BJA

British Journal of Anaesthesia, 116 (1): 100–12 (2016)

doi: 10.1093/bja/aev255
Advance Access Publication Date: 25 July 2015
Regional Anaesthesia

REGIONAL ANAESTHESIA

Neuraxial block and postoperative epidural analgesia: effects on outcomes in the POISE-2 trial†

K. Leslie[1,2,3,4,*], D. McIlroy[5], J. Kasza[4], A. Forbes[4], A. Kurz[6], J. Khan[7,8,9,10], C. S. Meyhoff[11], R. Allard[12], G. Landoni[13], X. Jara[14], G. Lurati Buse[15], K. Candiotti[16], H-S. Lee[17], R. Gupta[18], T. VanHelder[19], W. Purayil[20], S. De Hert[21], T. Treschan[22] and P. J. Devereaux[7,8,9,23]

[1]Department of Anaesthesia and Pain Management, Royal Melbourne Hospital, Melbourne, Australia, [2]Anaesthesia, Perioperative and Pain Medicine Unit, [3]Department of Pharmacology, University of Melbourne, Melbourne, Australia, [4]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia, [5]Department of Anaesthesia and Perioperative Medicine, Alfred Hospital and Monash University, Melbourne, Australia, [6]Department of Outcomes Research, Cleveland Clinic, Cleveland, USA, [7]Population Health Research Institute, Hamilton Health Sciences and McMaster University, Hamilton, Canada, [8]Departments of Clinical Epidemiology, [9]Biostatistics, McMaster University, Hamilton, Canada, [10]Department of Anesthesiology, University of Toronto, Toronto, Canada, [11]Department of Anaesthesiology, Herlev Hospital and University of Copenhagen, Herlev, Denmark, [12]Department of Anesthesiology and Perioperative Medicine, Kingston General Hospital and Queen's University, Kingston, Canada, [13]Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute and Vita-Salute University, Milan, Italy, [14]Department of Anesthesiology, Clinica Santa Maria and Universidad de Los Andes, Santiago, Chile, [15]Department of Anaesthesiology, Juravinski Hospital, Hamilton, Canada, [16]Department of Anesthesiology, Perioperative Medicine and Pain Management, University of Miami, Miami, USA, [17]Department of Anesthesiology, Sultanah Aminah Hospital, Johor Bahru, Malaysia, [18]Department of Medicine, Fortis Escorts Hospital, Jaipur, India, [19]Department of Anesthesia, Hamilton General Hospital, Hamilton, Canada, [20]Department of Anaesthesia, Westfort Hi-tech Hospital, Thrissur, India, [21]Department of Anaesthesiology, Ghent University Hospital, Ghent, Belgium, [22]Department of Anaesthesiology, Duesseldorf University Hospital, Duesseldorf, Germany, and [23]Department of Medicine, McMaster University, Hamilton, Canada

*Corresponding author. E-mail: kate.leslie@mh.org.au

Abstract

Background: We assessed associations between intraoperative neuraxial block and postoperative epidural analgesia, and a composite primary outcome of death or non-fatal myocardial infarction, at 30 days post-randomization in POISE-2 Trial subjects.
Methods: 10 010 high-risk noncardiac surgical patients were randomized aspirin or placebo and clonidine or placebo. Neuraxial block was defined as intraoperative spinal anaesthesia, or thoracic or lumbar epidural anaesthesia. Postoperative epidural

† This Article is accompanied by Editorial Aev353.
Accepted: June 5, 2015

analgesia was defined as postoperative epidural local anaesthetic and/or opioid administration. We used logistic regression with weighting using estimated propensity scores.

Results: Neuraxial block was not associated with the primary outcome [7.5% *vs* 6.5%; odds ratio (OR), 0.89; 95% CI (confidence interval), 0.73–1.08; *P*=0.24], death (1.0% *vs* 1.4%; OR, 0.84; 95% CI, 0.53–1.35; *P*=0.48), myocardial infarction (6.9% *vs* 5.5%; OR, 0.91; 95% CI, 0.74–1.12; *P*=0.36) or stroke (0.3% *vs* 0.4%; OR, 1.05; 95% CI, 0.44–2.49; *P*=0.91). Neuraxial block was associated with less clinically important hypotension (39% *vs* 46%; OR, 0.90; 95% CI, 0.81–1.00; *P*=0.04). Postoperative epidural analgesia was not associated with the primary outcome (11.8% *vs* 6.2%; OR, 1.48; 95% CI, 0.89–2.48; *P*=0.13), death (1.3% *vs* 0.8%; OR, 0.84; 95% CI, 0.35–1.99; *P*=0.68], myocardial infarction (11.0% *vs* 5.7%; OR, 1.53; 95% CI, 0.90–2.61; *P*=0.11], stroke (0.4% *vs* 0.4%; OR, 0.65; 95% CI, 0.18–2.32; *P*=0.50] or clinically important hypotension (63% *vs* 36%; OR, 1.40; 95% CI, 0.95–2.09; *P*=0.09).

Conclusions: Neuraxial block and postoperative epidural analgesia were not associated with adverse cardiovascular outcomes among POISE-2 subjects.

Key words: anaesthesia, epidural; anaesthesia, spinal; death; myocardial infarction; stroke

Key points

- The interaction between neuraxial anaesthesia or analgesia and a primary outcome of death or nonfatal myocardial infarction was studied.
- In a subanalysis of the POISE-2 Trial, neuraxial anaesthesia or postoperative epidural analgesia was not associated with death, myocardial infraction or stroke in high-risk noncardiac surgery subjects, in contrast to findings from the POISE-1 Trial.
- Neuraxial anaesthesia was associated with less hypotension than general anaesthesia.
- Additional large randomized controlled trials of the impact of anaesthetic technique on cardiovascular outcome are necessary.

The effects of intraoperative neuraxial block and postoperative epidural analgesia on major cardiovascular outcomes after noncardiac surgery remain controversial.[1–4] No large randomized controlled trial in at-risk patients focused on cardiovascular morbidity and mortality has been published in the last decade[5 6] and no trial is registered with major clinical trials registries worldwide.[7–11] Systematic reviews continue to summarize the results of small and heterogeneous studies.[12] *Post hoc* analyses of large multi-centre randomized controlled trials of other interventions, in which large numbers of patients at high risk of adverse cardiovascular outcomes received intraoperative neuraxial block or postoperative epidural analgesia, therefore remain one of the options for exploring this controversy.[13 14] In such an analysis of the POISE-1 Trial subjects we reported that neuraxial block was associated with increased odds of the composite primary outcome (cardiovascular death, nonfatal myocardial infarction and nonfatal cardiac arrest) and secondary outcome of myocardial infarction.[13]

The POISE-2 Trial presents another such opportunity. In POISE-2, 10 010 noncardiac surgery patients at risk of cardiovascular complications were randomized using a factorial design to aspirin or placebo and clonidine or placebo, and were followed for 30 days for a composite primary outcome of death or nonfatal myocardial infarction.[15] Many subjects had surgery under neuraxial block, with or without general anaesthesia, and received postoperative epidural analgesia. A pre-specified subgroup analysis of the main study revealed a significant interaction (*P*=0.01) between clonidine treatment and neuraxial block: clonidine was associated with increased risk of the primary outcome in subjects who did not receive neuraxial block [hazard ratio, 1.30; 95% confidence interval (CI), 1.05–1.60] but not in subjects who did receive neuraxial block (hazard ratio, 0.89; 95% CI, 0.58–1.38).[16] This effect was counter to the direction of our a priori hypothesis, but was not adjusted for potentially confounding factors.

The primary aim of the current *post hoc* study was to determine the relationship between intraoperative neuraxial block or postoperative epidural analgesia and the primary outcome within 30 days of randomization in the POISE-2 Trial. Secondary aims included further exploration of the apparent interaction between clonidine and intraoperative neuraxial block with respect to the primary outcome.

Methods

The POISE-2 Trial protocol was registered with ClinicalTrials.gov (NCT00182874) and the main results have been published.[16 17] The trial was multi-centred, blinded, randomized and placebo-controlled. Patients were recruited if they were aged ≥45 yr, were undergoing noncardiac surgery and fulfilled at least one of the following criteria: history of coronary artery disease, peripheral vascular disease, stroke, planned major vascular surgery or any three of nine cardiovascular risk criteria. Patients were excluded if they had a contraindication to administration of aspirin or clonidine or had a bare-metal stent inserted <six weeks or drug-eluting coronary stent inserted <one yr before randomization. Patients taking aspirin chronically had to stop it at least 72 h before surgery to be eligible. Ethics committee approval was obtained at all centres and written consent was provided by all subjects.

In POISE-2, aspirin (200 mg) or placebo was administered preoperatively and for 30 days (in aspirin-naïve subjects) or seven days (in subjects who had been taking aspirin chronically before randomization) at a 100 mg dose. Clonidine (0.2 mg) or placebo was administered preoperatively and was continued for three days. Troponin or creatine kinase-myocardial band assays were monitored during the first three days after surgery. The primary outcome was a composite of death or nonfatal myocardial infarction within 30 days of randomization. Secondary outcomes included death, myocardial infarction, stroke and clinically important hypotension, which was defined as a systolic arterial pressure of <90 mm Hg recorded at least once any time in the study period and requiring treatment or study drug discontinuation.

The current analysis was designed and executed *post hoc*, according to a statistical analysis plan that was prospectively approved by the POISE-2 Trial Publications Committee. Neuraxial block was defined as intraoperative administration of spinal

anaesthesia, or thoracic or lumbar epidural anaesthesia, with or without general anaesthesia or nerve block. Postoperative epidural analgesia was defined as postoperative administration of epidural local anaesthetic and/or opioid. No further data about the decision to use neuraxial block and/or postoperative epidural analgesia or the details of these techniques were recorded in the POISE-2 Trial.

Data analysis

Baseline characteristics were summarized as mean (SD) or (range) for continuous variables and number (%) for categorical variables. Groups were compared using analysis of variance and χ^2 tests, respectively.

Neuraxial block and postoperative epidural analgesia were not randomly assigned in the POISE-2 Trial. An inverse probability of treatment weighting technique therefore was used to reduce the bias of these nonrandomized treatment comparisons. Similar methods were used in our *post hoc* analysis of the POISE-1 Trial.[13]

The inverse probability of treatment weighting approach is one of a class of methods known as propensity score methods.[18] The unifying property of these methods is that the estimated probability that each patient will receive the intervention (the propensity score), is used to obtain a sample in which characteristics are balanced between the treatment groups. In contrast to data from randomized trials, balance is only possible for the covariates that are included in the model used to estimate the propensity score. The covariate of participating countries was handled through grouping the 23 countries into the following regions recruiting >10% of the patients each: 1) Canada; 2) USA; 3) Central and South America; 4) Europe; 5) South Africa, Pakistan, India and Malaysia, and 6) Hong Kong and Australia.

Balance of characteristics between groups was assessed using standardized differences (the difference between the percentage/mean between groups, divided by the standard deviation).[19] The standardized difference is expressed as a percentage, and characteristics with absolute values ≥10% are considered to represent a meaningful imbalance between groups.[20] Propensity score approaches assume that each patient has a positive probability of both receiving the intervention and not receiving the intervention (known as the positivity assumption), leading to our exclusion of spinal surgery patients from all comparisons in this analysis, as they were not eligible for neuraxial block. For each of the treatment comparisons, groups in which none or few of the patients received the intervention, were excluded to satisfy the positivity assumption. Patients with multiple or unknown types of neuraxial block, patients having surgery under local anaesthesia only and patients having more than one type of surgery were excluded from all analyses.

Logistic models for each intervention dependent on baseline characteristics, were used to estimate propensity scores. Following standard recommendations,[19] logistic regression models were selected iteratively, by first including all baseline characteristics, assessing the balance between groups using standardized differences, then including interaction terms as appropriate, until no further imbalance could be removed. The development occurred without reference to the outcome variables.

The 'common support' condition, implied by the positivity assumption,[21] states that in each treatment group there must be comparable subjects in the other treatment group.[22] Subjects in each treatment group that do not have subjects in the other group with similar propensity scores are thus in violation of this condition and were excluded from analyses. For example, for the neuraxial block comparison, those patients receiving neuraxial block with higher propensity scores than any subjects not receiving neuraxial block were excluded, as were subjects who did not receive neuraxial block with a lower propensity score than that of any subject who did receive neuraxial block. In this way, subjects in each neuraxial block treatment group without a comparable counterpart in the other group were excluded from analyses. This process ensured that the analysis only included neuraxial block subjects who were most similar to the no neuraxial block subjects. The common support condition was applied to all neuraxial and postoperative epidural analgesia analyses.

To estimate the association with the treatment for the primary outcome, death, myocardial infarction, stroke and clinically important hypotension, each subject was weighted by the inverse of the probability of receiving the treatment they actually received, and the logistic regression model for the outcome was fitted with the treatment as the sole predictor, with odds ratios (OR) and 95% CIs for the effect of treatment estimated. If any covariates remained unbalanced between the two groups, these were included as additional covariates in additional regression models.

To assess the sensitivity of estimates to extreme inverse probability of treatment weights, for each comparison, weights were truncated at the 1st and 99th percentiles, and outcome regression models were estimated again.

To assess the interaction of neuraxial block and clonidine, adjusted ORs for clonidine were estimated in subjects receiving and not receiving neuraxial block.

Secondary analyses were undertaken to assess the impact of the following interventions: general anaesthesia alone *vs* spinal anaesthesia alone (as few subjects received spinal anaesthesia combined with general anaesthesia); general anaesthesia alone *vs* thoracic epidural combined with general anaesthesia (as few subjects received thoracic epidural alone); general anaesthesia alone *vs* lumbar epidural with or without general anaesthesia (as too few subjects had lumbar epidural to allow separate comparisons with or without general anaesthesia); no postoperative epidural analgesia *vs* postoperative epidural analgesia; and postoperative epidural opioid alone *vs* postoperative local anaesthetic with or without opioid.

All analyses were conducted using Stata version 12 (Stata Corporation, College Station, TX, USA) Statistical significance was ascribed at $P<0.05$.

Results

In total 8924 subjects were included in the neuraxial block analysis and 2827 subjects were included in the postoperative epidural analgesia analysis. The reasons for exclusions from the analyses are outlined in Table 1.

Neuraxial block was administered to 3986 (45%) of the 8924 subjects who were included in the neuraxial block analysis. These subjects were more likely to be male and to be presenting for vascular or orthopaedic surgery than subjects not receiving neuraxial block (Table 2). There were differences in the percentages of included subjects receiving neuraxial block in different regions (Canada=62%, USA=27%, Europe=41%, Central and South America=31%, South Africa/Pakistan/India/Malaysia=47%, Hong Kong and Australia=26%). Baseline imbalances between intervention groups were reduced to acceptable levels by propensity score weighting and exclusion of subjects to ensure satisfaction of the common support assumption. Weighting also reduced imbalance with respect to the spinal anaesthesia and thoracic

Table 1 Exclusions and final sample sizes for each of the analyses. *Includes 198 patients without general anaesthesia or neuraxial block, four with unknown anaesthesia type, 222 with multiple types of neuraxial block, 217 having spinal surgery and 293 having >one type of surgery; †Postoperative analgesia is defined as one or more of epidural opioid, epidural local anaesthetic, continuous nerve block or parenteral opioid analgesia; ‡Only 172 (4.8%) of these patients received postoperative epidural analgesia; §Includes nine observations dropped for predicting treatment perfectly; ‖Includes 1934 patients who had postoperative analgesia without epidural analgesia, 97 with epidural local anaesthetic only, 263 with epidural opioid only and 533 with epidural local anaesthetic and opioid; ¶Includes 125 with epidural local anaesthetic only, 340 with epidural opioid only and 606 with epidural local anaesthetic and opioid; **The 'common support' condition states that in each treatment group there must be comparable patients in the other treatment group

10 010 patient enrolled in POISE-2 Trial Main and sub-analysis groups	Excluded from all analyses*	Other exclusions	Missing data	'Common support' condition**	Final sample size
No neuraxial block *vs* neuraxial block	934	–	130	22	8924
General anaesthesia *vs* thoracic epidural with general anaesthesia	934	3749 given neither general anaesthesia nor thoracic epidural 976 having orthopaedic surgery 307 having low risk surgery 523 from Central and South America 372 from South Africa, Pakistan, India and Malaysia	18	5	3126
General anaesthesia *vs* spinal anaesthesia	934	1820 given neither general anaesthesia alone nor spinal anaesthesia alone (includes 162 given both general anaesthesia and spinal anaesthesia) 371 having thoracic surgery	90	285	6510
General anaesthesia *vs* lumbar epidural with or without general anaesthesia	934	4036 given neither general anaesthesia nor lumbar epidural 371 having thoracic surgery 1959 having general surgery 319 having low risk surgery one with extreme inverse probability of treatment weight (>100)	68	190	2132
No postoperative epidural analgesia *vs* postoperative epidural analgesia	934	2513 not receiving any postoperative analgesia† 3607 not receiving any neuraxial block during surgery‡	68§	61	2827‖
Postoperative epidural local anaesthetic with or without opioid *vs* postoperative epidural opioid	934	7959 not receiving postoperative epidural analgesia 12 having low-risk surgery	10	24	1071¶

Table 2 Neuraxial block baseline characteristics. *Except for heart rate, systolic blood pressure and BMI which are presented as mean (SD) and age as mean (range). Std diff, standardized difference; COX, cyclooxygenase; NSAID, non-steroidal anti-inflammatory; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; CCB, calcium channel blocker

Characteristic	Unweighted				Propensity score weighted			
	No neuraxial block (*n*=4938) % (*n*)*	Neuraxial block (*n*=3986) % (*n*)*	Std diff (%)	*P*-value	No neuraxial block %*	Neuraxial block %*	Std diff (%)	*P*-value
Sex (female)	47.8 (2360)	45.5 (1812)	4.7	0.028	45.6	45.3	0.5	0.848
Coronary artery disease history	22.7 (1121)	22.3 (889)	1.0	0.654	23.4	23.2	0.4	0.891
Peripheral vascular disease history	7.6 (377)	9.0 (360)	−5.1	0.017	8.3	8.8	−1.7	0.516
Stroke history	5.8 (285)	4.8 (191)	4.4	0.041	5.7	5.9	−0.8	0.771
Congestive heart failure history	3.3 (163)	3.0 (118)	2.0	0.360	3.2	3.2	−0.1	0.977
Transient ischaemic attack history	3.4 (166)	3.9 (157)	−3.1	0.147	4.0	3.9	0.4	0.885
Diabetes on oral hypoglycaemic or insulin	39.3 (1939)	35.3 (1408)	8.2	<0.001	37.5	37.0	1.0	0.692
Hypertension	85.8 (4239)	86.6 (3452)	−2.2	0.302	85.9	86.2	−1.0	0.709
Preoperative serum creatinine elevated	3.5 (171)	2.6 (104)	5.0	0.020	2.9	2.7	1.0	0.658
Smoking history	26.5 (1310)	23.3 (930)	7.4	0.001	25.9	26.0	−0.3	0.898
Emergency/urgent surgery	8.2 (404)	5.4 (215)	11.1	<0.001	7.0	6.3	2.6	0.321
Preoperative medications (7 days before surgery)								
Aspirin	20.6 (1019)	26.3 (1049)	−13.4	<0.001	22.8	23.1	−0.8	0.763
COX-2 inhibitor	2.4 (120)	7.5 (300)	−23.6	<0.001	4.5	4.6	−0.5	0.858
Prophylactic antithrombotic agent	4.1 (202)	4.4 (175)	−1.5	0.484	4.3	3.9	1.9	0.410
NSAID/non-COX-2 inhibitor	6.6 (328)	11.0 (440)	−15.5	<0.001	8.7	8.6	0.4	0.878
ACEI/ARB/direct renin inhibitor	55.8 (2757)	60.8 (2423)	−10.1	<0.001	57.3	57.7	−0.9	0.733
Rate controlling CCB	5.3 (262)	5.2 (207)	0.5	0.813	5.4	5.2	0.8	0.767
Dihydropyridine CCB	24.2 (1194)	24.6 (981)	−1.0	0.637	23.7	24.0	−0.7	0.782
Beta-blocker	30.7 (1518)	25.8 (1030)	10.9	<0.001	28.6	28.8	−0.5	0.858
Statin	44.1 (2177)	48.4 (1930)	−8.7	<0.001	45.5	46.1	−1.3	0.627
Insulin or oral diabetic drug	40.2 (1986)	36.3 (1446)	8.1	<0.001	38.6	38.0	1.1	0.670
Surgery type				<0.001				0.950
Vascular	4.3 (211)	8.3 (332)	−16.8		5.7	5.9	−0.7	
Thoracic	7.2 (354)	4.7 (189)	10.3		6.1	6.0	0.3	
Orthopaedic	21.2 (1045)	61.1 (2436)	−88.8		39.6	39.2	0.9	
Urological/gynaecological	21.3 (1051)	10.8 (432)	28.7		16.5	16.3	0.7	
General	39.9 (1968)	12.2 (488)	66.3		27.4	28.3	−2.1	
Low risk	6.3 (309)	2.7 (109)	17.1		4.6	4.3	1.7	
Region				<0.001				0.541
Canada	25.3 (1247)	50.2 (1999)	−53.2		34.4	35.4	−2.1	
USA	21.7 (1071)	10.0 (397)	32.6		16.6	17.2	−1.7	
Central & South America	13.2 (654)	7.5 (300)	18.8		10.7	9.5	3.8	
Europe	18.8 (926)	16.2 (647)	6.6		17.6	17.6	0.0	
South Africa, Pakistan, India, Malaysia	10.7 (530)	11.7 (466)	−3.0		13.1	12.1	3.1	
Hong Kong & Australia	10.3 (510)	4.4 (177)	22.7		7.6	8.2	−2.2	
Treatment group				0.934				0.991
Clonidine placebo+aspirin	25.0 (1234)	25.0 (996)	0.0		24.8	25.1	−0.6	
Clonidine+aspirin placebo	25.5 (1257)	24.9 (993)	1.3		25.2	25.3	−0.3	

Clonidine+aspirin	24.7 (1218)	25.1 (1000)	−1.0		24.8	24.5	0.7		
Clonidine placebo+aspirin placebo	24.9 (1229)	25.0 (997)	−0.3		25.2	25.1	0.2		
Age (yr)	68.2 (45–103)	70.5 (45–96)	−22.8	<0.001	69.1 (10.8)	69.1 (9.6)	−0.7	0.790	
BMI (kg m^{-2})	29.3 (7.0)	29.6 (7.2)	−4.0	0.060	29.3 (7.1)	29.2 (7.1)	1.4	0.610	
Preoperative heart rate (beats min^{-1})	75.6 (13.5)	76.2 (13.3)	−4.7	0.026	75.8 (14.3)	75.7 (12.6)	0.4	0.891	
Preoperative systolic arterial pressure (mm Hg)	142.9 (24.1)	145.5 (24.9)	−10.7	<0.001	143.9 (25.7)	143.8 (22.8)	0.7	0.797	

epidural sub-analyses, however a number of variables remained imbalanced with respect to the lumbar epidural sub-analysis (absolute value of standardized differences >10%) (Supplementary material, Tables S1–S3).

Postoperative epidural analgesia was administered to 893 (32%) of the 2827 subjects who were included in the postoperative epidural analgesia analysis. These subjects were more likely to be male and less likely to be presenting for orthopaedic surgery than subjects not receiving postoperative epidural analgesia (Table 3). There were differences in the percentages of included subjects receiving postoperative epidural analgesia in different regions (Canada=24%, USA=50%, Europe=49%, Central and South America=38%, South Africa/Pakistan/India/Malaysia=16%, Hong Kong and Australia=37%). Baseline imbalances between postoperative epidural analgesia and no postoperative epidural analgesia subjects were reduced by propensity score weighting, however a number of variables remained imbalanced (absolute value of standardized differences >10%). Weighting reduced imbalance to acceptable levels between postoperative epidural local anaesthetic with or with opioid and postoperative epidural opioid alone (Supplementary material, Table S4).

Neuraxial block was not associated with the primary outcome (OR, 0.89; 95% CI, 0.73–1.08; *P*=0.24), death (OR, 0.84; 95% CI, 0.53–1.35; *P*=0.48), myocardial infarction (OR, 0.91; 95% CI, 0.74–1.12; *P*=0.36) or stroke (OR, 1.05; 95% CI, 0.44–2.49; *P*=0.91). The odds of an association between neuraxial block and clinically important hypotension was 0.90 (95% CI, 0.81–1.00; *P*=0.04) (Table 4). The odds of the primary outcome in clonidine-treated patients not having neuraxial block was 0.91 (95% CI, 0.70–1.19) and in clonidine-treated patients having neuraxial block was 1.28 (95% CI, 0.96–1.71) (*P* value for interaction=0.087) (Table 5).

Spinal anaesthesia alone was associated with lower odds of the primary outcome (OR, 0.44; 95% CI, 0.33–0.57; *P*<0.001), death (OR, 0.41; 95% CI, 0.19–0.86; *P*=0.02), myocardial infarction (OR, 0.46; 95% CI, 0.35–0.60; *P*<0.001) and clinically important hypotension (OR, 0.37; 95% CI, 0.32–0.43; *P*<0.001) than general anaesthesia alone. Thoracic epidural combined with general anaesthesia was associated with greater odds of clinically important hypotension than general anaesthesia alone (OR, 2.06; 95% CI, 1.60–2.66; *P*<0.001). There were no statistically significant associations with any of the outcomes in the lumbar epidural analyses (Table 4).

Postoperative epidural analgesia was not associated with a significant effect on the primary outcome (OR, 1.48; 95% CI, 0.89–2.48; *P*=0.13), death (OR, 0.84; 95% CI, 0.35–1.99; *P*=0.68), myocardial infarction (OR, 1.53; 95% CI, 0.90–2.61; *P*=0.11), stroke (OR, 0.65; 95% CI, 0.18–2.32; *P*=0.50) or clinically important hypotension (OR, 1.40; 95% CI, 0.95–2.09; *P*=0.09). Postoperative epidural local anaesthetic with or without opioid was associated with greater odds of clinically important hypotension than postoperative epidural opioid alone (OR, 1.74; 95% CI, 1.29–2.34; *P*<0.001) (Table 4). Sensitivity analyses produced similar results to the original analyses (Supplementary material, Tables S5 and S6).

Discussion

The principal result of these *post hoc* analyses was that neuraxial block and postoperative epidural analgesia were not associated with the primary outcome, death, myocardial infarction or stroke. However our sub-analyses suggest that there may be a difference between spinal anaesthesia and thoracic epidural anaesthesia with respect to adverse outcomes that could be explored

Table 3 Postoperative epidural analgesia baseline characteristics. *Except for heart rate, systolic blood pressure and BMI which are presented as mean (SD) and age as mean (range). Std diff, standardized difference; COX, cyclooxygenase; NSAID, non-steroidal anti-inflammatory; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; CCB, calcium channel blocker

Characteristic	Unweighted				Propensity score weighted			
	No postoperativeepidural (*n*=1934) % (*n*)*	Postoperative epidural (*n*=893) % (*n*)*	Std Diff (%)	*P*-value	No postoperativeepidural %*	Postoperativeepidural %*	Std diff (%)	*P*-value
Sex (female)	50.9 (985)	39.4 (352)	23.3	<0.001	47.4	40.4	14.1	0.166
Coronary artery disease history	20.7 (401)	20.2 (180)	1.4	0.724	21.4	21.7	−0.7	0.943
Peripheral vascular disease history	7.0 (135)	11.4 (102)	−15.4	<0.001	9.2	15.8	−22.9	0.094
Stroke history	4.4 (85)	4.0 (36)	1.8	0.657	4.7	3.5	6.1	0.402
Congestive heart failure history	3.2 (61)	2.6 (23)	3.5	0.400	2.8	3.7	−5.6	0.571
Transient ischaemic attack history	4.0 (77)	4.4 (39)	−1.9	0.631	4.3	4.4	−0.7	0.947
Diabetes on oral hypoglycaemic or insulin	36.2 (701)	32.4 (289)	8.2	0.044	36.9	40.9	−8.4	0.429
Hypertension	89.2 (1726)	83.8 (748)	16.1	<0.001	87.2	90.4	−9.4	0.292
Preoperative serum creatinine elevated	2.0 (39)	2.2 (20)	−1.5	0.700	2.4	3.2	−5.7	0.673
Smoking history	19.3 (373)	32.6 (291)	−30.7	<0.001	21.7	20.8	2.3	0.776
Emergency/urgent surgery	5.4 (105)	5.7 (51)	−1.2	0.760	5.5	6.1	−2.9	0.693
Preoperative medications (7 days before surgery)								
Aspirin	26.0 (503)	26.8 (239)	−1.7	0.671	25.2	29.1	−8.9	0.380
COX-2 inhibitor	10.3 (199)	2.5 (22)	32.4	<0.001	7.5	8.0	−2.0	0.907
Prophylactic antithrombotic agent	2.9 (56)	2.8 (25)	0.6	0.887	2.6	4.0	−8.5	0.306
NSAID/non-COX-2 inhibitor	12.2 (235)	6.0 (54)	21.3	<0.001	9.6	8.1	5.5	0.530
ACEI/ARB/direct renin inhibitor	63.4 (1227)	59.7 (533)	7.7	0.055	63.8	61.5	4.7	0.633
Rate controlling CCB	5.3 (102)	4.5 (40)	3.7	0.368	5.1	6.3	−5.6	0.622
Dihydropyridine CCB	26.8 (518)	21.8 (195)	11.6	0.005	24.5	28.6	−9.6	0.337
Beta-blocker	25.5 (494)	27.2 (243)	−3.8	0.347	26.3	24.2	4.8	0.620
Statin	50.5 (976)	46.2 (413)	8.4	0.037	50.1	51.7	−3.2	0.752
Insulin or oral diabetic drug	37.0 (715)	33.5 (299)	7.3	0.072	37.6	41.3	−7.7	0.467
Surgery type				<0.001				0.990
Vascular	3.5 (68)	16.3 (146)	−43.9		7.4	7.0	1.3	
Thoracic	0.6 (11)	16.1 (144)	−58.6		6.7	5.1	6.0	
Orthopaedic	84.4 (1632)	18.0 (161)	177.5		62.9	65.2	−6.0	
Urological/gynaecological	4.1 (80)	17.0 (152)	−42.8		8.7	7.7	3.3	
General	6.0 (117)	31.9 (285)	−69.9		13.2	13.6	−1.2	
Low risk	1.3 (26)	0.6 (5)	8.1		1.1	1.3	−2.6	
Region				<0.001				0.834
Canada	58.3 (1128)	39.8 (355)	37.8		52.8	55.5	−5.6	
USA	9.5 (184)	20.6 (184)	−31.4		12.0	10.9	3.1	
Central & South America	5.4 (104)	7.3 (65)	−7.8		6.0	5.9	0.6	
Europe	10.4 (201)	21.4 (191)	−30.4		14.6	12.0	7.2	
South Africa, Pakistan, India, Malaysia	11.6 (224)	4.9 (44)	24.4		9.5	10.9	−5.1	
Hong Kong & Australia	4.8 (93)	6.0 (54)	−5.5		5.1	4.8	1.1	

Treatment group				0.821							0.799
Clonidine placebo+aspirin	25.2 (488)	23.9 (213)	3.2		26.4		30.4		−9.2		
Clonidine+aspirin placebo	25.5 (493)	25.2 (225)	0.7		25.8		25.5		0.8		
Clonidine+aspirin	24.6 (476)	25.9 (231)	−2.9		25.3		22.0		7.6		
Clonidine placebo+aspirin placebo	24.7 (477)	25.1 (224)	−1.0		22.5		22.2		0.7		
Age (yr)	70.5 (45–96)	69.7 (45–94)	8.2	0.044	70.3 (11.6)		69.7 (7.3)		6.4	0.483	
BMI (kg m^{-2})	30.8 (7.5)	28.4 (6.9)	32.8	<0.001	30.1 (8.6)		30.1 (5.9)		1.0	0.930	
Preoperative heart rate (beats min^{-1})	76.5 (13.2)	76.0 (13.9)	3.3	0.414	76.9 (17.7)		76.8 (10.9)		0.7	0.949	
Preoperative systolic arterial pressure (mm Hg)	147.7 (25.2)	142.4 (24.5)	21.2	<0.001	147.7 (28.8)		146.0 (19.6)		6.8	0.488	

further with appropriately designed randomized controlled trials.

The existing literature can be argued to support conflicting viewpoints on the effect of neuraxial block on adverse cardiovascular outcomes.[3 14] The current analysis adds to previous reports, supporting the view that neuraxial block does not alter cardiovascular outcomes and that the decision to use neuraxial block should be based on other criteria.[5 6 12 23 24] None of the available evidence is definitive. The largest randomized trials (Park and colleagues,[5,6] *n*=1021; the MASTER trial, *n*=915) were underpowered for death and myocardial infarction. Systematic reviews necessarily summarize small studies, many are of inferior quality and conducted decades ago,[12 23 25–27] and concern is mounting about the risk of type 1 error from repeated testing.[28] Large retrospective studies[24 29 30] and *post hoc* analyses of large randomized trials of other interventions[13] provide high numbers of events but are limited by the methods available to minimize bias.[14 31–34] Despite this lack of definitive evidence, many anaesthetists still believe that neuraxial block represents a useful intervention to reduce perioperative mortality.[1]

We conducted a similar *post hoc* analysis of the POISE-1 Trial that randomized patients to metoprolol or placebo.[13 35] In that analysis, neuraxial block was associated with increased odds of the primary outcome (cardiovascular death, non-fatal myocardial infarction and non-fatal cardiac arrest) (OR, 1.24; 95% CI, 1.02–1.49) and myocardial infarction (OR, 1.32; 95% CI, 1.07–1.64). The POISE-1 and POISE-2 sub-analyses included similar numbers of subjects receiving neuraxial block (*n*=3909 and *n*=3986, respectively). The baseline covariates available for propensity score development and details of neuraxial block were similar in the two studies. Although POISE-1 randomized more men; more subjects having vascular surgery; and more subjects with coronary artery disease and peripheral vascular disease than POISE-2, event rates were similar.[16 35] We conclude that the differences in results might result from random error.

We urged cautious interpretation of our initial finding of an interaction between clonidine and neuraxial block with respect to the primary outcome because it was counter to the direction of our a priori hypothesis.[16] Supporting this, after excluding patient groups for whom neuraxial block was not an option and adjusting for baseline variables related to the decision to use neuraxial block, we found no significant interaction. The reversal of the original direction of effect[16] in the current analyses further supports our conclusion of no significant interaction between clonidine and neuraxial block.

Our secondary analyses suggested that spinal anaesthesia was associated with lower odds of the primary outcome, death, myocardial infarction and clinically important hypotension than general anaesthesia. Lower odds of adverse outcomes in the spinal anaesthesia group were also demonstrated in *post hoc* analyses of the POISE-1 Trial, although in that case statistical significance was not reached.[13] Our results are consistent with a recent observational study in hip fracture patients,[30] but inconsistent with systematic reviews that do not support a difference in cardiovascular outcomes after hip fracture surgery,[27] total hip arthroplasty[36] or lower limb orthopaedic surgery.[37] However, none of these studies differentiated between spinal and epidural anaesthesia.

Our secondary analyses also suggested that thoracic epidural with general anaesthesia was associated with greater odds of clinically important hypotension than general anaesthesia alone. This result is consistent with our POISE-1 analysis[13] and a previous systematic review.[38] As clinically important hypotension was independently associated with myocardial infarction in

Table 4 Estimated associations with outcomes. *Primary outcome, death and non-fatal myocardial infarction within 30 days of randomization. †Postoperative analgesia with continuous nerve block and/or parenteral opioid. OR, odds ratio; CI, confidence interval; GA, general anaesthesia

	No neuraxial block (*n*=4938)		**Neuraxial block (*n*=3986)**		**Unadjusted analysis**		**Inverse probability weighted analysis**	
No neuraxial block *vs* neuraxial block	*n*	%	*n*	%	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Primary outcome*	321	6.5	298	7.5	1.16 (0.99, 1.37)	0.072	0.89 (0.73, 1.08)	0.243
Death	68	1.4	41	1.0	0.74 (0.50, 1.10)	0.138	0.84 (0.53, 1.35)	0.477
Myocardial infarction	273	5.5	274	6.9	1.26 (1.06, 1.50)	0.009	0.91 (0.74, 1.12)	0.361
Stroke	19	0.4	12	0.3	0.78 (0.38, 1.61)	0.505	1.05 (0.44, 2.49)	0.912
Clinically important hypotension	2255	45.7	1554	39.0	0.76 (0.70, 0.83)	<0.001	0.90 (0.81, 1.00)	0.042
	GA (*n*=4027)		**Spinal anaesthesia (*n*=2483)**		**Unadjusted analysis**		**Inverse probability weighted analysis**	
GA *vs* spinal anaesthesia	*n*	%	*n*	%	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Primary outcome	280	7.0	139	5.6	0.79 (0.64, 0.98)	0.031	0.44 (0.33, 0.57)	<0.001
Death	59	1.5	17	0.7	0.46 (0.27, 0.80)	0.005	0.41 (0.19, 0.86)	0.019
Myocardial infarction	238	5.9	130	5.2	0.88 (0.71, 1.10)	0.253	0.46 (0.35, 0.60)	<0.001
Stroke	16	0.4	8	0.3	0.81 (0.35, 1.90)	0.628	0.89 (0.28, 2.78)	0.842
Clinically important hypotension	1872	46.5	794	32.0	0.54 (0.49, 0.60)	<0.001	0.37 (0.32, 0.43)	<0.001
	GA (*n*=2562)		**Thoracic epidural (*n*=564)**		**Unadjusted analysis**		**Inverse probability weighted analysis**	
GA *vs* thoracic epidural with GA	*n*	%	*n*	%	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Primary outcome	168	6.6	58	10.3	1.63 (1.19, 2.23)	0.002	1.31 (0.90, 1.89)	0.160
Death	34	1.3	7	1.2	0.93 (0.41, 2.12)	0.871	0.81 (0.32, 2.07)	0.666
Myocardial infarction	143	5.6	54	9.6	1.79 (1.29, 2.48)	<0.001	1.42 (0.96, 2.09)	0.080
Stroke	10	0.4	3	0.5	1.36 (0.37, 4.97)	0.638	1.80 (0.43, 7.60)	0.422
Clinically important hypotension	1423	55.5	393	69.7	1.84 (1.51, 2.24)	<0.001	2.06 (1.60, 2.66)	<0.001
	GA (*n*=1898)		**Lumbar epidural (*n*=234)**		**Unadjusted analysis**		**Inverse probability weighted analysis**	
GA *vs* lumbar epidural±GA	*n*	%	*n*	%	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Primary outcome	160	8.4	30	12.8	1.60 (1.05, 2.42)	0.027	1.08 (0.51, 2.30)	0.846
Death	23	1.2	8	3.4	2.89 (1.28, 6.53)	0.011	0.92 (0.39, 2.20)	0.857
Myocardial infarction	142	7.5	25	10.7	1.48 (0.94, 2.32)	0.087	1.11 (0.49, 2.51)	0.803
Stroke	7	0.4	0	0.0	–	–	–	–
Clinically important hypotension	990	52.2	86	36.8	0.53 (0.40, 0.71)	<0.001	0.84 (0.54, 1.31)	0.449
	No epidural (*n*=1934)		**Epidural (*n*=893)**		**Unadjusted analysis**		**Inverse probability weighted analysis**	
No postoperative epidural analgesia *vs* postoperative epidural analgesia	*n*	%	*n*	%	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Primary outcome	120	6.2	105	11.8	2.01 (1.53, 2.65)	<0.001	1.48 (0.89, 2.48)	0.133
Death	16	0.8	12	1.3	1.63 (0.77, 3.47)	0.202	0.84 (0.35, 1.98)	0.684
Myocardial infarction	111	5.7	98	11.0	2.02 (1.52, 2.69)	<0.001	1.53 (0.90, 2.61)	0.115
Stroke	7	0.4	4	0.4	1.24 (0.36, 4.24)	0.733	0.65 (0.18, 2.32)	0.505
Clinically important hypotension	694	35.9	562	62.9	3.03 (2.57, 3.58)	<0.001	1.40 (0.95, 2.09)	0.092
	Opioid (*n*=340)		**Local anaesthetic opioid (*n*=731)**		**Unadjusted analysis**		**Inverse probability weighted analysis**	

Postoperative epidural opioid *vs* postoperative epidural local anaestheticopioid	*n*	%	*n*	%	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Primary outcome	39	11.5	79	10.8	0.94 (0.62, 1.41)	0.747	1.01 (0.65, 1.59)	0.954
Death	7	2.1	10	1.4	0.66 (0.25, 1.75)	0.403	0.63 (0.21, 1.89)	0.408
Myocardial infarction	34	10.0	72	9.8	0.98 (0.64, 1.51)	0.939	1.11 (0.69, 1.77)	0.675
Stroke	2	0.6	4	0.5	0.93 (0.17, 5.10)	0.933	1.22 (0.21, 7.02)	0.823
Clinically important hypotension	194	57.1	495	67.7	1.58 (1.21, 2.06)	0.001	1.74 (1.29, 2.34)	<0.001

Table 5 Subgroup analysis of the primary outcome and neuraxial block. Estimated interaction terms for neuraxial block and clonidine and *P*-value for interaction. OR, odds ratio; CI, confidence interval

Subgroup	Placebo (*n*=4456)		Clonidine (*n*=4468)		Unadjusted analysis		Inverse probability weighted analysis	
	n	%	*n*	%	OR (95% CI)	*P*-value for interaction	OR (95% CI)	*P*-value for interaction
No neuraxial block	163	3.7	158	3.5	0.96 (0.77, 1.21)	0.032	0.91 (0.70, 1.19)	0.087
Neuraxial block	127	2.9	171	3.8	1.38 (1.09, 1.75)		1.28 (0.96, 1.71)	

the main POISE-2 analysis, prevention and/or treatment of clinically important hypotension in patients having operations where thoracic epidural, is an option that must be a significant focus for future work. We did not replicate our finding from POISE-1 where thoracic epidural with general anaesthesia was associated with higher odds of the primary outcome or myocardial infarction than general anaesthesia alone.[13] This may be as a result of a type I error.

These sub-analyses suggest that neuraxial block should not be considered a homogeneous intervention. This argument is supported by our pre-specified plan to explore the effects of three neuraxial techniques in the same analysis, the consistency of these results with our POISE-1 analysis[13] and by the differential effect of the two techniques on the risk of clinically important hypotension (decreased for spinal anaesthesia and increased for thoracic epidural anaesthesia). On the other hand, the well-established and repeatedly-demonstrated danger of drawing firm conclusions from sub-group analyses (of *post hoc* analyses) must be recognized.[39] It should also be noted though that general anaesthesia was administered to thoracic epidural patients but not spinal anaesthesia patients and the effect of this is uncertain.

Postoperative epidural analgesia was not associated with altered cardiovascular outcomes, although postoperative epidural analgesia with local anaesthetic, with or without opioid, was associated with more clinically important hypotension than postoperative epidural opioid alone. A systematic review of randomized trials of postoperative epidural analgesia with local anaesthetics, opioids or both compared with systemic opioids in aortic surgery patients, concluded that myocardial infarction risk was reduced but mortality risk was unchanged by postoperative epidural analgesia.[40] However, comparable reviews in hip and knee joint replacement[41] and open abdominal surgery[42] patients found no evidence for effects on cardiovascular outcomes, although hypotension was more common in patients receiving epidural analgesia in the orthopaedic review.[41] Hypotension resulting from sympathetic nervous system block is a well-known effect of epidural local anaesthetic,[41 43] and might be mechanistically linked to adverse postoperative outcomes and could have implications for the appropriate venue for postoperative care in these patients.

This analysis has strengths and limitations. The analysis included more subjects than previous randomized controlled trials[5 6] and systematic reviews.[12 37 40 41] Patients were at high risk of adverse cardiovascular events and were monitored closely for predefined efficacy and safety outcomes in a clinical trial context. The quality and fidelity of our data minimizes ascertainment bias, misclassification of important variables and missing data. The size of the database allows a precision of effect-size estimates not usually possible outside of administrative mega-databases; however, administrative data frequently suffers from ascertainment bias and misclassification of covariates.

Our analyses have limitations, many of which are shared by our analysis of POISE-1 Trial subjects,[4 13 14] and other observational studies. The POISE-2 Trial was designed to test hypotheses about the randomized interventions and not neuraxial block and postoperative epidural analgesia. We did not record the reasons for choosing neuraxial block or postoperative epidural analgesia over other techniques, and it is clear from regional variations that local preferences exist. The broad classification of surgery type in POISE-2 meant that exclusion of subjects who were ineligible for the interventions might have been inaccurate. Propensity methods were applied in an attempt to ameliorate these issues,[19] however these methods do not create baseline equality with respect to unmeasured or unknown confounders, and we had difficulty with residual baseline imbalance of known confounders in several sub-groups. We have little data on the details of the anaesthetic and postoperative analgesic techniques used: the quality and extent of anaesthesia and postoperative analgesia in the neuraxial or postoperative epidural patients and their comparator groups is likely to be important.[2] Neuraxial block and postoperative epidural analgesia might have influenced other aspects of care, such as haemodynamic and antiplatelet agent/anticoagulant management, the conduct of general anaesthesia and the use of plexus and nerve blocks, however we have no information of these aspects of care. We made an a priori decision to limit our analyses to the cardiovascular outcomes that were considered in our POISE-1 analysis,[13] as these were the focus of the POISE-2 Trial as well.[16 17] Respiratory outcomes associated with increased mortality such as pneumonia and the need for postoperative mechanical ventilation were not specifically assessed in the POISE-2 Trial[16 17] and likely affect overall outcomes.[38] Finally the sample size available for this analysis did not allow us to rule out smaller, but still potentially clinically meaningful, differences in outcomes according to anaesthesia type. The confidence intervals around our estimates of effects demonstrate that our analyses have not ruled out potentially clinically meaningful differences in outcomes according to anaesthesia type.

Papers about neuraxial block and postoperative epidural analgesia typically conclude with a call for more randomized controlled trial evidence.[12 13 24 25 29 30 36 38 40 42] We agree that this issue will not be settled without such evidence, but are also of the opinion that it is unlikely to be settled by one 'mega' trial. Significant variation in outcomes associated with different patient groups and different neuraxial block and postoperative epidural techniques have been demonstrated.[12 13 24 25 29 30 36 38 40 42] A suite of trials in high-risk patients having common operations often managed with these techniques, and associated with significant postoperative pain and adverse outcomes, will therefore be required.

In conclusion, intraoperative neuraxial block and postoperative epidural analgesia were not associated with altered odds of adverse cardiovascular outcomes in high-risk noncardiac surgery patients participating in the POISE-2 Trial, and there was no significant interaction between clonidine and neuraxial block. These findings contrast with the results of our *post hoc* analysis of the POISE-1 Trial. The effect of these techniques on adverse cardiovascular outcomes remains unresolved and large randomized controlled trials are required.

Authors' contributions

Study design/planning: K.L., J.K., A.F., P.D.
Study conduct: K.L., D.M., A.K., J.K., R.A., K.C., S.D., R.G., X.J., G.L., H.L., G.L-B., C.M., W.P., T.T., T.V., P.D.
Data analysis: K.L., J.K., A.F.
Writing paper: K.L., D.M., A.F., A.K., P.D.
Revising paper: All authors.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Declaration of interest

None declared.

Funding

Canadian Institutes of Health Research, the Commonwealth Government of Australia's National Health and Medical Research Council (APP1004149) and the Spanish Ministry of Health and Social Policy.

References

1. Landoni G, Rodseth R, Santini F, *et al*. Randomized evidence for reduction of perioperative mortality. *J Thorac Cardiovasc Anesth* 2012; **26**: 764–72
2. Kooij F, Schlack W, Preckel B, Hollmann M. Does regional analgesia for major surgery improve outcome? Focus on epidural analgesia. *Anesth Analg* 2014; **119**: 740–4
3. Memtsoudis S, Liu S. Do neuraxial techniques affect perioperative outcomes? The story of vantage points and number games. *Anesth Analg* 2014; **119**: 501–2
4. Popping D, Van Aken H, Brodner G, Wenk M. It is not the epidural that is dangerous, but the person who gives it. *Br J Anaesth* 2014; **112**: 392–3
5. Park W, Thompson J, Lee K. Effect of epidural anesthesia and analgesia on perioperative outcomes. *Ann Surg* 2001; **234**: 560–71
6. Rigg J, Jamrozik K, Myles P, *et al*. Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial. *Lancet* 2002; **359**: 1276–82
7. U.S. National Institutes of Health. ClinicalTrials.gov. Available from http://clinical.trials.gov (accessed 13 January 2015)
8. European Medicines Agency. EU Clinical Trials Register. Available from http://www.clinicaltrialsregister.eu (accessed 13 January 2015)
9. U.S. National Institute of Public Health. Japan Primary Registries Network. Available from http://www.who.int/ictrp/network/jprn2/en (accessed 13 January 2015)
10. BioMed Central Ltd. ISRCTN Registry. Available from http://www.isrctn.com (accessed 13 January 2015)
11. National Health and Medical Research Council. Australian and New Zealand Clinical Trials Registry. Available at http://www.anzctr.org.au (accessed on 13 January 2015)
12. Guay J, Choi P, Suresh S, Albert N, Kopp S, Pace N. Neuraxial anesthesia for the prevention of postoperative mortality and major morbidity: An overview of Cochrane systematic reviews. *Anesth Analg* 2014; **119**: 716–25
13. Leslie K, Myles P, Devereaux P, *et al*. Neuraxial block, death and serious cardiovascular morbidity and mortality in the POISE Trial. *Br J Anaesth* 2013; **111**: 382–90
14. Cook T, Columb M. Neuraxial block, death and serious cardiovascular morbidity in patients in the POISE trial: propensities, probabilities, and possibilities. *Br J Anaesth* 2013; **111**: 327–31
15. POISE Trial Investigators. Rationale and design of the PeriOperative ISchemic Evaluation-2 (POISE-2) Trial: A 2×2 factorial randomized controlled trial of acetyl-salicylic acid versus placebo and clonidine versus placebo in patients undergoing noncardiac surgery. *Am Heart J* 2014; **167**: 804–9
16. Devereaux P, Sessler D, Leslie K, *et al*. Clonidine in patients having non-cardiac surgery. *N Engl J Med* 2014; **370**: 1504–13
17. Devereaux P, Mrkobrada M, Sessler D, *et al*. Aspirin in patients undergoing noncardiac surgery. *N Engl J Med* 2014; **370**: 1494–503
18. Austin P, Small D. The use of bootstrapping when using propensity-score matching without replacement: a simulation study. *Stat Med* 2014; **33**: 4306–19
19. Williamson E, Forbes A. Introduction to propensity scores. *Respirology* 2014; **19**: 625–35
20. Normand S-L, Landrum M, Guadagnoli E, *et al*. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: A matched analysis using propensity scores. *J Clin Epidemiol* 2001; **54**: 387–98
21. Petersen M, Porter K, Gruber S, Wang Y, van der Laan M. Diagnosing and responding to violations in the positivity assumption. *Stat Methods Med Res* 2012; **21**: 31–54
22. Williamson E, Morley R, Lucas A, Carpenter J. Propensity scores: From naïve enthusiasm to intuitive understanding. *Stat Methods Med Res* 2012; **21**: 273–93
23. Barbosa F, Jucá M, Castro A, Cavalcante J. Neuraxial anaesthesia for lower-limb revascularization. *Cochrane Database Syst Rev* 2013; **7**: CD007083
24. Neuman M, Rosenbaum P, Ludwig J, Zubizaretta J, Silber J. Anesthesia technique, mortality and length of stay after hip fracture surgery. *JAMA* 2014; **311**: 2508–17
25. Rodgers A, Walker N, Schug S, *et al*. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. *Br Med J* 2000; **321**: 1–12
26. Beattie W, Badner N, Choi P. Epidural analgesia reduces postoperative myocardial infarction: a meta-analysis. *Anesth Analg* 2001; **93**: 853–8
27. Parker M, Handoll H, Griffiths R. Anaesthesia for hip fracture surgery in adults. *Cochrane Database Syst Rev* 2004; **4**: CD000521
28. Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analyses may be inconclusive—trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. *Int J Epidemiol* 2009; **38**: 287–98
29. Wijeysundera D, Beattie W, Austin P, Hux J, Laupacis A. Epidural anaesthesia and survival after intermediate-to-high risk non-cardiac surgery: a population-based cohort study. *Lancet* 2008; **372**: 562–9
30. Memtsoudis S, Sun X, Chiu Y, *et al*. Perioperative comparative effectiveness of anesthetic technique in orthopedic patients. *Anesthesiology* 2013; **118**: 1046–58
31. Barrington M, Scott D. Do we need to justify epidural analgesia beyond pain relief? *Lancet* 2008; **372**: 514–5
32. Neuman M, Brummett C. Trust, but verify: Examining the role of observational data in perioperative decision-making. *Anesthesiology* 2013; **118**: 1008–10
33. Bulka C, Wanderer J, Ehrenfeld J. Anesthesia technique and outcomes after hip fracture surgery. *JAMA* 2014; **312**: 1801–2
34. Raw R, Todd M, Hindman J, Mueller M. The overpowered mega-study is a new class of study needing a new way of being reviewed. *Anesthesiology* 2014; **120**: 238–47
35. POISE Study Group. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet* 2008; **371**: 1839–47
36. Macfarlane A, Prasad G, Chan V, Brull R. Does regional anaesthesia improve outcome after total hip arthroplasty? A systematic review. *Br J Anaesth* 2009; **103**: 335–45
37. Barbosa F, CastroII A, de Sousa-Rodrigues C. Neuraxial anesthesia for orthopedic surgery: systematic review and meta-analysis of randomized clinical trials. *Sao Paulo Med J* 2013; **131**: 411–21
38. Popping D, Elia N, Marret E, Remy C, Tramer M. Protective effects of epidural analgesia on pulmonary complications after abdominal and thoracic surgery: a meta-analysis. *Arch Surg* 2008; **143**: 990–9

39. Sun X, Ioannidis J, Agoritsas T, Alba A, Guyatt G. How to use a subgroup analysis: users' guide to the medical literature. *JAMA* 2014; **311**: 405–11
40. Nishimori M, Low J, Zheng H, Ballantyne J. Epidural pain relief versus systemic opioid-based pain relief for abdominal aortic surgery. *Cochrane Database Syst Rev* 2012; **11**: CD005059
41. Choi P, Bhandari M, Scott J, Douketis J. Epidural analgesia for pain relief following hip or knee replacement. *Cochrane Database Syst Rev* 2003; **3**: CD003071
42. Hughes M, Ventham N, McNally S, Harrison E, Wigmore S. Analgesia after open abdominal surgery in the setting of enhanced recovery surgery: A systematic review and meta-analysis. *JAMA Surgery* 2014; **149**: 1224–30
43. Butterworth J. Clinical pharmacology of local anesthetics. In: Cousins M, Carr D, Horlocker T, Bridenbaugh P, eds. *Neural Blockade in Clinical Anaesthesia and Pain Management, 4th Edition*. Philadelphia: Wolters Kluwer/Lippincott Wilkins & Williams, 2009; 96–113

Handling editor: H. C. Hemmings