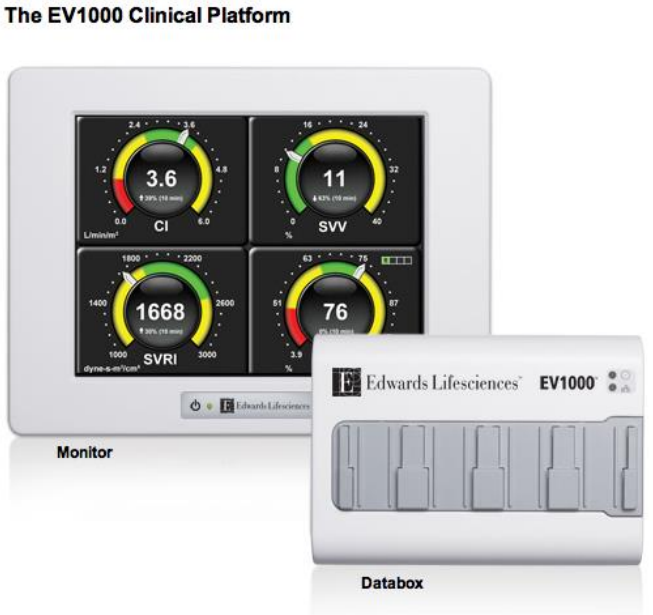
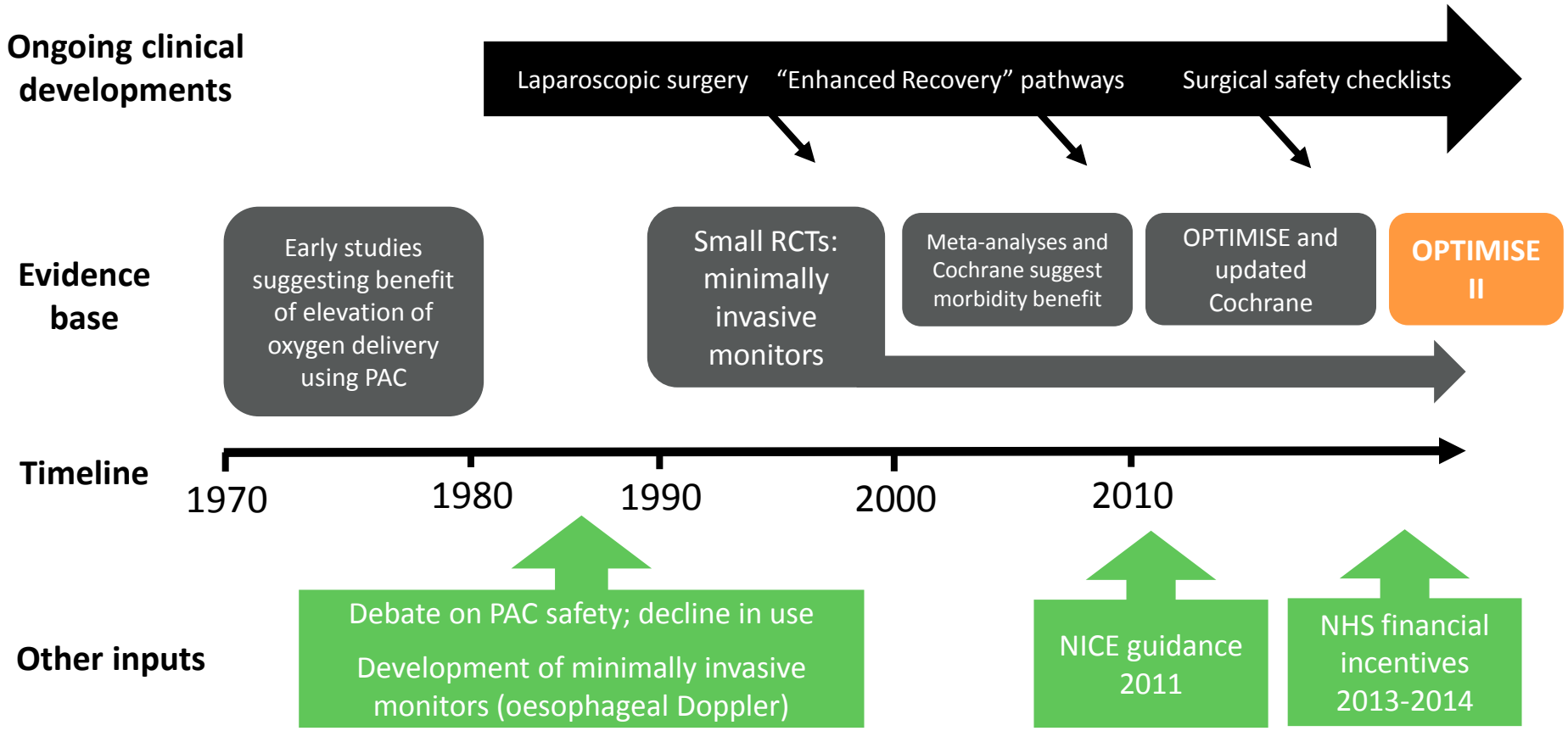
Trial slide set

Modern cardiac output monitoring

- Now much less invasive
- Simple to use (nurse led)
- Reduced cost
- Safe





Evolution of evidence base for GDHT

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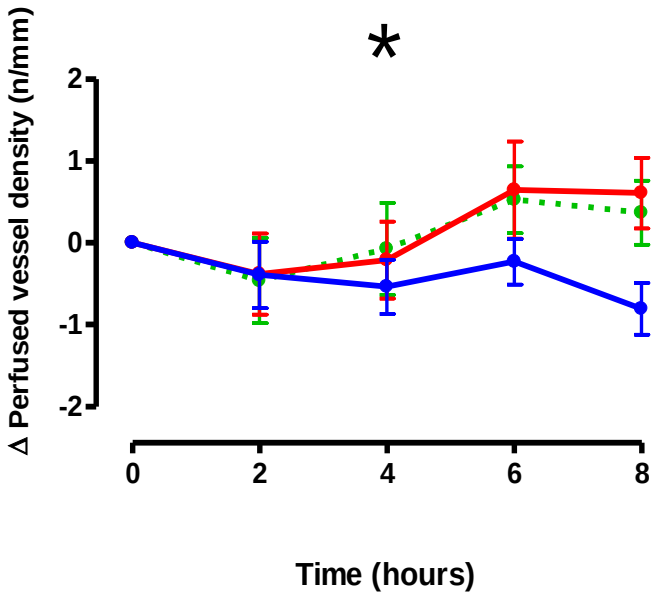
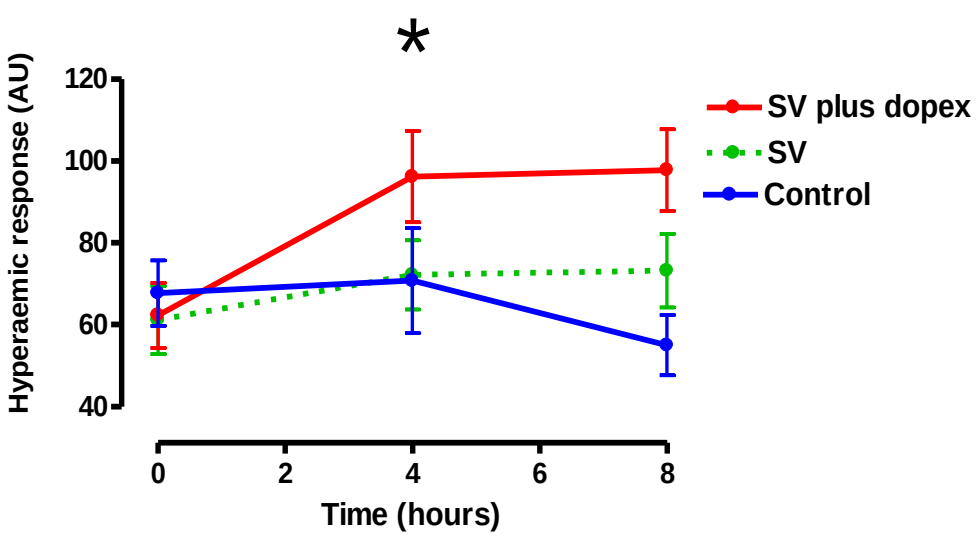
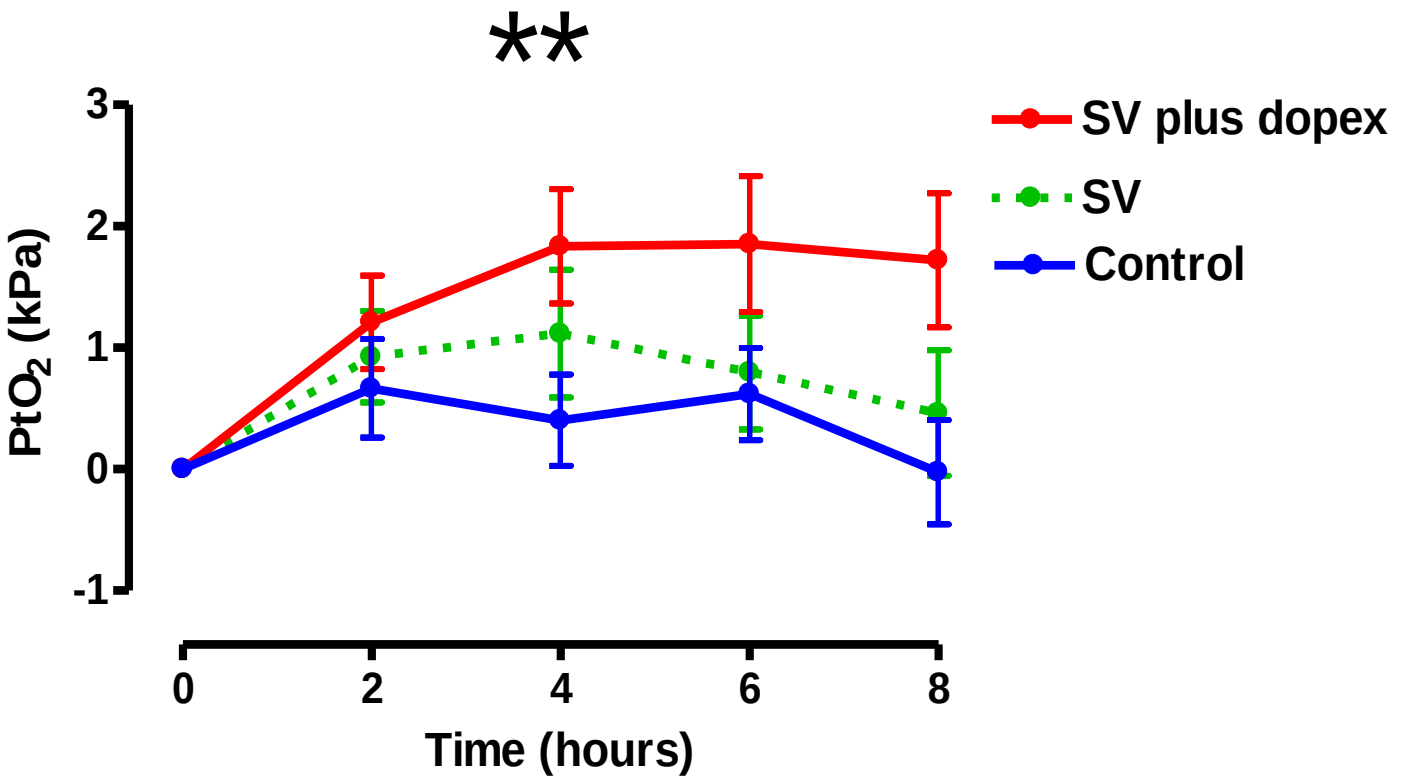




Effect of fluid and low dose inotrope on microvascular flow after surgery

Jhanji et al. *Crit Care* 2010 14: R151



Effect of fluid and low dose inotrope on tissue oxygenation after surgery

Jhanji et al. *Crit Care* 2010 14: R151

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of a Perioperative, Cardiac Output–Guided Hemodynamic Therapy Algorithm on Outcomes Following Major Gastrointestinal Surgery

A Randomized Clinical Trial and Systematic Review

Rupert M. Pearse, MD; David A. Harrison, PhD; Neil MacDonald, FRCA; Michael A. Gillies, FRCA; Mark Blunt, FRCA; Gareth Ackland, PhD; Michael P.W. Grocott, MD; Aoife Ahern, BSc; Kathryn Griggs, MSc; Rachael Scott, PhD; Charles Hinds, FRCA; Kathryn Rowan, PhD; for the OPTIMISE Study Group

IMPORTANCE Small trials suggest that postoperative outcomes may be improved by the use of cardiac output monitoring to guide administration of intravenous fluid and inotropic drugs as part of a hemodynamic therapy algorithm.

OBJECTIVE To evaluate the clinical effectiveness of a perioperative, cardiac output-guided hemodynamic therapy algorithm.

DESIGN, SETTING, AND PARTICIPANTS OPTIMISE was a pragmatic, multicenter, randomized, observer-blinded trial of 734 high-risk patients aged 50 years or older undergoing major gastrointestinal surgery at 17 acute care hospitals in the United Kingdom. An updated systematic review and meta-analysis were also conducted including randomized trials published from 1966 to February 2014.

INTERVENTIONS Patients were randomly assigned to a cardiac output-guided hemodynamic therapy algorithm for intravenous fluid and inotrope (dopexamine) infusion during and 6 hours following surgery (n=368) or to usual care (n=366).

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of predefined 30-day moderate or major complications and mortality. Secondary outcomes were morbidity on day 7; infection, critical care–free days, and all-cause mortality at 30 days; all-cause mortality at 180 days; and length of hospital stay.

RESULTS Baseline patient characteristics, clinical care, and volumes of intravenous fluid were similar between groups. Care was nonadherent to the allocated treatment for less than 10% of patients in each group. The primary outcome occurred in 36.6% of intervention and 43.4% of usual care participants (relative risk [RR], 0.84 [95% CI, 0.71-1.01]; absolute risk reduction, 6.8% [95% CI, −0.3% to 13.9%]; $P = .07$). There was no significant difference between groups for any secondary outcomes. Five intervention patients (1.4%) experienced cardiovascular serious adverse events within 24 hours compared with none in the usual care group. Findings of the meta-analysis of 38 trials, including data from this study, suggest that the intervention is associated with fewer complications (intervention, 488/1548 [31.5%] vs control, 614/1476 [41.6%]; RR, 0.77 [95% CI, 0.71-0.83]) and a nonsignificant reduction in hospital, 28-day, or 30-day mortality (intervention, 159/3215 deaths [4.9%] vs control, 206/3160 deaths [6.5%]; RR, 0.82 [95% CI, 0.67-1.01]) and mortality at longest follow-up (intervention, 267/3215 deaths [8.3%] vs control, 327/3160 deaths [10.3%]; RR, 0.86 [95% CI, 0.74-1.00]).

CONCLUSIONS AND RELEVANCE In a randomized trial of high-risk patients undergoing major gastrointestinal surgery, use of a cardiac output-guided hemodynamic therapy algorithm compared with usual care did not reduce a composite outcome of complications and 30-day mortality. However, inclusion of these data in an updated meta-analysis indicates that the intervention was associated with a reduction in complication rates.

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Editorial

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Group Information: The members of the OPTIMISE Study Group are listed at the end of this article.

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Pearse RM and coauthors

Effect of a Perioperative, Cardiac Output–Guided Hemodynamic Therapy Algorithm on Outcomes Following Major Gastrointestinal Surgery: A Randomized Clinical Trial and Systematic Review

Published online May 19, 2014

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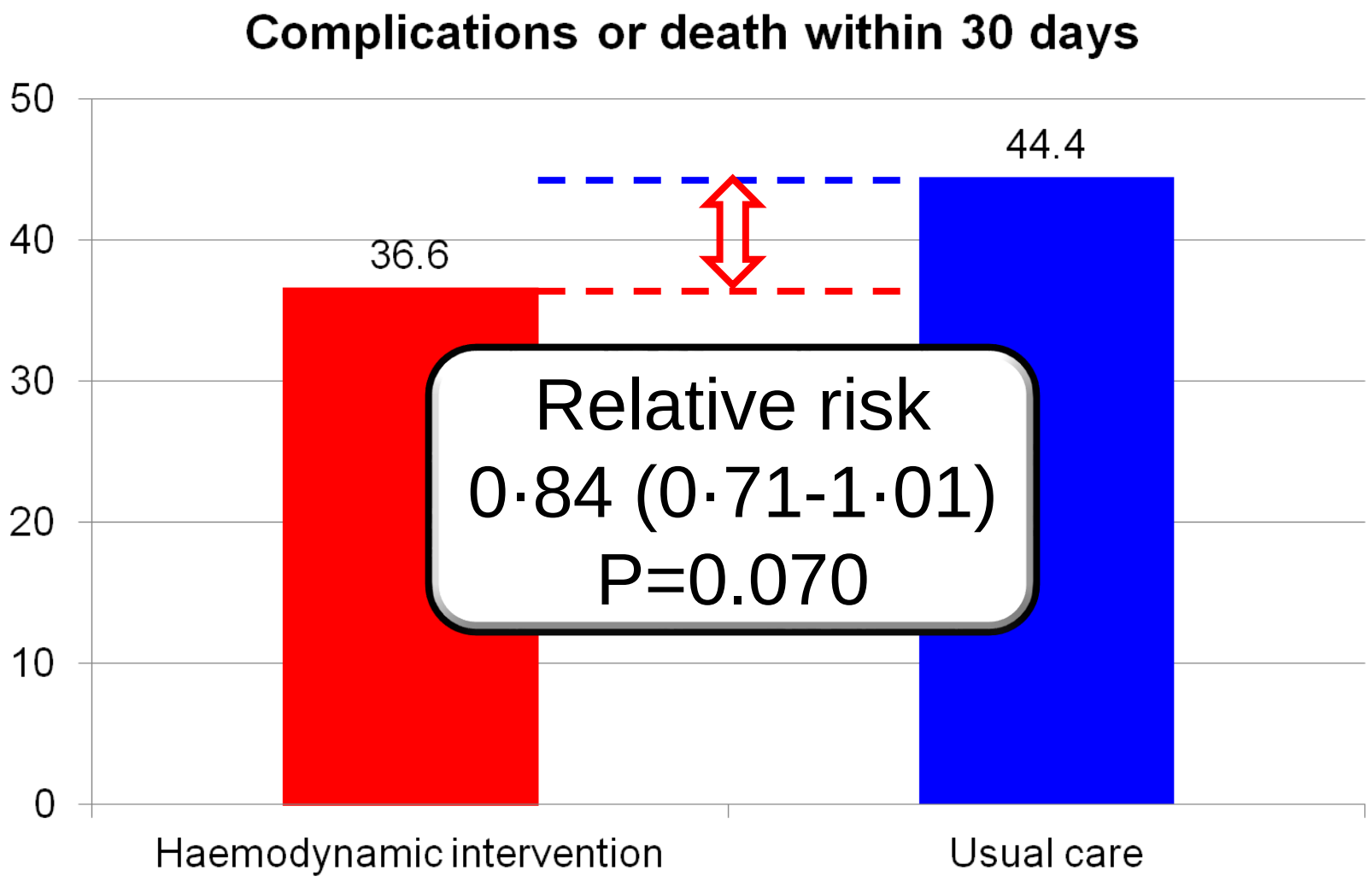
Primary outcome



Pearse et al. *JAMA* 2014; 311: 2181-90.

Secondary outcomes

	Intervention	Usual care	Relative risk (95% CI)	p
Morbidity Survey	182 (66·2)	195 (67·9)	0·97 (0·87-1·09)	0·72
Infection	87 (23·8)	108 (29·7)	0·80 (0·63-1·02)	0·079
Hospital stay	10 (7-14)	11 (7-17)	--	0·054
Survivors	10 (7-14)	11 (7-17)		
Non-survivors	7 (3-33)	16 (9-36)		
Critical care free days	27 (26-29)	28 (25-29)	--	0·98

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Pearse et al. *JAMA* 2014; 311: 2181-90.

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Sub-group analyses

	Intervention	Usual care	Adjusted odds ratio (95% CI)	p-value
Urgency of surgery				0·53
Elective	127 (35·9)	152 (43·3)	0·72 (0·52-0·99)	
Non-elective	7 (58·3)	6 (46·2)	1·24 (0·23-6·74)	
Surgical procedure				0·70
Upper gastrointestinal	39 (36·1)	47 (41·2)	0·83 (0·47-1·47)	
Lower gastrointestinal	56 (33·5)	62 (38·0)	0·82 (0·51-1·31)	
Small bowel +/- pancreas	37 (43·0)	47 (56·6)	0·53 (0·28-0·99)	
Urology/gynae	2 (40·0)	2 (50·0)	0·62 (0·04-10·20)	
Timing of recruitment				0·019
Early (first 10 per site)	33 (42·3)	28 (34·1)	1·51 (0·75-3·01)	
Late (subsequent patients)	100 (35·0)	129 (46·7)	0·59 (0·41-0·84)	

Cardiac Adverse Events in the first OPTIMISE Trial

- Five intervention patients (1·4%) at 24 hrs
- None in usual care patients at 24 hrs
- Cardiovascular event rate similar at 30 days
- None of these findings statistically significant

Pearse et al. *JAMA* 2014; 311: 2181-90.

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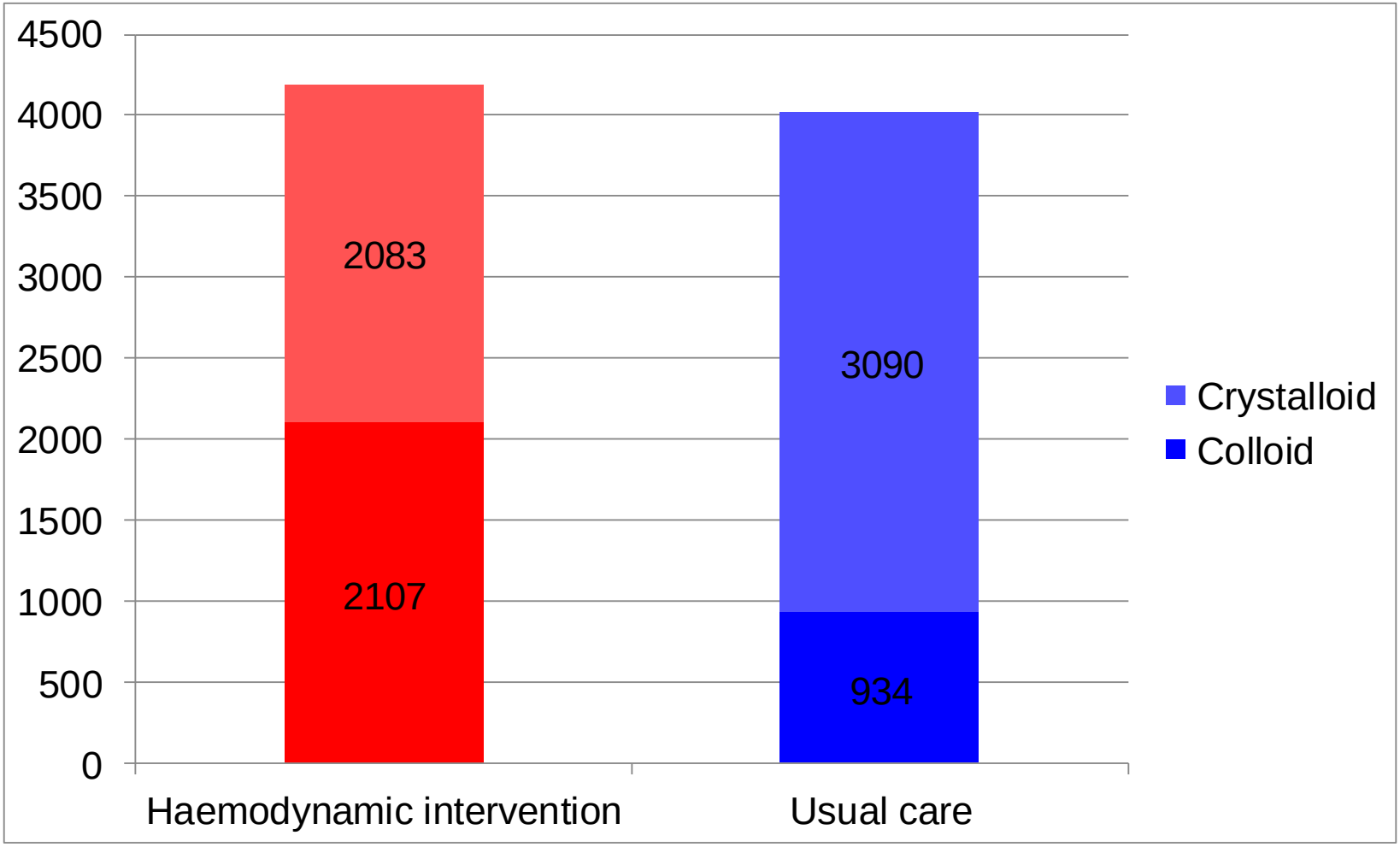
Fluid use in the first OPTIMISE trial



Pearse et al. *JAMA* 2014; 311: 2181-90.

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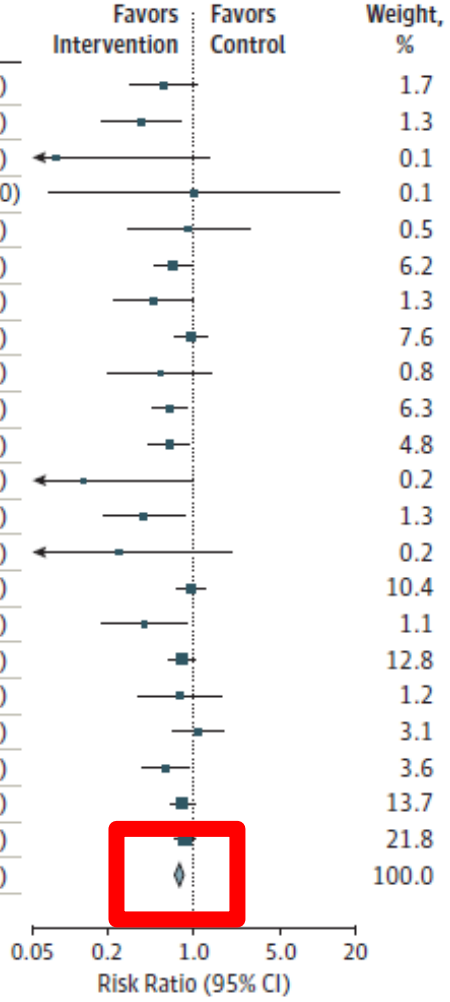
The first OPTIMISE Trial:

Secondary studies

Source	Intervention No. of Events	Intervention Total No.	Control No. of Events	Control Total No.	Risk Ratio (95% CI)
Shoemaker et al,[20] 1988	8	28	30	60	0.57 (0.30-1.08)
Berlauk et al,[21] 1991	11	68	9	21	0.38 (0.18-0.79)
Mythen et al,[22] 1995	0	30	6	30	0.08 (0.00-1.31)
Sinclair et al,[23] 1997	1	20	1	20	1.00 (0.07-14.90)
Ueno et al,[24] 1998	4	16	5	18	0.90 (0.29-2.78)
Wilson et al,[25] 1999	38	92	28	46	0.68 (0.48-0.95)
Lobo et al,[26] 2000	6	19	12	18	0.47 (0.23-0.99)
Jerez et al,[27] 2001	53	181	65	209	0.94 (0.70-1.28)
Conway et al,[28] 2002	5	29	9	28	0.54 (0.20-1.40)
Pearse et al,[14] 2005	27	62	41	60	0.64 (0.46-0.89)
Wakeling et al,[29] 2005	24	67	38	67	0.63 (0.43-0.93)
Noblett et al,[30] 2006	1	51	8	52	0.13 (0.02-0.98)
Donati et al,[31] 2007	8	68	20	67	0.39 (0.19-0.83)
Smetkin et al,[32] 2009[a]	1	20	4	20	0.25 (0.03-2.05)
Jhanji et al,[6] 2010	57	90	30	45	0.95 (0.73-1.23)
Mayer et al,[33] 2010	6	30	15	30	0.40 (0.18-0.89)
Cecconi et al,[34] 2011	16	20	20	20	0.80 (0.64-1.02)
Challand et al,[35] 2012	10	89	13	90	0.78 (0.36-1.68)
Brandstrup et al,[36] 2012[a]	23	71	24	79	1.07 (0.66-1.71)
Salzwedel et al,[37] 2013[a]	21	79	36	81	0.60 (0.39-0.93)
Goepfert et al,[38] 2013[a]	34	50	42	50	0.81 (0.65-1.01)
OPTIMISE, 2014	134	368	158	365	0.84 (0.70-1.01)
Total	488	1548	614	1476	0.77 (0.71-0.83)

Heterogeneity: $\chi^2_{21} = 30.44$; $P = .08$; $I^2 = 31\%$
Test for overall effect: $z = 6.22$; $P < .001$



Updated systematic review

Pearse et al. *JAMA* 2014; 311: 2181-90.

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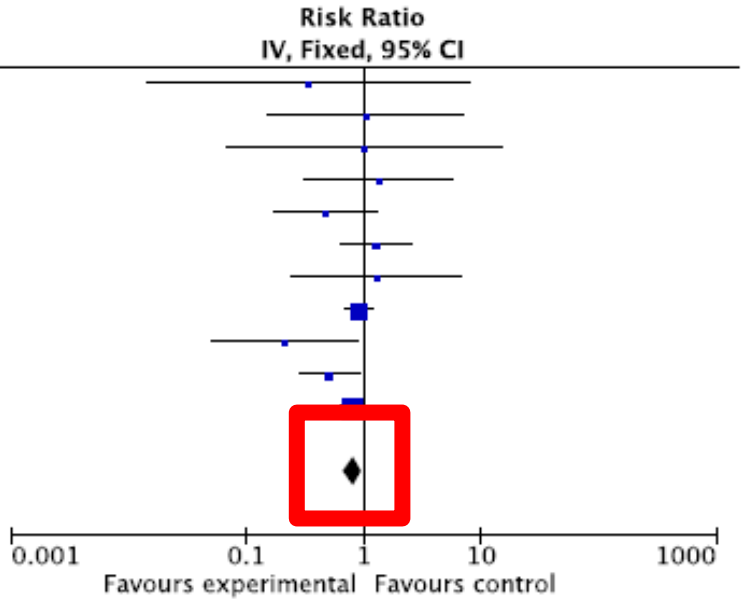
Study or Subgroup	Protocol Events	Protocol Total	Control Events	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI	Year
Mythen 1995	0	30	1	30	0.3%	0.33 [0.01, 7.87]	1995
Bender 1997	2	51	2	53	0.7%	1.04 [0.15, 7.10]	1997
Sinclair 1997	1	20	1	20	0.4%	1.00 [0.07, 14.90]	1997
Valentine 1998	4	60	3	60	1.3%	1.33 [0.31, 5.70]	1998
Lobo 2000	4	19	8	18	2.6%	0.47 [0.17, 1.30]	2000
Wakeling 2005	14	67	11	67	5.2%	1.27 [0.62, 2.60]	2005
Van der Linden 2010	3	20	2	17	1.0%	1.27 [0.24, 6.76]	2010
Jhanji 2010	52	90	29	45	34.1%	0.90 [0.68, 1.19]	2010
Pillai 2011	2	32	10	34	1.3%	0.21 [0.05, 0.90]	2011
*Salzwedel 2013	13	79	26	81	7.7%	0.51 [0.28, 0.92]	2013
*Optimise 2014	87	368	108	365	45.5%	0.80 [0.63, 1.02]	2014
Total (95% CI)		**836**		**790**	**100.0%**	**0.81 [0.69, 0.95]**	
Total events	182		201				

Heterogeneity: $Chi^2 = 9.90$, df = 10 (P = 0.45); $I^2 = 0\%$

Test for overall effect: Z = 2.57 (P = 0.01)



Updated systematic review: Infection

Pearse et al. *JAMA* 2014; 311: 2181-90.

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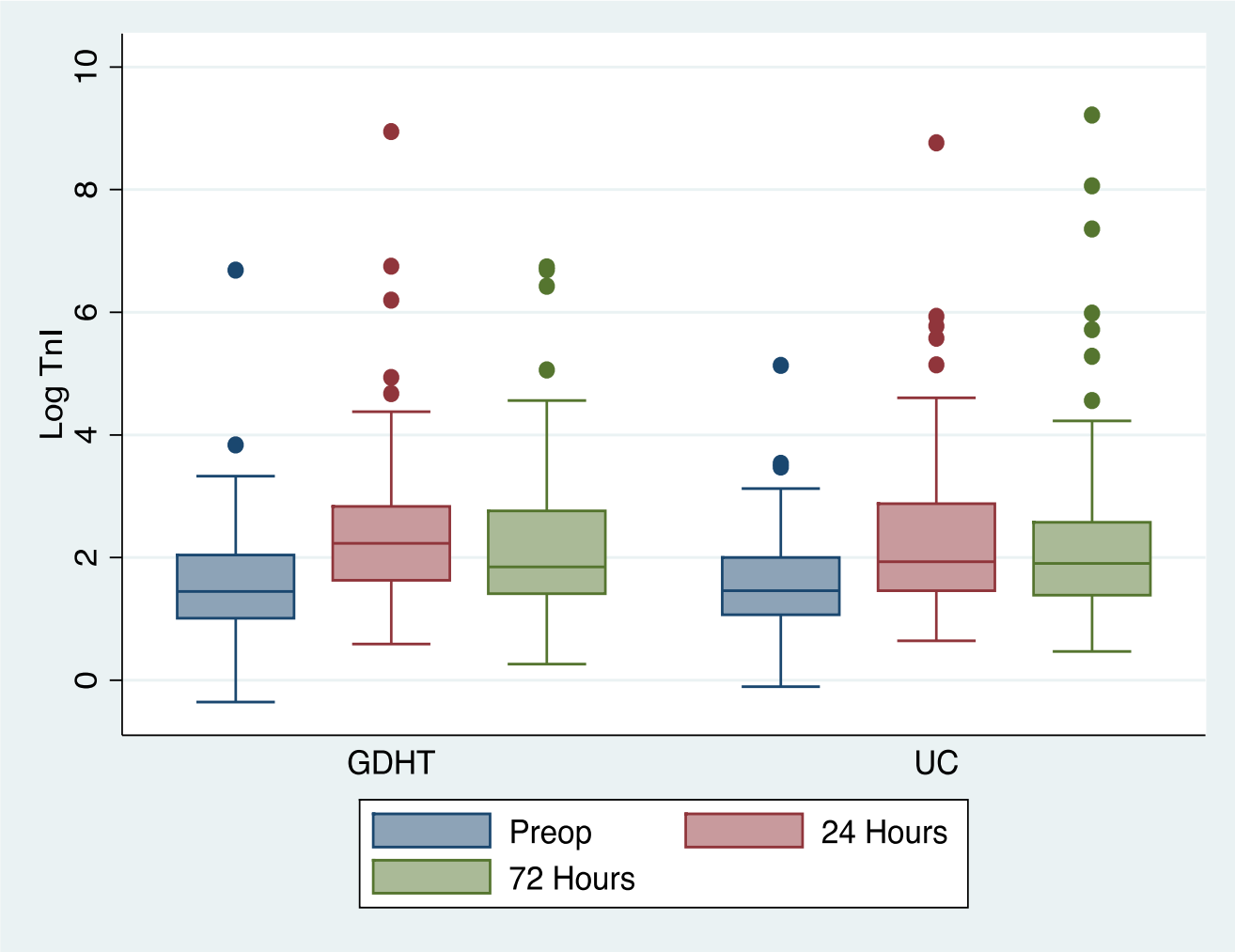

GDHT did not increase myocardial injury

Gillies et al. *Brit J Anaesth* 2015; 115: 227-33.

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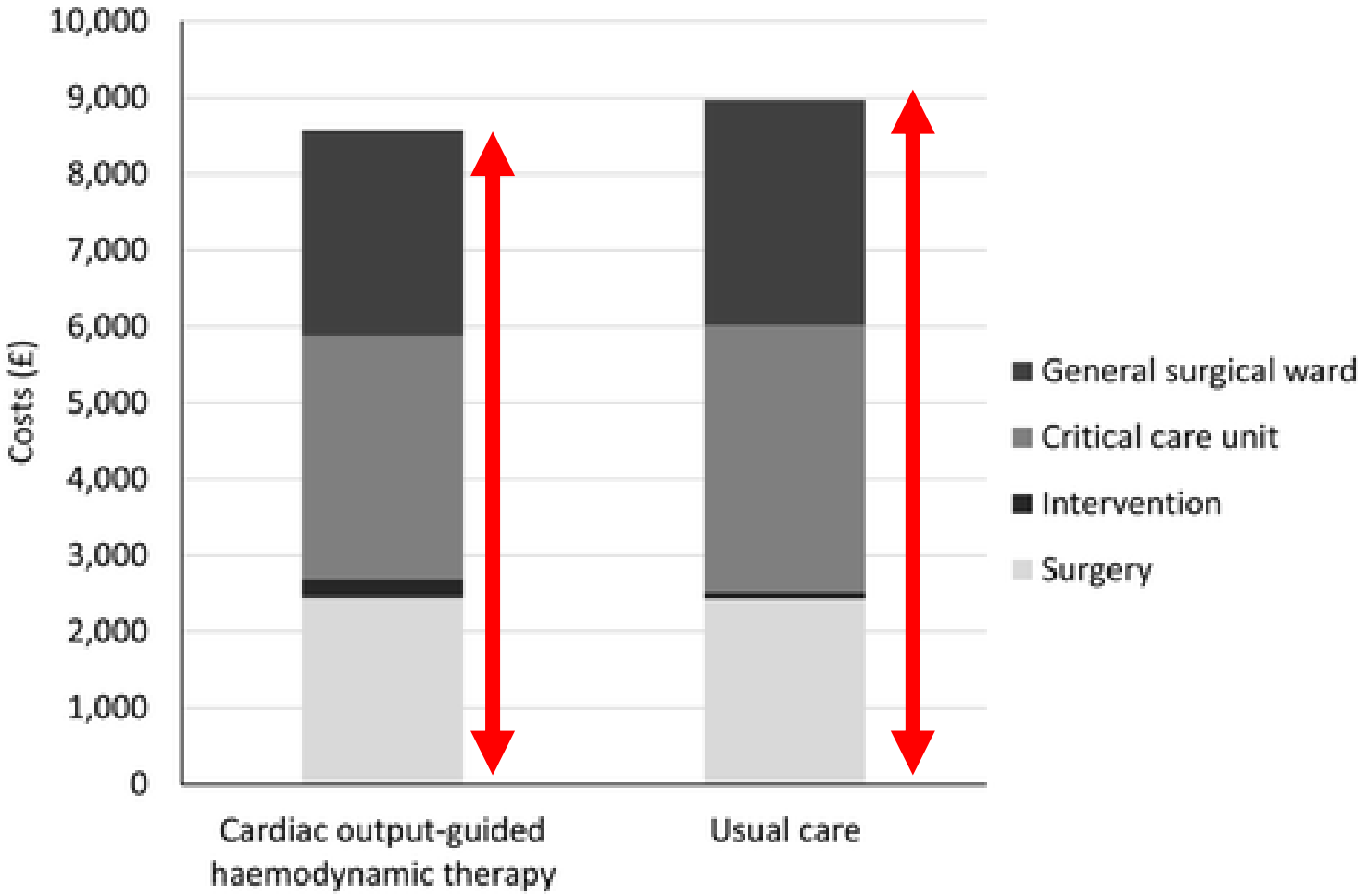
£10,000 GBP ≈ $14,500 USD



Cardiac output guided therapy likely to be cost effective

Sadique et al. *Periop Med* 2015; 4: 13.

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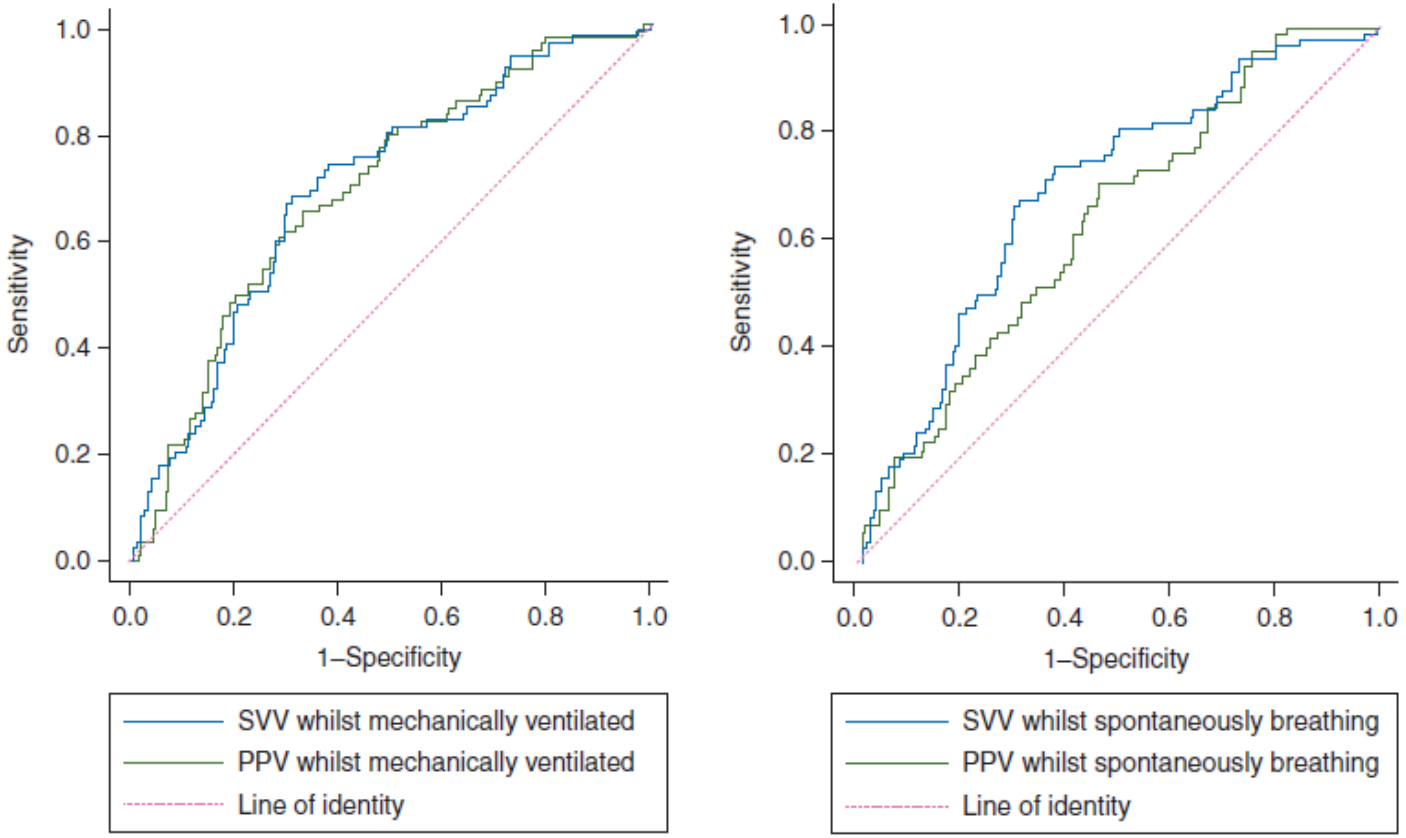
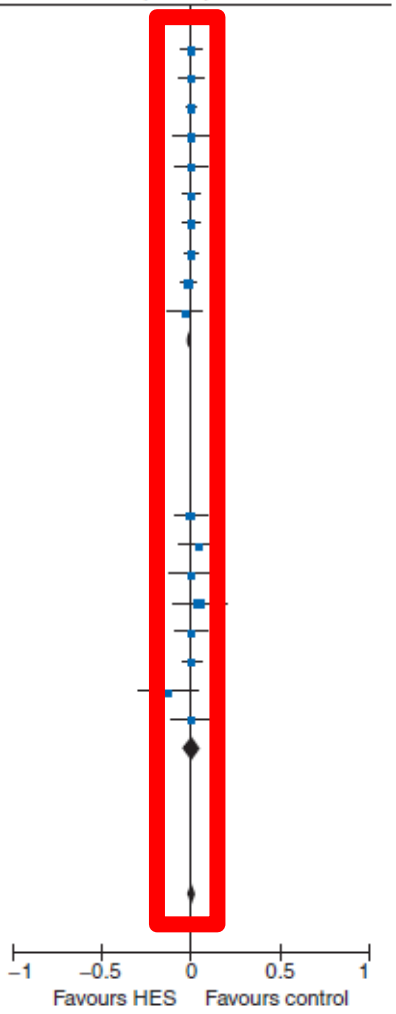


Stroke volume and pulse pressure variation less reliable during spontaneous breathing

MacDonald et al. *Brit J Anaesth* 2015; 114: 598–604.

Study or subgroup	HES Events	HES Total	Control Events	Control Total	Weight	Risk difference M–H, fixed, 95% CI
Cardiac surgery						
Alavi and colleagues[20]	0	32	0	60	6.1%	0.00 [–0.05, 0.05]
Diehl and colleagues[22]	0	33	0	27	4.4%	0.00 [–0.06, 0.06]
Hecht-Dolnik and colleagues[9]	0	78	0	78	11.5%	0.00 [–0.02, 0.02]
Kuitunen and colleagues[28]	0	30	0	15	2.9%	0.00 [–0.10, 0.10]
Munsch and colleagues[32]	0	20	0	20	2.9%	0.00 [–0.09, 0.09]
Ooi and colleagues[33]	0	45	0	45	6.6%	0.00 [–0.04, 0.04]
Sirvinskas and colleagues[34]	0	40	0	40	5.9%	0.00 [–0.05, 0.05]
Van der Linden and colleagues[35]	0	55	0	55	8.1%	0.00 [–0.03, 0.03]
Van der Linden and colleagues[36]	0	64	1	68	9.7%	–0.01 [–0.06, 0.03]
Verheij and colleagues[37]	0	17	2	50	3.7%	–0.04 [–0.14, 0.06]
Subtotal (95% CI)		**414**		**458**	**62.0%**	**–0.00 [–0.02, 0.01]**
Total events	0		3			
Heterogeneity: χ^2=1.12, df=9 (P=1.00); I^2=0%						
Test for overall effect: Z=0.58 (P=0.56)						
Non-cardiac/mixed surgery						
Dehne and colleagues[21]	0	45	0	15	3.3%	0.00 [–0.09, 0.09]
Feldheiser and colleagues[23]	1	26	0	24	3.7%	0.04 [–0.06, 0.14]
Godet and colleagues[24]	2	32	2	33	4.8%	0.00 [–0.11, 0.12]
Gondos and colleagues[25]	15	50	38	150	11.1%	0.05 [–0.10, 0.19]
Guo and colleagues[26]	0	20	0	22	3.1%	0.00 [–0.09, 0.09]
Hung and colleagues[27]	0	41	0	39	5.9%	0.00 [–0.05, 0.05]
Mahmood and colleagues[30]	1	42	3	20	4.0%	–0.13 [–0.29, 0.04]
Marik and colleagues[31]	0	15	0	15	2.2%	0.00 [–0.12, 0.12]
Subtotal (95% CI)		**271**		**318**	**38.0%**	**0.00 [–0.12, 0.12]**
Total events	19		43			
Heterogeneity: χ^2=3.27, df=7 (P=0.86); I^2=0%						
Test for overall effect: Z=0.16 (P=0.87)						
Total (95% CI)		**685**		**776**	**100.0%**	**–0.00 [–0.02, 0.02]**
Total events	19		46			
Heterogeneity: χ^2=4.33, df=17 (P=1.00); I^2=0%						
Test for overall effect: Z=0.12 (P=0.91)						
Test for subgroup differences: χ^2=0.11, df=1 (P=0.74); I^2=0%						



Which fluid….. is starch safe for surgical patients?

Gillies et al. *Brit J Anaesth* 2014; 112: 25–34.

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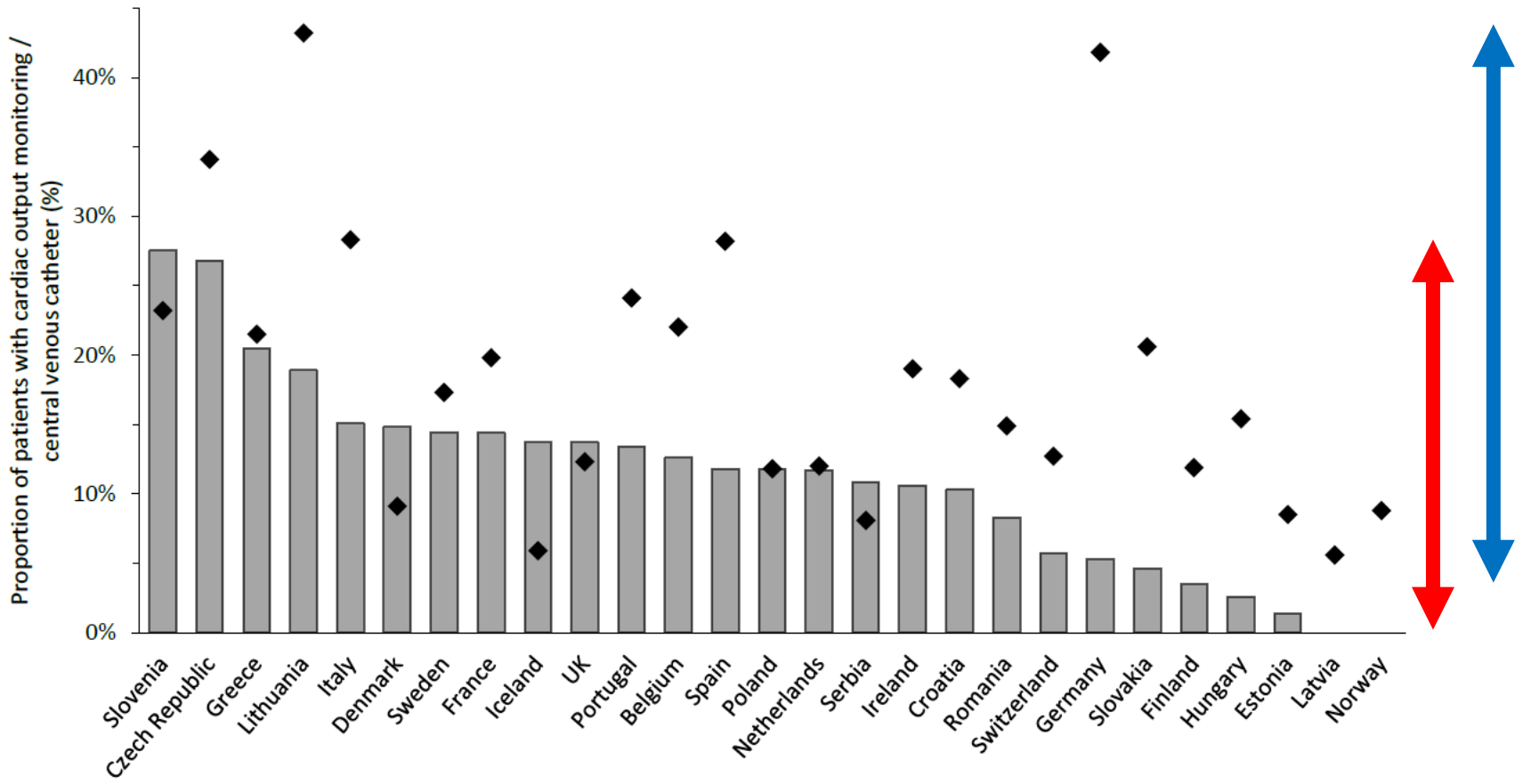

International variation in use of cardiac output and central venous pressure monitoring

Ahmad et al. *Perioperative Med* 2015; 4: 8.


Optimise II

Trial population

Major elective gastrointestinal surgery

Age ≥65 years and ≥ASA II

Estimate: 50,000 NHS (UK) patients per year

Intervention

- OPTIMISE treatment algorithm
- Fluid guided by stroke volume
- Low dose inotrope infusion
- Low rate maintenance fluid
- Edwards Lifesciences monitor

Intervention: fluid

- Fluid chosen from a ‘safe list’
- Colloid or crystalloid for replacement
- Fluid unlikely to help when SVV <5%
- Low rate maintenance fluid important:
- 5% dextrose does not cause hyponatraemia

Summary

General haemodynamic measures

1. 5% dextrose at 1 ml/kg/hr
2. Transfuse blood to maintain haemoglobin >80 g/l
3. Clinician retains discretion to adjust therapy if concerned about risks of hypovolaemia or fluid overload
4. Mean arterial pressure 60-100 mmHg; $Sp0_2$ ≥94%; temperature 37°C; heart rate <100 bpm

Administering fluid to a stroke volume end-point

1. 250ml colloid boluses to achieve a maximal value of stroke volume [*Note: Start inotrope after first fluid challenge – see below*]
2. Fluid challenges should not be continued in patients who are not fluid responsive in terms of a stroke volume increase
3. Fluid responsiveness is defined as a stroke volume increase ≥10%
4. If stroke volume decreases further fluid challenge(s) are indicated
5. Persistent stroke volume responsiveness suggests continued fluid loss
6. Fluid challenge is not recommended if SVV is less than 5%

Low dose inotrope infusion

1. Start fixed rate infusion of dobutamine (2.5µg/kg/min) or dopexamine (0.5µg/kg/min) after first fluid challenge.
2. Halve dose if heart rate rises to the greater of (a) >120% of baseline value or (b) >100bpm for more than 30 minutes.
3. Stop infusion if tachycardia persists.

What if blood or IV fluid is required regardless of stroke volume?

1. If blood products or additional fluid challenges are required, then stroke volume should still be monitored to identify any change in maximal stroke volume

Comparison

- Usual perioperative care
- Broad criteria to emphasise good care
- Avoids practice misalignment
- No cardiac output monitoring as routine

Outcome measures

Primary: Hospital acquired infection

Secondary: 180-day mortality

Acute Kidney Injury

Quality Adjusted Life Years

Cardiovascular events (safety)

Statistical aspects

- Simple two arm randomised trial
- Sample size: 2502 patients
- Minimisation by procedure and country
- Careful consideration of co-variates

Trial delivery

Sponsor:	Queen Mary University of London
CTU:	Pragmatic Clinical Trials Unit (QMUL)
Database:	Online with in-built randomisation
National:	Leadership team in each country
Goal:	Fifty sites each recruiting fifty patients
Funders:	NIHR and Edwards Lifesciences

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