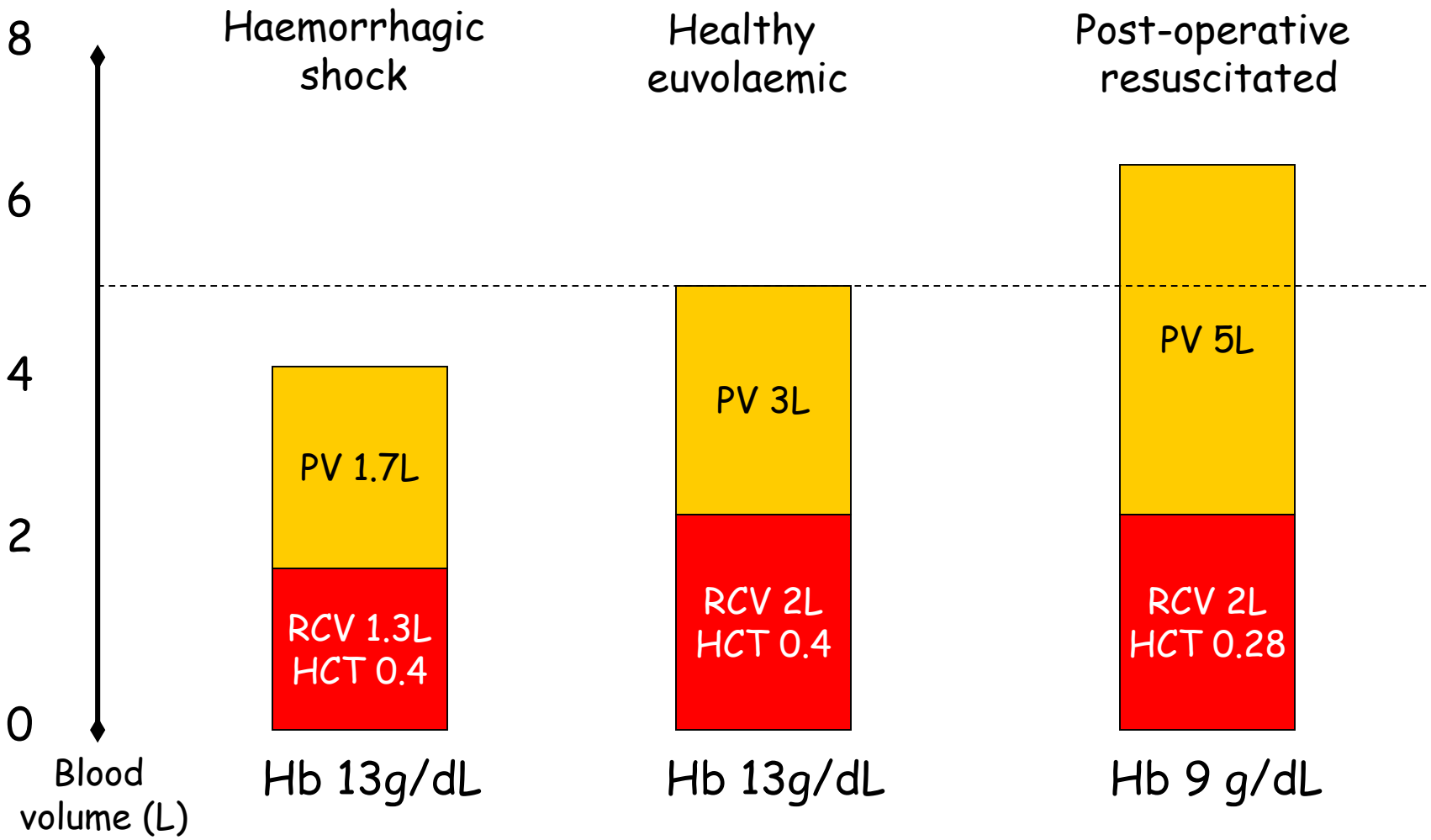
Reduced red cell survival

Reduced red cell production

- Abnormal iron metabolism
- Nutritional deficiencies
- Inappropriate erythropoietin production

Abnormal red cell production

What does haemoglobin concentration or HCT mean?

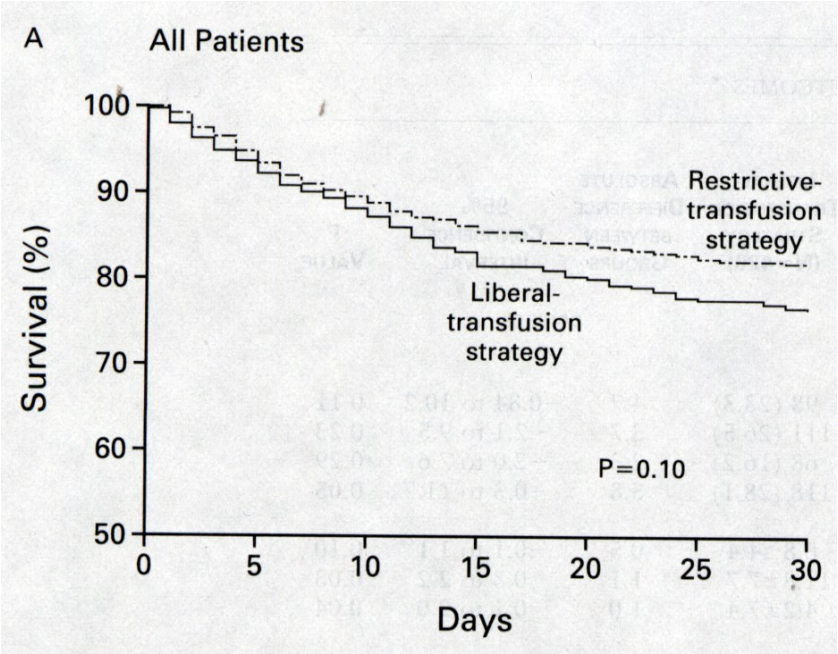


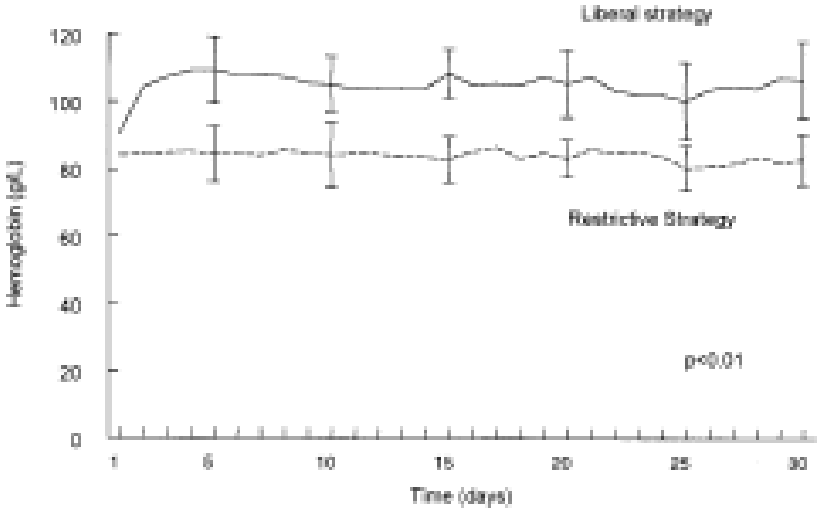
A MULTICENTER, RANDOMIZED, CONTROLLED CLINICAL TRIAL OF TRANSFUSION REQUIREMENTS IN CRITICAL CARE

PAUL C. HÉBERT, M.D., GEORGE WELLS, PH.D., MORRIS A. BLAJCHMAN, M.D., JOHN MARSHALL, M.D., CLAUDIO MARTIN, M.D., GIUSEPPE PAGLIARELLO, M.D., MARTIN TWEEDDALE, M.D., PH.D., IRWIN SCHWEITZER, M.SC., ELIZABETH YETISIR, M.SC., AND THE TRANSFUSION REQUIREMENTS IN CRITICAL CARE INVESTIGATORS FOR THE CANADIAN CRITICAL CARE TRIALS GROUP*

"TRICC" NEJM 1999

70g/L vs 100g/L

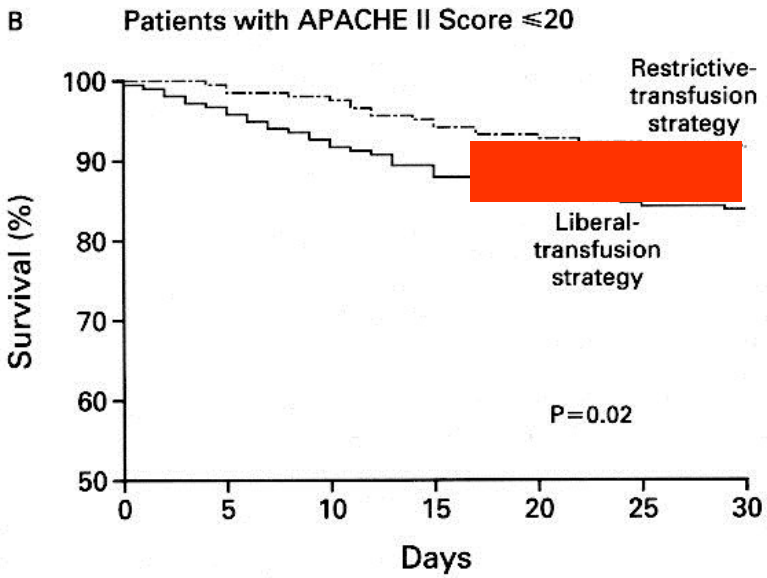


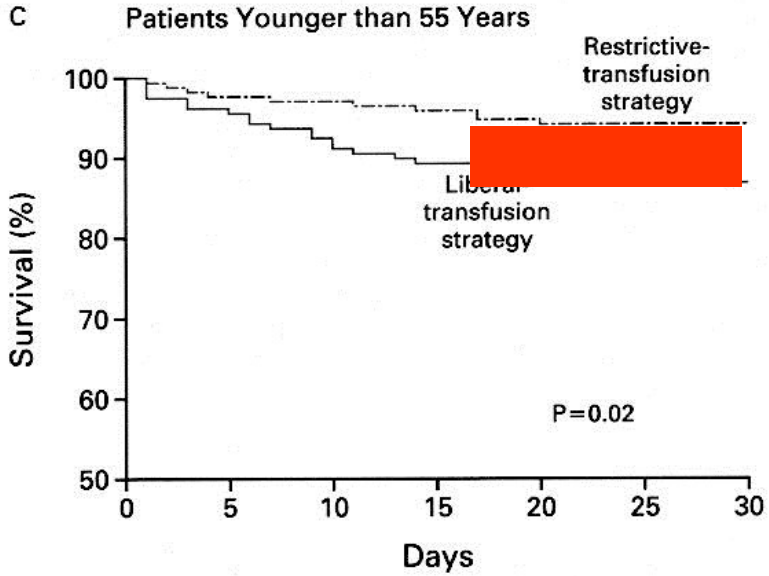


Aggregate mortality at 60 days 25%
Difference in mortality at 60 days 3-8% overall

Main differences:
[1] Degree of anaemia
[2] Exposure to stored non-leucodepleted red cells

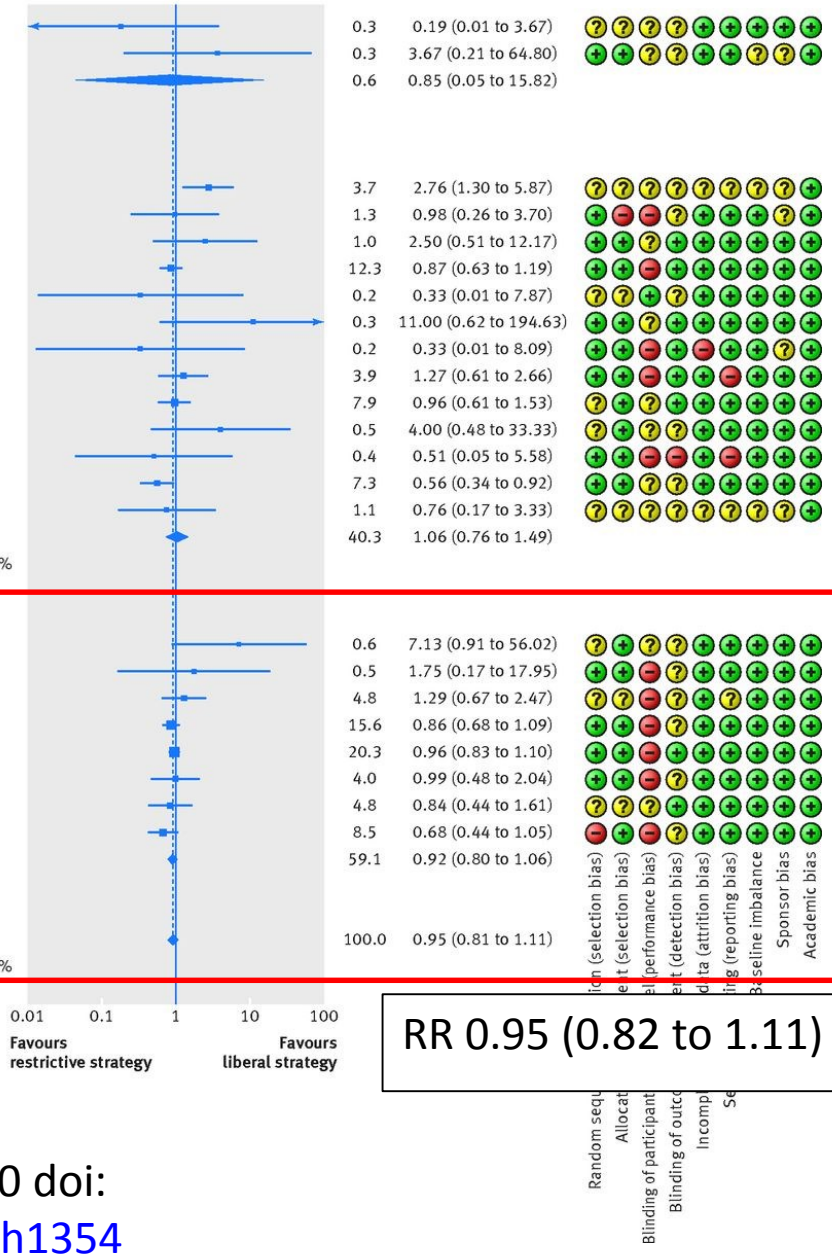
Mean time in study 11 days
Difference in RBC exposure 2.7 units
Difference in proportion exposed 33%





Mortality

Study or subgroup	No of events/total: Restrictive transfusion	No of events/total: Liberal transfusion	Weight (%)	Risk ratio M-H to random (95% CI)
2.14.1 Trauma and acute blood loss				
Blair 1986[29]	0/26	2/24	0.3	0.19 (0.01 to 3.67)
Zygun 2009[43]	3/20	0/10	0.3	3.67 (0.21 to 64.80)
Subtotal	3/46	2/34	0.6	0.85 (0.05 to 15.82)
Test for heterogeneity: τ^2=2.22, χ^2=1.99, df=1, P=0.16, I^2=50%				
Test for overall effect: z=0.11, P=0.91				
2.14.2 Perioperative setting				
Almeida 2013[11]	23/101	8/97	3.7	2.76 (1.30 to 5.87)
Bush 1997[30]	4/50	4/49	1.3	0.98 (0.26 to 3.70)
Carson 1998[32]	5/42	2/42	1.0	2.50 (0.51 to 12.17)
Carson 2011[15]	66/1001	76/998	12.3	0.87 (0.63 to 1.19)
Cholette 2011[33]	0/30	1/30	0.2	0.33 (0.01 to 7.87)
Foss 2009[28]	5/60	0/60	0.3	11.00 (0.62 to 194.63)
Grover 2006[36]	0/109	1/109	0.2	0.33 (0.01 to 8.09)
Hajjar 2010[7]	15/249	12/253	3.9	1.27 (0.61 to 2.66)
Parker 2013[12]	26/100	27/100	7.9	0.96 (0.61 to 1.53)
Shehata 2012[41]	4/25	1/25	0.5	4.00 (0.48 to 33.33)
So-Osman 2010-13[45]	1/299	2/304	0.4	0.51 (0.05 to 5.58)
Villanueva 2013[6]	23/444	41/445	7.3	0.56 (0.34 to 0.92)
Wu 2011[42]	3/112	4/114	1.1	0.76 (0.17 to 3.33)
Subtotal	175/2622	179/2626	40.3	1.06 (0.76 to 1.49)
Test for heterogeneity: τ^2=0.11, χ^2=20.18, df=12, P=0.06, I^2=41%				
Test for overall effect: z=0.35, P=0.73				
2.14.3 Critical care				
Carson 2013[8]	7/54	1/55	0.6	7.13 (0.91 to 56.02)
Cooper 2011[71]	2/24	1/21	0.5	1.75 (0.17 to 17.95)
Hébert 1995[37]	13/33	11/36	4.8	1.29 (0.67 to 2.47)
Hébert 1999[4]	95/416	111/419	15.6	0.86 (0.68 to 1.09)
Holst 2014[9]	216/502	223/496	20.3	0.96 (0.83 to 1.10)
Lacroix 2007[5]	14/320	14/317	4.0	0.99 (0.48 to 2.04)
Robertson 2014[40]	14/99	17/101	4.8	0.84 (0.44 to 1.61)
Walsh 2013[10]	19/51	27/49	8.5	0.68 (0.44 to 1.05)
Subtotal	380/1499	405/1494	59.1	0.92 (0.80 to 1.06)
Test for heterogeneity: τ^2=0.00, χ^2=7.74, df=7, P=0.36, I^2=10%				
Test for overall effect: z=1.18, P=0.24				
Total (95% CI)	558/4167	586/4154	100.0	0.95 (0.81 to 1.11)
Test for heterogeneity: τ^2=0.03, χ^2=29.98, df=22, P=0.12, I^2=27%				
Test for overall effect: z=0.64, P=0.527				
Test for subgroup differences: χ^2=0.59, df=2, P=0.74, I^2=0%				

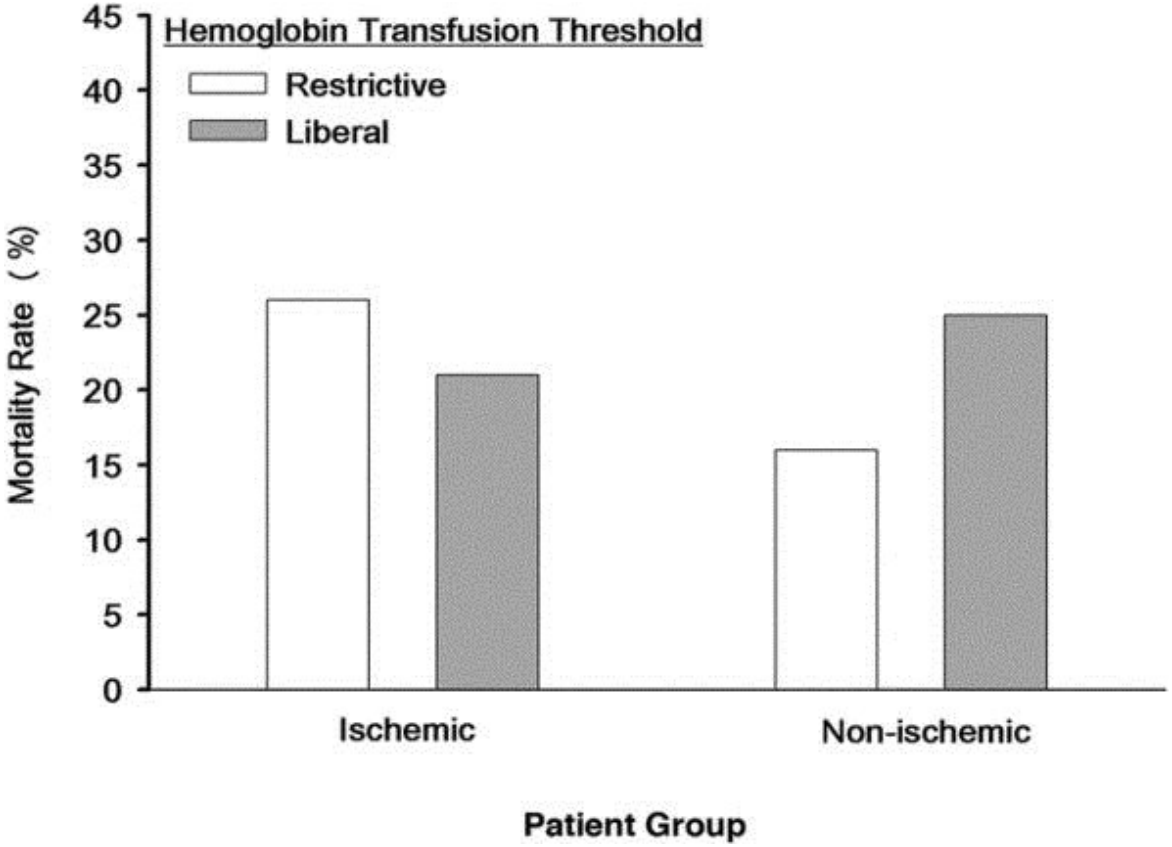


RR 0.95 (0.82 to 1.11)

Lars B Holst et al. BMJ 2015; 350 doi: http://dx.doi.org/10.1136/bmj.h1354

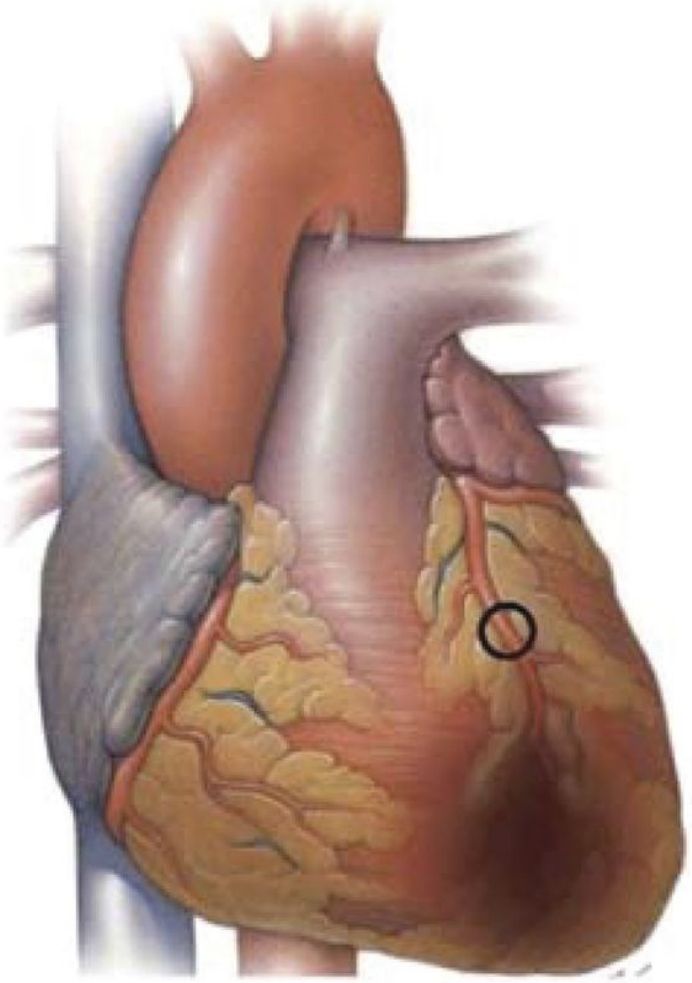
Randomization in clinical trials of titrated therapies: Unintended consequences of using fixed treatment protocols *.

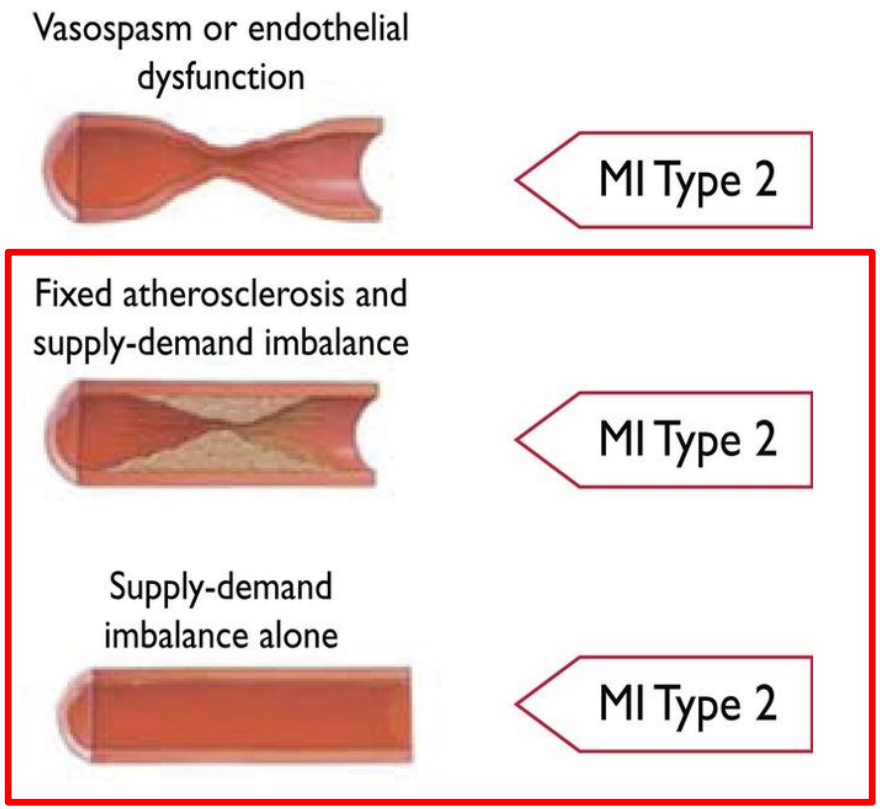
Deans, Katherine et al. Critical Care Medicine. 35(6):1509-1516, June 2007.
DOI: 10.1097/01.CCM.0000266584.40715.A6



Practice misalignment in “fixed” intervention trials

Differentiation between myocardial infarction (MI) types 1 and 2 according to the condition of the coronary arteries.



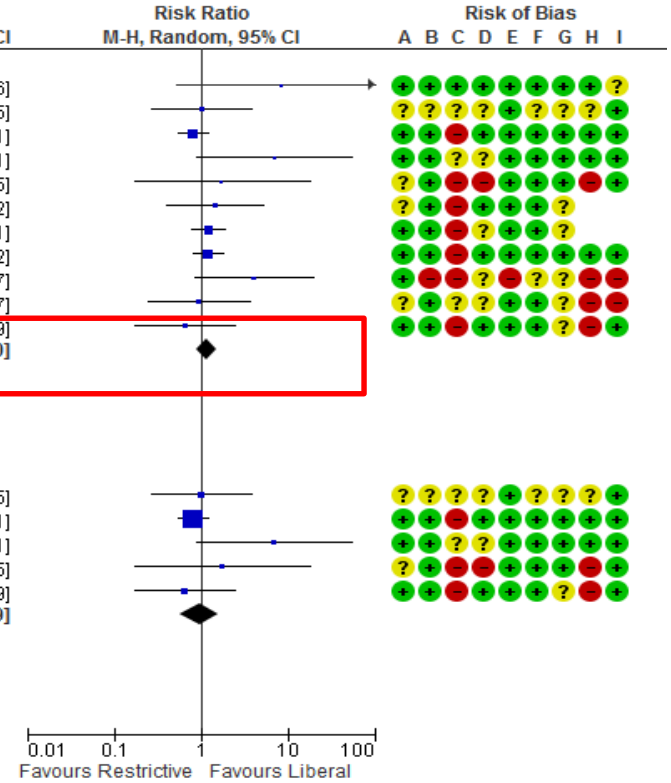


Thygesen K et al. Eur Heart J 2012;eurheartj.ehs184

Mortality in patients with chronic cardiovascular disease

Docherty AM, et al. BMJ. http://dx.doi.org/10.1136/bmj.i1351

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 All studies						
Almeida 2015	7	22	0	12	0.9%	8.48 [0.53, 136.76]
Bush 1997	4	49	4	50	3.8%	1.02 [0.27, 3.85]
Carson 2011	43	1008	52	995	27.7%	0.82 [0.55, 1.21]
Carson 2013	7	55	1	55	1.6%	7.00 [0.89, 55.01]
Cooper 2011	2	24	1	21	1.3%	1.75 [0.17, 17.95]
Gregersen 2015	6	34	3	25	4.0%	1.47 [0.41, 5.32]
Hebert 1999	29	111	31	146	23.9%	1.23 [0.79, 1.91]
Holst 2014	33	75	24	66	26.5%	1.21 [0.80, 1.82]
Jairath 2015	6	49	2	67	2.8%	4.10 [0.86, 19.47]
Parker 2013	4	70	4	67	3.7%	0.96 [0.25, 3.67]
Walsh 2013	3	17	4	15	3.8%	0.66 [0.18, 2.49]
Subtotal (95% CI)		**1514**		**1519**	**100.0%**	**1.15 [0.88, 1.50]**
Total events	144		126			
Heterogeneity: Tau² = 0.03; Chi² = 11.58, df = 10 (P = 0.31); I² = 14%						
Test for overall effect: Z = 1.04 (P = 0.30)						
1.1.2 Randomised by CVD						
Bush 1997	4	49	4	50	12.8%	1.02 [0.27, 3.85]
Carson 2011	43	1008	52	995	64.1%	0.82 [0.55, 1.21]
Carson 2013	7	55	1	55	5.7%	7.00 [0.89, 55.01]
Cooper 2011	2	24	1	21	4.5%	1.75 [0.17, 17.95]
Walsh 2013	3	17	4	15	12.8%	0.66 [0.18, 2.49]
Subtotal (95% CI)		**1153**		**1136**	**100.0%**	**0.96 [0.58, 1.59]**
Total events	59		62			
Heterogeneity: Tau² = 0.06; Chi² = 4.67, df = 4 (P = 0.32); I² = 14%						
Test for overall effect: Z = 0.17 (P = 0.87)						



Test for subgroup differences: Chi² = 0.40, df = 1 (P = 0.53), I² = 0%

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias
(H) Assessment of Cardiovascular Event
(I) Definition of Cardiovascular Event

Mortality at 30 days: **RR 1.15 (0.88 to 1.50)**

Holst et al Systematic Review

All comers (*including CVD*): **RR 0.86 (0.74 to 1.01)**

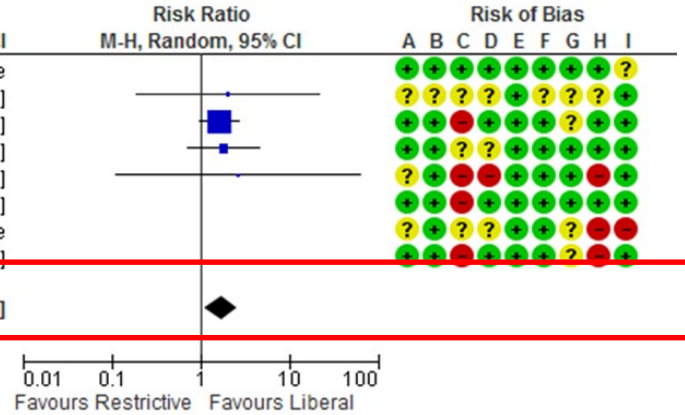
Acute coronary syndrome and pulmonary oedema in patients with chronic cardiovascular disease

Docherty AM, et al. BMJ. http://dx.doi.org/10.1136/bmj.i1351

A

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
Almeida 2015	0	22	0	12		Not estimable
Bush 1997	2	49	1	50	3.4%	2.04 [0.19, 21.79]
Carson 2011	38	1008	23	1005	72.5%	1.65 [0.99, 2.74]
Carson 2013	11	54	6	54	22.3%	1.83 [0.73, 4.60]
Cooper 2011	1	24	0	21	1.9%	2.64 [0.11, 61.54]
Holst 2014	6	75	2	66	0.0%	2.64 [0.55, 12.64]
Parker 2013	0	70	0	67		Not estimable
Walsh 2013	1	17	0	15	0.0%	2.67 [0.12, 60.93]
Total (95% CI)		**1135**		**1130**	**100.0%**	**1.71 [1.11, 2.65]**
Total events	52		38			

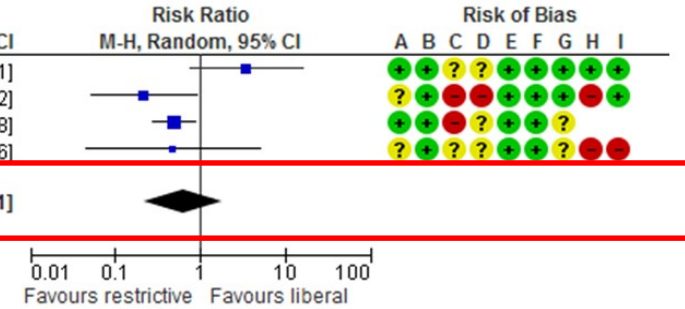
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 3 (P = 0.99); I² = 0%
Test for overall effect: Z = 2.43 (P = 0.01)



B

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
Carson 2013	7	55	2	55	23.0%	3.50 [0.76, 16.11]
Cooper 2011	2	24	8	21	24.3%	0.22 [0.05, 0.92]
Hebert 1999	14	160	35	197	39.1%	0.49 [0.27, 0.88]
Parker 2013	1	70	2	67	13.6%	0.48 [0.04, 5.16]
Total (95% CI)		**309**		**340**	**100.0%**	**0.63 [0.22, 1.81]**
Total events	24		47			

Heterogeneity: Tau² = 0.65; Chi² = 7.42, df = 3 (P = 0.06); I² = 60%
Test for overall effect: Z = 0.86 (P = 0.39)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
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(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias
(H) Assessment of Cardiovascular Event
(I) Definition of Cardiovascular Event

ACS: RR 1.71 (0.11 to 2.65); I^2 0%
Absolute risk difference ≈2%; NNT ≈50

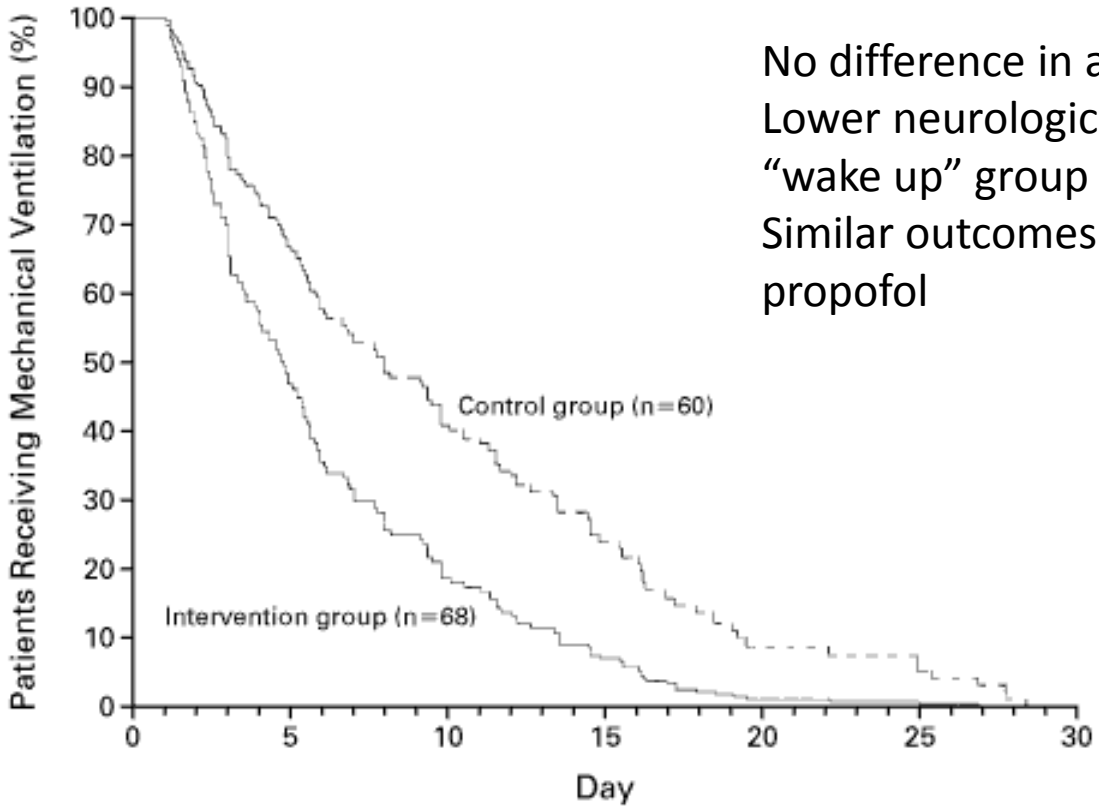
What is the ideal sedation state for a critically ill mechanically ventilated patient without a brain injury?

- Opens eyes only to physical stimulus
- Opens eyes briefly to voice
- Opens eyes to voice and maintains eye contact
- Awake without stimulation

Daily Interruption of Sedative Infusions in Critically Ill Patients Undergoing Mechanical Ventilation

John P. Kress, M.D., et al

NEJM 2000 Volume 342:1471-1477

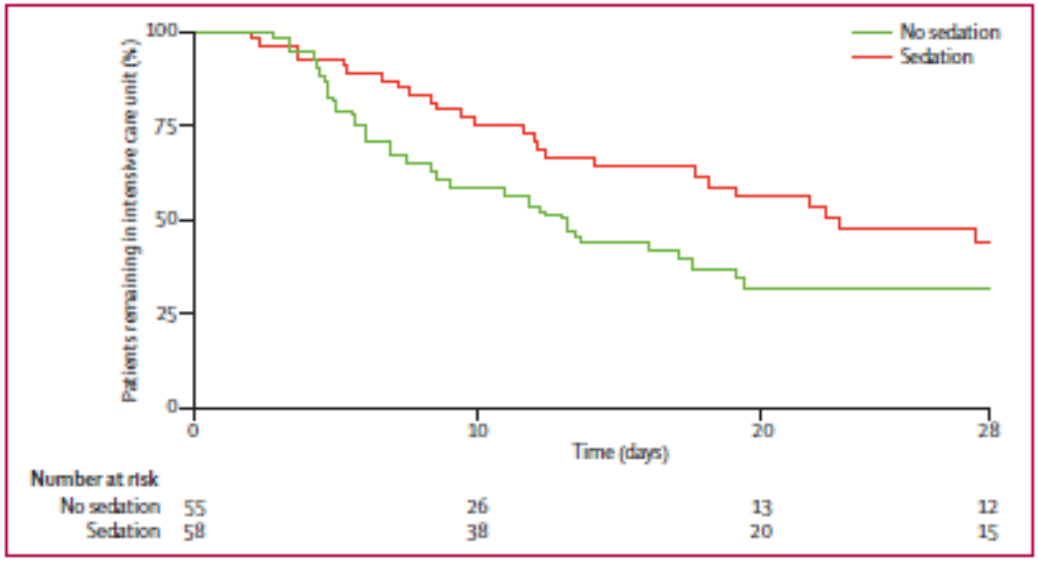


No difference in adverse events
Lower neurological investigation rates in "wake up" group
Similar outcomes with midazolam and propofol

A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial

Thomas Strøm, Torben Martinussen, Palle Toft

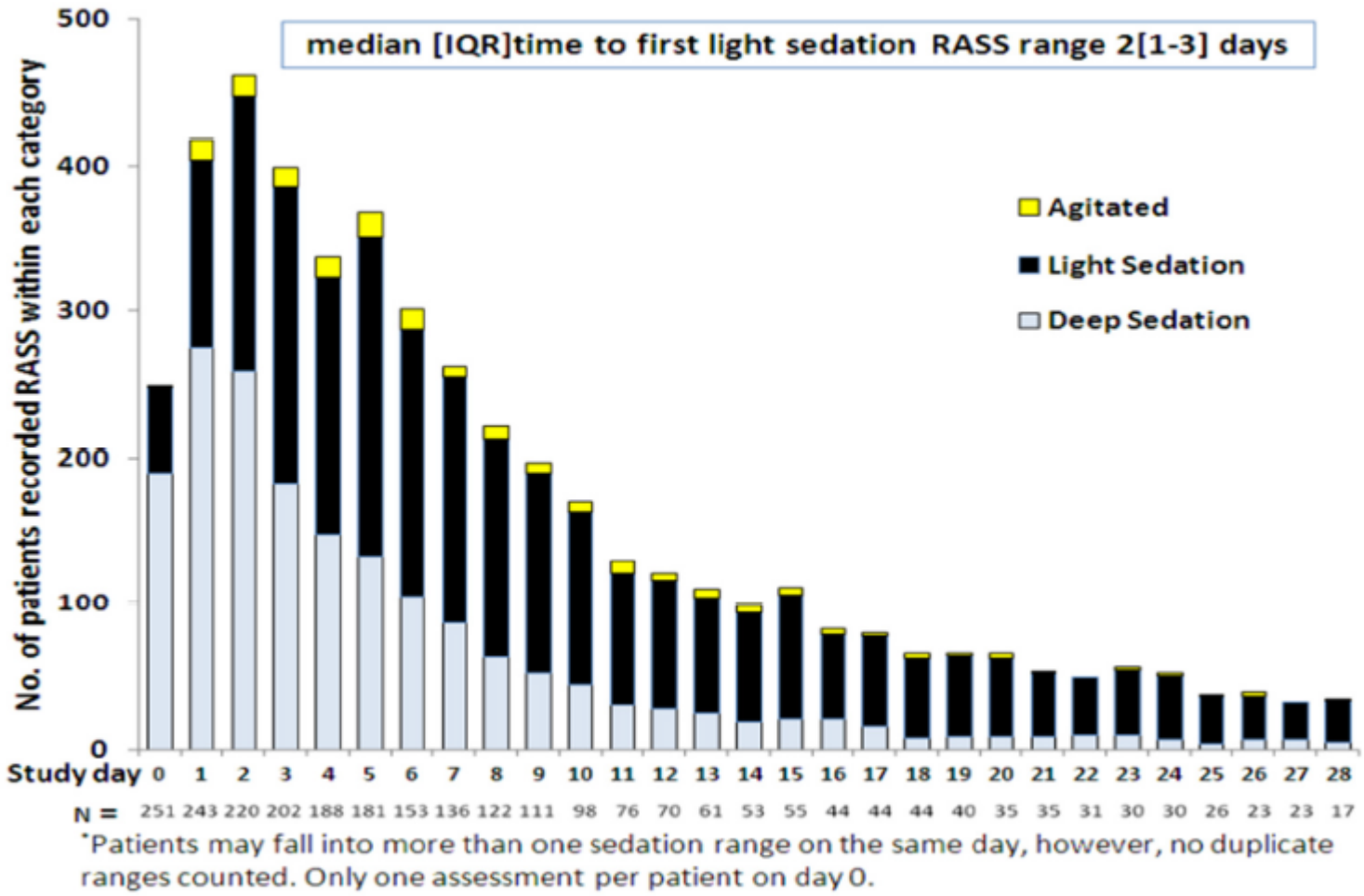
Lancet 2010; 375: 475–80



Trend to lower mortality
Lower ventilation days
Higher nursing resource use
Higher rates of agitation in non-sedated group
No patient-based psychological/experience measure

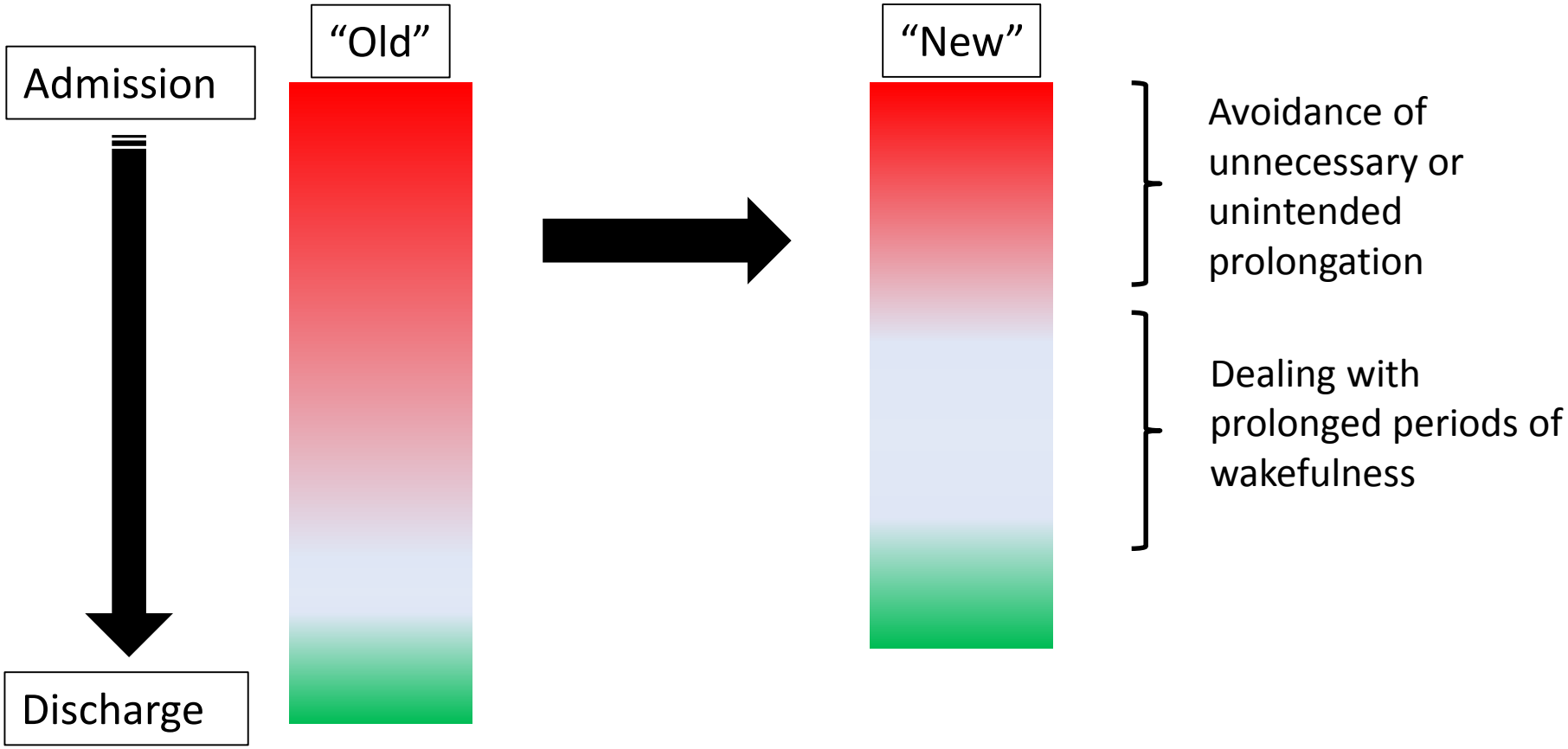
ANZICS observational study

AJRCCM 2012; 186: 724-731.

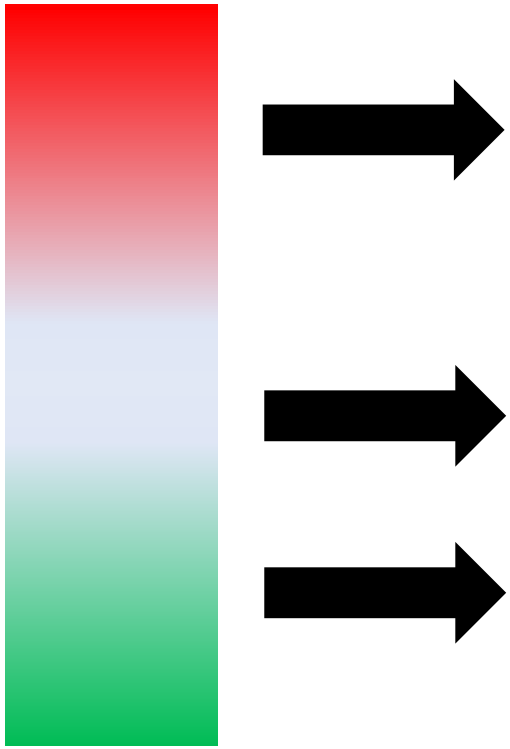


Early deep sedation associated with higher mortality (in adjusted analyses)

Implications of minimising sedation



Implications of minimising sedation



Tolerance of intubation and invasive ventilation

- Analgesia
- Antinociception
- Airway reflexes

Minimising risk of delirium

Managing agitation

Managing Pain/discomfort

JCN Journal of Clinical Nursing

Journal of Clinical Nursing

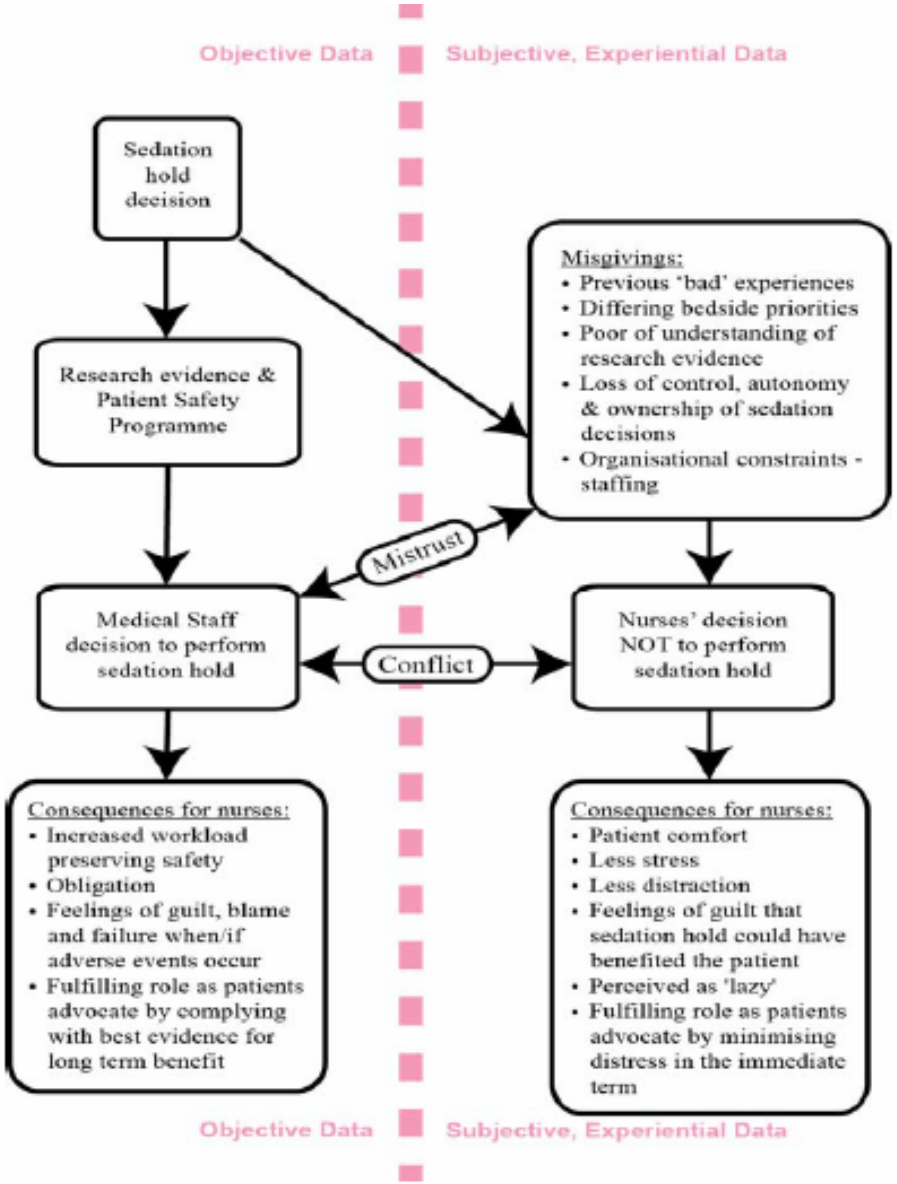
ORIGINAL ARTICLE

'Targeting' sedation: the lived experience of the intensive care nurse

Kirsty Everingham, Tonks Fawcett and Tim Walsh

- Conflict, power, fear, and guilt cycles
- "Damned if you do; damned if you don't"

"I just think that people waking up is one of the hardest things we have to witness here, because people are uncomfortable, they get a fright. You know it is quite nerve racking sometimes because you don't know what is going to happen…"



Doing less better

- Using interventions to make physiology look ‘normal’ does not usually improve outcomes in ICU
- In many cases outcomes may be worse:
  - Glycaemic control
  - Blood gases
  - Blood albumin concentration
- Implementing the ‘basics’ well almost certainly has greater patient benefit overall than expensive or complex therapies

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