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## EDITORIAL III

# Neuraxial block, death and serious cardiovascular morbidity in patients in the POISE trial: propensities, probabilities, and possibilities

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This month in the *BJA* is published an important, and perhaps controversial, study by Professor Leslie and colleagues.[1] The authors have used data from the POISE study (which randomized patients with increased risk of cardiovascular events to

perioperative β-block or placebo) to perform a secondary analysis and *post hoc* examination of the effect of central neuraxial block (CNB) on outcome. The same outcomes as used in POISE were used for this study: myocardial infarction, stroke, hypotension, death and a composite of death, non-fatal myocardial infarction, and non-fatal cardiac arrest. In addition to examining the effect of CNB overall, the authors examined outcomes in subgroups: intrathecal, thoracic, and lumbar epidural, where possible also examining these interventions with and without general anaesthesia. The most notable finding the authors report is an almost three-fold increase in the composite outcome with thoracic epidural and general anaesthesia compared with general anaesthesia alone. They also report an overall increase in the composite outcome with CNB. Of particular note, they do not find a statistically significant increased rate of stroke or death in the overall group or any sub-group.

What then are the strengths and limitations of this study, how generalizable are the results and should it lead anaesthetists to change practice?

As the authors indicate this is perhaps one of the first studies to raise the possibility that CNB, and particularly thoracic epidural combined with general anaesthesia might not only fail to offer patients benefit but may lead to harm. The study is larger than any randomized controlled trial (RCT) on the topic: indeed since the MASTER study which randomized 915 patients[2] there have been notably few RCTs on the topic of CNB. On the face of it, therefore, this study might raise considerable concerns over the continuing use of thoracic epidurals combined with general anaesthesia. There is evidence that around the time of the publication of the MASTER study the use of perioperative epidurals reduced in Australasia,[3] America[4] and in the UK.[5 6] Should this study accelerate that trend?

Before jumping to this conclusion there are several aspects of the study that merit exploration.

Importantly, all patients in the study were recruits to the POISE study and therefore by definition at increased risk of cardiovascular complications (the main inclusion criteria for the POISE trial). The study not only focuses on patients with cardiovascular disease but also focuses on cardiovascular outcomes. Indeed important non-cardiovascular outcomes such as respiratory, renal, gastrointestinal, and infective complications are not captured or discussed at all. It is, therefore, notable that while several individual and composite cardiovascular outcomes are significantly increased in the thoracic epidural group, death is not in this, or any group. These issues raise a number of questions. First are the results of this study generalizable to other patients, for instance those who are fitter, those without cardiovascular risk or those with other risks, such as severe respiratory disease? Secondly, might the focus on cardiovascular complications lead to misleading conclusions on the burden of complications overall: how can the frequency of myocardial infarction, hypotension and the composite outcome be increased yet mortality remains unchanged? One possibility is that CNB may reduce other complications (e.g. respiratory, gastrointestinal, renal, infective, and thromboembolic) not captured in this study and thereby improve overall non-cardiovascular outcome. There is of course evidence that CNB can have beneficial effects on respiratory,[2 7 8] gastrointestinal,[7 9 10] renal,[7 11] infective,[12 13] and thrombotic[14] outcomes after major surgery. Studies also attest to cardiovascular benefits of epidural techniques.[7 15] Of note, most outcome benefit appears to be limited to thoracic (specifically high and mid thoracic) epidurals.[7 10 15] Any effects on mortality remain uncertain and controversial.

In order to understand the study better it is necessary to consider the methodology used: that of propensity-score matching (PSM). In conducting scientific research such as a clinical trial, we rely on randomization to evenly distribute known, and more importantly in this context, unknown or unrecognized, variables that may confound the experiment. Often, it is not possible to have a randomized design for logical or logistical reasons. PSM is a mathematical technique that attempts to control for the lack of randomization in a data set and has been used to try and identify causal effects. Essentially, all patients in the study are assigned a probability or propensity score for receiving a non-randomized intervention, in this case, neuraxial analgesia. This score is generated by analysing the available variables that may influence the likelihood of having received the intervention or not. The aim is then to match patients in the intervention group to patients with similar propensity scores in the control group and then test the hypothesis. The usefulness of the results therefore relies entirely on the ability of propensity scoring to match the groups in all matters of importance when comparing the groups. In this study, it also relies on the outcomes of the POISE study being the appropriate ones on which to measure benefit from CNB. Four points should become obvious with PSM: (i) there is no randomization, (ii) unknown or unrecognized confounders are not controlled for (so if the chosen dataset does not include these factors their effects may be missed), (iii) it is a mathematical attempt only, and (iv) it is no longer an experiment! This final point is of crucial importance as it helps us differentiate causality from association. A good example of this is the controversy that was stirred by Connors and colleagues[16] who used PSM to show that the use of pulmonary artery catheters (PAC) increased mortality in critically ill patients. Dalen and Bone[17] then prematurely called for a moratorium on the use of the PAC in an accompanying editorial. The controversy led to the PAC-MAN trial[18] that was a randomized controlled trial of the use of the PAC and which found no evidence of harm to support the PSM report by Connors and colleagues[16] Other issues with PSM are that robust intention-to-treat analyses are clearly not possible. Even treatment-received and per-protocol analyses may be confounded with lack of any data on the actual effectiveness of the 'intervention', in this case the analgesic efficacy of the neuraxial block. The necessary use of 'common support' conditions in the PSM analyses where patients with extremes of propensity score cannot be matched for the intervention can lead to censoring of important information. So although PSM can be used to test, prove, and disprove various hypotheses, these will not be proper hypotheses of causality.

Further examination of the MASTER study is relevant here. The MASTER study, which examined outcome differences in patients with and without epidural analgesia for surgery, considered to be at high risk of complications, is regarded by some as the most definitive RCT on the topic. Somewhat surprisingly however, for some it shows lack of outcome benefit with epidural analgesia (no statistically significant difference in mortality) while for others it supports epidurals improving outcome [7% absolute and 23% relative risk reduction in respiratory failure in epidural group, $P=0.02$, number needed to treat (NNT) 14]. The comparison between the current study (increase in cardiovascular system complications, no effect on mortality) and MASTER (decrease in respiratory complications, no effect on mortality) is notable. Before leaving the MASTER study it is worth also exploring exactly what it did show: the study primary endpoint was the occurrence of 'death or major complication' which was anticipated to occur in 40–50%. The study was powered to be able to detect a 10% absolute risk reduction (ARR) and 20% relative risk reduction (RRR) in this composite primary outcome. Mortality was predicted to be 10%. In total, 915 patients were randomized and 888 completed the study. The retrospective power of the study to detect a difference in mortality can easily be examined.[19] If the baseline mortality was indeed 10% (as *predicted*) the study had only 15% power to detect a 20% RRR or 2% ARR (10–8%). Although the primary outcome did occur in >50% of patients in both groups (no significant difference between groups) the mortality rate was lower in both groups than predicted (epidural 5.1%, no epidural 4.3%, $P=0.67$). Further *post hoc* power analysis shows that with an *observed* baseline mortality of 4.3% the number of patients needed to detect a 20% RRR in mortality approximates 14 000 patients (80% power and $P<0.05$). The conclusion is that while MASTER is an important study, and while it provides evidence that epidural analgesia reduces respiratory failure after major surgery, it shows how difficult it is to find evidence of any effects of epidural analgesia on mortality, which is typical of the analysis of rare events.

Since the MASTER study the 3rd National Audit Project of the Royal College of Anaesthetists has provided generally reassuring data regarding major *neurological* sequelae of CNB in all settings.[20] However, despite these reassuring findings it is notable that the project was not designed to capture either the outcome benefits of CNB, or any potential adverse effects of CNB on non-neurological outcomes.

A second question is whether the current study has face validity. The authors argue the mechanism for an increase in cardiovascular morbidity is an increase in hypotension. This seems reasonable on first inspection, especially as it is one of the mechanisms that might have led to excess adverse outcomes in the POISE study. Further inspection reveals a more complex picture. Patients in the β-blocker arm of the POISE study experienced a higher rate of stroke and mortality but a lower rate of myocardial infarction than those in the placebo group. These findings have been attributed in part to an increased rate of hypotension (and bradycardia) in the β-blocked group. In the current paper, CNB was associated with a statistically significant increase in myocardial infarction but not hypotension, stroke, or death. The thoracic epidural sub group was associated with a statistically significant increase in hypotension and myocardial infarction, but not stroke or death. The spinal group was associated with a statistically significant *decrease* in hypotension compared with general anaesthesia (itself a finding of questionable face validity) but no statistical increase in other outcomes. These findings, of a different distribution of cardiovascular complications in POISE and in the present study, tend to suggest that if CNB in general (and thoracic epidurals particularly) do increase adverse cardiovascular outcomes the mechanism(s) might be different from those caused by β-blockers in the POISE study.

Finally, how does the current study compare to recent studies examining a similar clinical setting and using similar methodology. Wijeysundera and colleagues used an administrative database and propensity score methods to explore the impact of epidural use on outcome from patients undergoing elective surgery.[21] The authors reported 'a small reduction in 30 day mortality'. In fact, this amounted to an 11% RRR in mortality. In this study, the baseline mortality was low at 2% leading to a NNT of ~450 patients to save one life. If such a RRR also applies in a high-risk group of patients the potential benefits would be considerably more far-reaching.[22] Neuman and colleagues[23] examined the outcomes of more than 18 000 patients undergoing hip fracture surgery and using a fixed effects logistic regression method found that spinal anaesthesia was associated with a statistically significant reduction in pulmonary complications and odds-adjusted mortality (odds ratio: 0.71, 95% CI 0.54–0.93, $P=0.014$): an observed reduction in cardiovascular complications lacked statistical significance.

While many studies focus on specific areas of morbidity (often in patient groups selected because of their high risk for those outcomes) we still lack an overall understanding of which particular outcomes occur most commonly after major elective and emergency surgery. A better understanding of which complications arise most commonly in which patient groups and after various types of surgery might better enable us to target perioperative care including analgesic strategies.

So what can we conclude from this study? First it should be acknowledged as an important study, despite the limitations the authors document. As a result of the methodology, mixed results and lack of clear association between putative cause (hypotension) and effect (stroke, myocardial infarction, and death) the study should be considered to be more hypothesis-generating than hypothesis-testing. The evidence 'in the round' suggests that neuraxial blocks have a very low-procedural risk and many potential benefits, though some of these may be restricted to specific patient groups. Perioperative complications have a dramatic impact on survival that extends well beyond the hospital stay.[24] However, the anaesthetic community remains divided, because of a lack of clear evidence, over whether CNB provides overall outcome benefits

or not and which groups should be targeted for its use. One practical suggestion from the current study is that the avoidance of hypotension for the duration of CNB (and perhaps for a period afterwards) may prevent cardiovascular complications of CNB and should be an active priority of all those using these techniques, whether in routine general ward management or in research.[25]

Leslie's study, could also usefully stimulate further research to examine not only cardiovascular or respiratory complications but all cause complications in an appropriately powered study. In order to have adequate power such a study could usefully examine high-risk patients who currently often receive CNB (ideally thoracic epidurals and general anaesthesia) and in which there is equipoise as to whether this is the right approach. Patients undergoing emergency laparotomy are likely to fall into this group as many receive epidural analgesia,[26] and the population has a high baseline mortality of 15% increasing to >25% in the elderly.[27] With the National Emergency Laparotomy Audit soon to start[28] this group might prove a useful starting point for such a study.

## Declaration of interest

T.M.C.: none I am aware of. I was the lead for the 3rd National Audit Project of the Royal College of Anaesthetists which generally had 'benign' findings in terms of CNB and adverse outcome. I am an Editor of *Perioperative Medicine* and Associate Editor of the *British Journal of Anaesthesia*. M.O.C: Editor of the *European Journal of Anaesthesiology*, Editorial Board Member of the *International Journal of Obstetric Anesthesia* and Associate Editorial Board Member of the *British Journal of Anaesthesia*.

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## EDITORIAL IV

# Does anaesthetic technique really matter for total knee arthroplasty?

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Total knee arthroplasty (TKA) is a common, painful surgical procedure requiring good quality anaesthesia and postoperative analgesia to provide best patient care and facilitate effective rehabilitation. More than 70 000 knee replacements are performed in the UK each year and this is projected to increase as the population ages and osteoarthritis, the most common reason for TKA, becomes more prevalent. Given ever increasing pressure on resource utilization the quality and the type of anaesthesia and postoperative pain relief can have a significant impact on ability to meet rehabilitation goals.[1–3] Studies have also demonstrated that poor pain control after knee replacement is associated with development of chronic pain[4] although our understanding of this area is only starting to develop.[5]

The anaesthetic management of patients undergoing TKA has undergone several refinements and transitions. In the past, general anaesthesia (GA) with systemic opioid analgesia alone was commonly used. Spinal anaesthesia, uniquely suited to lower extremity orthopaedic procedures, has gained prominence with several landmark studies demonstrating the superiority of spinal anaesthesia over GA in terms of morbidity and mortality.[6 7] Contemporary studies have continued to reinforce these data with recent epidemiological studies using large databases indicating a reduction in risk of morbidity and mortality with the use of neuraxial anaesthesia.[8 9] The mechanisms underlying these benefits remain to be fully understood but may include improvements in blood flow, cardiorespiratory benefits and a possible reduction in surgical stress response.[9] Outcomes such as pain relief, opioid consumption, and length of hospital stay (LOS) also favour spinal anaesthesia.[2 10] However, neuraxial anaesthesia is not without risk, and although rare, does have potential for spinal haematoma, infection, or abscess in contemporary practice.[11] Therefore, despite the perceived benefits of neuraxial anaesthesia, newer methods of providing anaesthesia for knee replacement need to be evaluated and existing techniques challenged.

In this issue of the *British Journal of Anaesthesia*, Harsten and colleagues[12] compare recovery from TKA after GA [specifically with total-i.v. anaesthesia using target-controlled infusions (TCI) of propofol and remifentanil] with spinal anaesthesia with bupivacaine in a randomized study of 120 patients. The authors demonstrate that patients in the GA group had a shorter time to meet discharge criteria (46 *vs* 52 h), less nausea and vomiting, better pain control (except for the first two postoperative hours), and less dizziness compared with the spinal anaesthesia group. The findings of this paper appear to contradict previous recommendations regarding spinal anaesthesia for TKA[13] and prompt an assessment of the reasons for disparity with previous results.

A closer examination of the study reveals both strengths and limitations. A major strength of this study is the comparison of a state-of-the-art general anaesthetic technique including multimodal analgesia with a basic spinal technique. Both of these relatively straightforward and common methods of anaesthesia would be feasible in all hospitals where total knee replacement procedures are currently performed. Many institutions across the world are unable to provide consistent, high-quality regional anaesthesia for their patients and in this regard demonstration of the effectiveness of a GA with multimodal analgesia technique is timely. The recovery time and time to reach discharge criteria are impressive in both groups and is currently faster than that achieved in many centres.

Some criticisms and observations with the techniques used in this study should be noted. First, the authors use a spinal

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BJA

CLINICAL PRACTICE

# Neuraxial block, death and serious cardiovascular morbidity in the POISE trial†

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## Editor's key points

- The incidence of significant cardiovascular problems associated with neuraxial block is poorly understood.
- Secondary analysis of a large study explores the association between cardiovascular events and neuraxial block.
- Some evidence was found for increased cardiovascular problems in high-risk patients receiving neuraxial block.
- This conflicts with some other studies and further research is urgently required in this area.

**Background.** This *post hoc* analysis aimed to determine whether neuraxial block was associated with a composite of cardiovascular death, non-fatal myocardial infarction (MI) and non-fatal cardiac arrest within 30 days of randomization in POISE trial patients.

**Methods.** A total of 8351 non-cardiac surgical patients at high risk of cardiovascular complications were randomized to β-blocker or placebo. Neuraxial block was defined as spinal, lumbar or thoracic epidural anaesthesia. Logistic regression, with weighting using estimated propensity scores, was used to determine the association between neuraxial block and primary and secondary outcomes.

**Results.** Neuraxial block was associated with an increased risk of the primary outcome [287 (7.3%) *vs* 229 (5.7%); odds ratio (OR), 1.24; 95% confidence interval (CI), 1.02–1.49; $P=0.03$] and MI [230 (5.9%) *vs* 177 (4.4%); OR, 1.32; 95% CI, 1.07–1.64; $P=0.009$] but not stroke [23 (0.6%) *vs* 32 (0.8%); OR, 0.76; 95% CI, 0.44–1.33; $P=0.34$], death [96 (2.5%) *vs* 111 (2.8%); OR, 0.87; 95% CI, 0.65–1.17; $P=0.37$] or clinically significant hypotension [522 (13.4%) *vs* 484 (12.1%); OR, 1.13; 95% CI, 0.99–1.30; $P=0.08$]. Thoracic epidural with general anaesthesia was associated with a worse primary outcome than general anaesthesia alone [86 (12.1%) *vs* 119 (5.4%); OR, 2.95; 95% CI, 2.00–4.35; $P<0.001$].

**Conclusions.** In patients at high risk of cardiovascular morbidity, neuraxial block was associated with an increased risk of adverse cardiovascular outcomes, which could be causal or because of residual confounding.

**Keywords:** anaesthesia, epidural; anaesthesia, spinal; death; myocardial infarction; stroke

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Neuraxial block may produce sympathetic nervous system block, reduce potent hypnotic and opioid requirements, and improve acute and chronic pain outcomes after operation.[1] Although some studies have suggested that neuraxial block reduces the risk of postoperative cardiac,[2] pulmonary,[3 4] and thrombotic[5 6] complications, neuraxial block may increase the risk of clinically significant hypotension that could increase the risk of death and major cardiovascular events.[4 7] However, investigating the effectiveness of neuraxial block using randomized trials has proved challenging.[8 9]

No really large randomized controlled trials of neuraxial block and its effects on major outcomes have been conducted despite ongoing interest in neuraxial block with or without general anaesthesia for non-cardiac surgery patients. Meta-analyses[2 4–6] of small and moderate-sized[3 10] trials, and analyses of prospectively collected datasets, therefore, continue to inform practice.

A substantial proportion of the patients recruited to the POISE trial on the effect of extended-release metoprolol succinate or placebo on 30-day outcomes received neuraxial block as a part of their perioperative care. In addition, because of the cardiovascular risk profile of the patients, adverse cardiovascular event rates were substantial. The POISE dataset, therefore, provides an opportunity to further explore the association of neuraxial block with major postoperative cardiovascular outcomes. The primary aim of this *post hoc* sub-analysis was to determine the relationship between neuraxial block and the composite outcome of cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal cardiac arrest occurring within 30 days after randomization in the POISE trial patients.

## Methods

This sub-analysis was designed after the main study began and was not part of the original protocol. The methods for this analysis were identical to those used in our prior analysis of the effect of nitrous oxide administration in POISE trial patients.[11] The POISE trial protocol was detailed elsewhere and was registered with ClinicalTrials.gov (NCT00182039).[12 13] The current analysis was not registered. Patients were eligible for this multi-centre, blinded, randomized controlled trial if they were aged $\geq$45 yr, were undergoing non-cardiac surgery with an expected hospital length of stay $\geq$24 h, and fulfilled at least one of the following criteria indicating high risk of cardiovascular morbidity: history of coronary artery disease, peripheral vascular disease, stroke, hospitalization for congestive heart failure, undergoing major vascular surgery, or any three of seven criteria (intrathoracic or intraperitoneal surgery, history of congestive heart failure, transient ischaemic attack, diabetes, serum creatinine $>$175 $\mu$mol litre$^{-1}$, age $>$70 yr, or undergoing emergency surgery). Patients were excluded if they met any of the following criteria: heart rate $<$50 beats min$^{-1}$, second- or third-degree heart block, asthma, already receiving a $\beta$-blocker, and coronary artery bypass surgery within 5 yr and no subsequent cardiac ischaemia since, low-risk surgical procedures, on verapamil or previous randomization into the trial. Ethics committee approval was obtained at all centres and informed consent was provided by all patients for the original trial.

A total of 8351 patients from 190 centres in 23 countries were randomized to extended-release metoprolol succinate or placebo, starting 2–4 h before surgery and continuing for 30 days. Study medication was withheld if the heart rate was $<$50 beats min$^{-1}$ or the systolic arterial pressure was $<$100 mm Hg. Troponins or creatine kinase - muscle/brain assays and electrocardiographs were used to monitor patients during the 30-day follow-up period. A blinded committee adjudicated cardiovascular outcomes. The dosage and monitoring regimens were described in detail previously.[12 13]

In the POISE trial, the primary outcome was a composite of cardiovascular death, non-fatal MI, and non-fatal cardiac arrest occurring within 30 days of randomization. Secondary outcomes included MI and stroke. Clinically significant hypotension was defined as a systolic arterial pressure of $<$90 mm Hg requiring fluid resuscitation, an inotropic agent, intra-aortic balloon pump, or study drug discontinuation.[12]

The current sub-analysis was designed and executed *post hoc*. Neuraxial block was defined as treatment with spinal, or lumbar or thoracic epidural anaesthesia, with or without additional general anaesthesia, or nerve block. We did not record the details of the decision to use neuraxial block; the specifics of neuraxial block when administered (i.e. timing of initiation, site, success and extent of neuraxial block, agents used, and duration of neuraxial block); the experience of the anaesthetist and postoperative team, and the influence of the use of neuraxial block on other aspects of perioperative care (e.g. anti-thrombotic medications). As well as the comparison of the neuraxial block and no neuraxial block groups, we made the following additional comparisons. For lumbar epidural, we compared general anaesthesia alone, lumbar epidural alone, and general anaesthesia combined with lumbar epidural. For thoracic epidural, we compared general anaesthesia alone and general anaesthesia combined with thoracic epidural (as few patients received thoracic anaesthesia alone). For spinal anaesthesia, we compared general anaesthesia alone and spinal alone (as few patients received general anaesthesia combined with spinal anaesthesia). Countries were grouped in regions as follows: (i) Australia and New Zealand; (ii) Central and South America; (iii) Canada; (iv) South-East Asia, China and Hong Kong; (v) Europe; and (vi) India.

### Data analysis

The data analysis was identical to that used in our analysis of the effect of nitrous oxide administration in POISE trial patients.[11] Baseline characteristics were summarized as number (%) for categorical variables and mean (SD) for continuous variables, and were compared between intervention groups using $\chi^2$ tests and analysis of variance, respectively.

Neuraxial block was administered at the discretion of the anaesthetists; that is, it was not randomly assigned. Patient characteristics were, therefore, imbalanced between

intervention groups, and so a propensity score technique was used to account for potential confounding. The propensity score is the probability of receiving the intervention, modelled as a function of observed variables, and can be used in various ways to adjust for confounding because of observed characteristics.[14 15] An inverse probability weighted approach was adopted, which uses the propensity score to create a 'pseudo-population' in which all measured characteristics are balanced between the intervention groups. However, propensity score methods do not facilitate the balance of unmeasured or unknown characteristics that may be achieved in a randomized controlled trial. Propensity score methods assume that every patient has a non-zero probability of receiving each studied intervention. Therefore, patients having cranial or head and neck surgery, for whom neuraxial block is not indicated, were excluded. For the lumbar epidural and spinal anaesthesia analyses, further exclusions were made for thoracic surgery, and for thoracic epidural, further exclusions were made for orthopaedic surgery. Patients receiving multiple types of neuraxial block were also excluded.

The propensity score was estimated using a logistic regression model (or, for lumbar epidural analyses, multinomial) in which the outcome was the intervention (neuraxial block). An iterative procedure was used to select independent variables to include in the model, initially including main effects for all characteristics listed in Table 1, adding interaction terms until no further imbalance could be removed. All analyses were repeated using a more comprehensive propensity score model including all region-by-covariate interactions, in order to investigate and account for geographical differences in administration of neuraxial block.

We then excluded any patients in the neuraxial group who had an estimated propensity score higher than that of any patient in the no-neuraxial group, and any patients in the no-neuraxial group with a propensity score lower than that of any patient receiving neuraxial block (known as a 'common support' condition).[14] For the three group lumbar comparison, an analogous condition involving three groups was imposed. This removed patients for whom no comparable patient existed in the other group, because the effect of the intervention could not be estimated for such patients.

Each patient was inversely weighted by the probability of that patient receiving the intervention that they did indeed receive (calculated using the propensity score). Within the weighted sample (the 'pseudo-population'), measured patient prognostic characteristics should be balanced between the intervention groups. This was assessed using standardized differences [the difference in the percentage (or mean) of each characteristic between the groups, divided by an estimate of the SD and expressed as a percentage][16] calculated both for the original sample and the weighted sample. It has been suggested that a standardized difference of $\geq$10% represents a meaningful imbalance.[17]

Odds ratios (ORs) and 95% confidence intervals (CIs) for the effect of neuraxial block on the primary composite outcome, MI, and stroke were estimated using logistic regression models for each outcome including the intervention group as the sole independent variable by applying a weighted analysis as described above. Characteristics that remained imbalanced in the weighted sample were additionally included as independent variables in the logistic regression model to remove any residual confounding by these variables.

Logistic regression was also used to estimate the effect of neuraxial block on the incidence of clinically significant hypotension, and the interaction with the randomized group (controlled-release metoprolol or placebo) was tested. To assess between-region variability in effect on the primary outcome, an interaction between intervention and geographical region was additionally included in the weighted logistic regression model.

To assess the sensitivity of results to a few individuals with large weights, the 1% of patients with the largest weights was excluded and all the analyses were repeated. Patients with missing data for surgery type or baseline heart rate or systolic arterial pressure were excluded from all analyses. Analyses were conducted using Stata version 11.1. A *P*-value of $<0.05$ was considered statistically significant.

## Results

In total, 7925 of the 8351 patients randomized to the POISE trial remained after exclusions were made for patients for whom the intervention was contraindicated ($n=364$), those with missing data ($n=15$) and those for whom no comparable patient existed in the other intervention group ($n=47$).

For lumbar epidural, exclusions were made for contraindications ($n=3445$), missing data ($n=9$), and lack of 'common support' (see 'Methods' section; $n=894$), leaving 4003 patients. For thoracic epidural, exclusions were made for contraindications ($n=4336$) and missing data ($n=9$). The group receiving thoracic epidural without general anaesthesia was too small for analysis ($n=51$) and so was excluded, as were two regions (Central/South America and India) where fewer than 5 patients were given thoracic epidural (excluding $n=852$). Lack of 'common support' excluded 200 patients, leaving an analysis sample of $n=2903$ patients for the thoracic epidural analysis. For spinal anaesthesia, contraindications, missing data, and lack of 'common support' excluded 3089, 12, and 28 patients, respectively. Too few patients received spinal anaesthesia in combination with general anaesthesia ($n=124$); so, these patients were excluded. The final spinal anaesthesia sample therefore contained 5098 patients.

Neuraxial block was administered to 3909 (49%) of the 7925 patients who were included in the neuraxial analysis. Patients receiving neuraxial block were more likely to be male, to have peripheral vascular disease and to be presenting for major vascular or orthopaedic surgery than those not receiving neuraxial block (Table 1). There was significant regional variation in the administration of neuraxial block, with 60% of included patients in India receiving neuraxial block compared with 41% of included patients in Australia/New Zealand. Imbalances between the intervention groups in the initial sample were reduced to minimal levels by the propensity score weighting (Table 1). In particular, the

**Table 1** Neuraxial block baseline characteristics ($n=7925$). *Except for age, heart rate and systolic arterial pressure which are presented as mean (SD); LMWH, low molecular weight heparin; Std Diff, standardized difference; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; †$\chi^2$-test (categorical variables) or analysis of variance (continuous variables), unweighted or weighted as appropriate; ‡all vascular surgery except carotid endarterectomy, vein stripping, and arterio-venous fistula surgery

| Characteristic | Unweighted—% (*n*) | | | | Propensity score weighted—% | | | |
|---|---|---|---|---|---|---|---|---|
| | No neuraxial block (*n*=4016) % (*n*)* | Neuraxial block (*n*=3909) % (*n*)* | Std Diff (%) | *P*-value† | No neuraxial block (*n*=4016) %* | Neuraxial block (*n*=3909) %* | Std Diff (%) | *P*-value† |
| Age (yr) | 69.2 (10.3) | 70 (10.6) | 6.9 | 0.002 | 69.6 (10.4) | 69.6 (10.4) | 0.9 | 0.79 |
| Age group (yr) | | | | | | | | |
| 45–54 | 10.4 (419) | 10.1 (395) | 1.1 | 0.007 | 10.2 | 10.2 | 0.0 | 0.99 |
| 55–64 | 22.5 (902) | 20.3 (794) | 5.2 | | 21.2 | 21.4 | 0.6 | |
| 65–74 | 34.9 (1402) | 34.6 (1353) | 0.6 | | 35.1 | 35.1 | 0.0 | |
| 75–84 | 27.5 (1106) | 28.8 (1125) | 2.8 | | 28 | 27.8 | 0.4 | |
| ≥85 | 4.7 (187) | 6.2 (242) | 6.8 | | 5.5 | 5.4 | 0.3 | |
| Sex (female) | 39.3 (1578) | 33.1 (1294) | 12.9 | <0.001 | 35.7 | 35.6 | 0.2 | 0.93 |
| Past history | | | | | | | | |
| Coronary artery disease | 42.5 (1705) | 42.1 (1644) | 0.8 | 0.72 | 42.6 | 42.5 | 0.2 | 0.93 |
| Peripheral vascular disease | 38.1 (1532) | 45.6 (1782) | 15.1 | <0.001 | 42.0 | 42.4 | 0.7 | 0.76 |
| Stroke thought because of atherothrombotic disease | 16.1 (645) | 12.8 (501) | 9.2 | <0.001 | 14.1 | 13.9 | 0.8 | 0.74 |
| Transient ischaemic attack history | 12.0 (483) | 7.9 (308) | 13.9 | <0.001 | 10.0 | 9.9 | 0.1 | 0.98 |
| Hospitalized for congestive heart failure | 2.6 (106) | 2.5 (98) | 0.8 | 0.71 | 2.6 | 2.6 | 0.2 | 0.92 |
| Documented heart failure | 6.4 (256) | 5.3 (207) | 4.6 | 0.04 | 5.9 | 6.0 | 0.2 | 0.93 |
| Preoperative serum creatinine >175 μmol litre$^{-1}$ | 5.4 (215) | 4.2 (166) | 5.2 | 0.02 | 4.8 | 4.9 | 0.3 | 0.90 |
| Diabetes on oral hypoglycaemic agent or insulin | 29.5 (1183) | 29.2 (1142) | 0.5 | 0.81 | 29.5 | 29.9 | 0.9 | 0.71 |
| Hypertension | 63.5 (2551) | 62.4 (2438) | 2.4 | 0.29 | 63.1 | 62.9 | 0.3 | 0.89 |
| Smoking status | | | | | | | | |
| Never | 42.4 (1702) | 39.8 (1554) | 5.3 | 0.05 | 41.2 | 41.2 | 0.1 | 0.99 |
| Current | 18.5 (744) | 19.8 (774) | 3.2 | | 19.2 | 19.1 | 0.2 | |
| Former | 39.1 (1570) | 40.4 (1581) | 2.8 | | 39.7 | 39.7 | 0.1 | |
| Preoperative medications | | | | | | | | |
| Aspirin | 35.8 (1439) | 36.9 (1441) | 2.1 | 0.34 | 35.8 | 35.7 | 0.2 | 0.92 |
| Clopidogrel | 4.4 (178) | 2.8 (109) | 8.8 | <0.001 | 3.5 | 3.5 | 0.5 | 0.84 |
| LMWH/unfractionated heparin | 7.5 (301) | 11.4 (446) | 13.4 | <0.001 | 9.0 | 9.1 | 0.5 | 0.84 |
| ACEI/ARB | 45.4 (1822) | 43.2 (1690) | 4.3 | 0.06 | 44.1 | 44.1 | 0.1 | 0.95 |
| Statin | 33.0 (1324) | 31.1 (1217) | 3.9 | 0.08 | 32.1 | 32.1 | 0.0 | 0.99 |
| Diuretic | 20.9 (841) | 21.4 (838) | 1.2 | 0.59 | 21.1 | 21.1 | 0.1 | 0.95 |
| Calcium channel blocker | 21.1 (847) | 22.8 (892) | 4.2 | 0.06 | 22.2 | 22.1 | 0.3 | 0.91 |
| Long-acting nitrates | 8.2 (329) | 8.8 (343) | 2.1 | 0.35 | 8.6 | 8.7 | 0.2 | 0.95 |
| Non-study β-blockers | 0.4 (18) | 0.3 (11) | 2.8 | 0.227 | 0.4 | 0.3 | 0.5 | 0.81 |
| Digoxin | 2.7 (108) | 3.2 (126) | 3.2 | 0.16 | 3 | 3.0 | 0.5 | 0.84 |
| Amiodarone | 1.3 (52) | 1.2 (45) | 1.3 | 0.56 | 1.3 | 1.3 | 0.4 | 0.88 |
| Oral anticoagulants | 3.2 (123) | 2.5 (96) | 3.7 | 0.10 | 2.9 | 3.0 | 0.2 | 0.94 |
| Type of surgery | | | | | | | | |
| Major vascular‡ | 32.5 (1307) | 41.2 (1609) | 17.9 | <0.001 | 36.5 | 36.7 | 0.5 | 0.96 |
| Other vascular | 9.0 (360) | 3.7 (146) | 21.6 | | 6.3 | 5.9 | 1.5 | |

*Continued*

**Table 1** *Continued*

| Characteristic | Unweighted—% (*n*) | | | | Propensity score weighted—% | | | |
|---|---|---|---|---|---|---|---|---|
| | No neuraxial block (*n*=4016) % (*n*)* | Neuraxial block (*n*=3909) % (*n*)* | Std Diff (%) | *P*-value† | No neuraxial block (*n*=4016) %* | Neuraxial block (*n*=3909) %* | Std Diff (%) | *P*-value† |
| Orthopaedic | 16.3 (656) | 28.0 (1096) | 28.5 | | 22.6 | 22.3 | 0.6 | |
| Intra-abdominal | 29.5 (1186) | 15.8 (616) | 33.4 | | 22.8 | 23.2 | 1.1 | |
| Other | 12.6 (507) | 11.3 (442) | 4.1 | | 11.9 | 11.8 | 0.2 | |
| Region | | | | | | | | |
| Australia and New Zealand | 12.3 (492) | 8.6 (335) | 12.1 | <0.001 | 10.7 | 11.1 | 1.3 | 0.99 |
| Central and South America | 19.4 (778) | 17.1 (667) | 6.0 | | 17.8 | 17.6 | 0.4 | |
| Canada | 42.9 (1723) | 42.6 (1666) | 0.6 | | 42.9 | 42.5 | 0.7 | |
| South-East Asia, China and Hong Kong | 13.6 (548) | 15 (587) | 3.9 | | 15.0 | 15.0 | 0.0 | |
| Europe | 4.5 (181) | 5.4 (210) | 4.0 | | 4.7 | 4.7 | 0.4 | |
| India | 7.3 (294) | 11.4 (444) | 13.9 | | 9.0 | 9.1 | 0.7 | |
| Emergency surgery | 12.3 (484) | 10.4 (406) | 6.0 | 0.007 | 11 | 10.9 | 0.4 | 0.88 |
| Preoperative heart rate (beats $min^{-1}$) | 77.8 (12.5) | 77.8 (12.1) | 0.1 | 0.96 | 77.8 (12.3) | 77.7 (12.1) | 0.6 | 0.79 |
| Preoperative systolic arterial pressure (mm Hg) | 138.5 (20.1) | 138.7 (19.4) | 1.4 | 0.55 | 138.6 (19.7) | 138.7 (19.6) | 0.3 | 0.89 |
| Randomized to metoprolol | 49.5 (1987) | 50.6 (1978) | 2.2 | 0.32 | 50 | 50 | 0.0 | 0.99 |

**Table 2** Estimated associations with the outcome for neuraxial block. OR, odds ratio; CI, confidence interval; *Wald-test *P*-value from unweighted/weighted logistic regression; †primary outcome, cardiovascular death, non-fatal MI, and non-fatal cardiac arrest

| | No neuraxial block (*n*=4016) | | Neuraxial block (*n*=3909) | | Unadjusted | | Propensity score adjusted | |
|---|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | OR (95% CI) | *P*-value* | OR (95% CI) | *P*-value* |
| Primary† | 229 | 5.7 | 287 | 7.3 | 1.31 (1.1, 1.57) | 0.003 | 1.24 (1.02, 1.49) | 0.03 |
| MI | 177 | 4.4 | 230 | 5.9 | 1.36 (1.11, 1.66) | 0.003 | 1.32 (1.07, 1.63) | 0.01 |
| Stroke | 32 | 0.8 | 23 | 0.6 | 0.74 (0.43, 1.26) | 0.27 | 0.76 (0.44, 1.34) | 0.35 |
| Death | 111 | 2.8 | 96 | 2.5 | 0.89 (0.67, 1.17) | 0.39 | 0.87 (0.65, 1.17) | 0.37 |
| Hypotension | 484 | 12.1 | 522 | 13.4 | 1.12 (0.98, 1.28) | 0.08 | 1.13 (0.99, 1.3) | 0.08 |

groups were well balanced for the randomized β-blocker treatment. For the analyses of specific neuraxial techniques, the weighting removed imbalance adequately for spinal anaesthesia and thoracic epidural (Supplementary Tables A1–3), but a few variables remained imbalanced for lumbar epidurals (standardized differences ~10). These were additionally included in regression models for lumbar analyses.

Neuraxial block (Table 2) was associated with an increased risk of the primary outcome (OR, 1.24; 95% CI, 1.02–1.49; *P*=0.03) and MI (OR, 1.32; 95% CI, 1.07–1.63; *P*=0.01) but not stroke (OR, 0.76; 95% CI, 0.44–1.34; *P*=0.35) or death (OR, 0.87; 95% CI, 0.65–1.17; *P*=0.37). Trimming the weights at the 99th percentile made a negligible difference: ORs and confidence limits were altered by <0.01. For the primary outcome, there was no significant evidence of between-region heterogeneity (*P*=0.11).

There was minimal evidence for an association between neuraxial block and clinically significant hypotension in either the unadjusted (OR, 1.12; 95% CI, 0.98–1.28; *P*=0.08) or propensity adjusted (OR, 1.13; 95% CI, 0.99–1.30; *P*=0.08) analyses. The *P*-value for the interaction between neuraxial block and randomized treatment with respect to clinically significant hypotension was 0.14 (i.e. the risk of hypotension with neuraxial block was not exacerbated by β-blockers).

The primary outcome, MI, and clinically significant hypotension were more commonly associated with general anaesthesia combined with thoracic epidural than with general anaesthesia alone (Table 3). Clinically significant hypotension was less commonly associated with spinal anaesthesia alone than with general anaesthesia alone (Table 3). Lumbar epidural anaesthesia was not associated with adverse outcomes (Table 4).

For details of the characteristics of the patients receiving neuraxial interventions, with perioperative factors, see Supplementary Tables A1–3.

## Discussion

In this *post hoc* sub-analysis, neuraxial block was associated with an increased risk of the primary composite outcome (cardiovascular death, non-fatal MI, and non-fatal cardiac arrest) and MI, but not stroke, death, or clinically significant hypotension in the POISE trial patients, who were at high risk of postoperative cardiovascular morbidity. Given the number of patients globally receiving neuraxial block, and in particular thoracic epidural combined with general anaesthesia, our observed increase in risk, if true, would impact a large number of patients. Our results should, however, be considered in the light of the study's limitations, as outlined below. There were marked geographical differences in the rates of neuraxial block, suggesting differences in regional preferences and ongoing uncertainty of benefit or risk with both techniques.

Our sub-group analyses revealed a three-fold increase in the risk of the primary outcome and MI in patients receiving general anaesthesia combined with thoracic epidural compared with general anaesthesia alone, whereas no such association was demonstrated for other subgroups. General anaesthesia combined with thoracic epidural was also significantly associated with clinically important hypotension. There was weaker association for general anaesthesia combined with lumbar epidural and the association was reversed for lumbar epidural and spinal anaesthesia alone.

These results of increased risk associated with neuraxial block patients (and especially thoracic epidural patients who also received general anaesthesia) contrast with previous work, where the estimated effects are consistently towards decreased risk or no effect. Rodgers and colleagues[5] included 141 studies published up to 1997 in their systematic review and reported decreased risk in epidural patients of death (OR, 0.70; 95% CI, 0.54–0.90) and MI (OR, 0.67; 95% CI, 0.45–1.00), although many studies were small and older studies reported more complications. However, moderate-sized randomized trials published subsequently reported no evidence of effect on these outcomes,[3 10] although improved pulmonary outcomes were noted.[3] Few of these studies entertained a hypothesis *a priori* that neuraxial block could be harmful.

Popping and colleagues[4] conducted a systematic review of randomized trials until 2006 that explored the potential adverse effects of epidural analgesia more fully. The odds of pneumonia (OR, 0.54; 95% CI, 0.43–0.68) and MI (OR, 0.55; 95% CI, 0.37–0.84) were significantly reduced in epidural patients (although the relative benefit decreased more than six-fold, from 1:4 to 1:25, over a 35-yr period). However, significant harmful effects of epidural analgesia were reported, including the risk of hypotension (OR, 2.03; 95% CI, 1.24–3.34). In this review, the site of catheter placement (lumbar *vs* thoracic) had no significant association with the outcome.

Perioperative hypotension is a proven risk factor for adverse postoperative outcomes,[13 18 19] and is a plausible means by which neuraxial block may lead to an increased risk of mortality and MI after surgery, through organ hypoperfusion, the consequences of fluid loading or both.[20] In the POISE trial, into which patients were selected because they were at high risk of cardiovascular morbidity, clinically significant hypotension (systolic arterial pressure of <90 mm Hg requiring treatment) was an independent

**Table 3** Estimated associations with outcomes for thoracic epidural and spinal. IPW, inverse probably weighted; OR, odds ratio; CI, confidence interval; MI, myocardial infarction; GA, general anaesthesia; TE, thoracic epidural; *Wald-test *P*-value from unweighted/weighted logistic regression; †primary outcome, cardiovascular death, non-fatal MI, and non-fatal cardiac arrest

| Outcome | GA alone (*n*=2194) | | TE with GA (*n*=709) | | Unadjusted | | | IPW | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | OR | 95% CI | *P*-value* | OR | 95% CI | *P*-value* |
| Primary† | 119 | 5.4 | 86 | 12.1 | 2.41 | 1.80, 3.22 | <0.001 | 2.95 | 2.00, 4.35 | <0.001 |
| MI | 100 | 4.6 | 78 | 11.0 | 2.59 | 1.90, 3.53 | <0.001 | 3.18 | 2.11, 4.80 | <0.001 |
| Stroke | 11 | 0.5 | 5 | 0.7 | 1.41 | 0.49, 4.07 | 0.526 | 1.51 | 0.44, 5.22 | 0.51 |
| Death | 39 | 1.8 | 13 | 1.8 | 1.03 | 0.55, 1.94 | 0.922 | 1.54 | 0.71, 3.34 | 0.27 |
| Hypotension | 309 | 14.1 | 200 | 28.2 | 2.39 | 1.95, 2.93 | <0.001 | 2.52 | 1.94, 3.26 | <0.001 |
| | GA alone (*n*=3673) | | Spinal (*n*=1425) | | Unadjusted | | | IPW | | |
| | *n* | % | *n* | % | OR | 95% CI | *P*-value* | OR | 95% CI | *P*-value* |
| Primary† | 215 | 5.9 | 99 | 6.9 | 1.20 | 0.94, 1.54 | 0.145 | 0.89 | 0.66, 1.19 | 0.42 |
| MI | 166 | 4.5 | 68 | 4.8 | 1.06 | 0.79, 1.41 | 0.699 | 0.74 | 0.54, 1.03 | 0.07 |
| Stroke | 24 | 0.7 | 4 | 0.3 | 0.43 | 0.15, 1.24 | 0.117 | 0.49 | 0.15, 1.60 | 0.24 |
| Death | 106 | 2.9 | 48 | 3.4 | 1.17 | 0.83, 1.66 | 0.367 | 0.95 | 0.61, 1.48 | 0.81 |
| Hypotension | 449 | 12.2 | 125 | 8.8 | 0.69 | 0.56, 0.85 | <0.001 | 0.66 | 0.51, 0.84 | 0.001 |

**Table 4** Estimated associations with outcomes for lumbar epidural. IPW, inverse probably weighted; OR, odds ratio; CI, confidence interval; MI, myocardial infarction; GA, general anaesthesia; LE, lumbar epidural; *Wald-test *P*-value from unweighted/weighted logistic regression; †primary outcome, cardiovascular death, non-fatal MI, and non-fatal cardiac arrest

| Outcome | Exposure | Event counts | | | Unadjusted | | | IPW | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Total | *n* | % | OR | 95% CI | *P*-value* | OR | 95% CI | *P*-value* |
| Primary† | GA alone | 3074 | 175 | 5.7 | 1.00 | | | 1.00 | | |
| | LE alone | 650 | 20 | 3.1 | 0.53 | (0.33, 0.84) | 0.007 | 0.74 | (0.40, 1.39) | 0.35 |
| | LE with GA | 279 | 31 | 11.1 | 2.07 | (1.38, 3.10) | <0.001 | 1.19 | (0.74, 1.92) | 0.47 |
| MI | GA alone | 3074 | 136 | 4.4 | 1.00 | | | 1.00 | | |
| | LE alone | 650 | 15 | 2.3 | 0.51 | (0.30, 0.88) | 0.015 | 0.85 | (0.43, 1.71) | 0.65 |
| | LE with GA | 279 | 26 | 9.3 | 2.22 | (1.43, 3.44) | <0.001 | 1.39 | (0.83, 2.33) | 0.21 |
| Stroke | GA alone | 3074 | 18 | 0.6 | 1.00 | | | 1.00 | | |
| | LE alone | 650 | 7 | 1.1 | 1.85 | (0.77, 4.44) | 0.170 | 0.78 | (0.30, 2.06) | 0.62 |
| | LE with GA | 279 | 1 | 0.4 | * | | | | | |
| Death | GA alone | 3074 | 80 | 2.6 | 1.00 | | | 1.00 | | |
| | LE alone | 650 | 11 | 1.7 | 0.64 | (0.34, 1.22) | 0.175 | 0.57 | (0.20, 1.61) | 0.29 |
| | LE with GA | 279 | 11 | 3.9 | 1.54 | (0.81, 2.92) | 0.190 | 1.28 | (0.56, 2.90) | 0.60 |
| Hypotension | GA alone | 3074 | 379 | 12.3 | 1.00 | | | 1.00 | | |
| | LE alone | 650 | 37 | 5.7 | 0.43 | (0.30, 0.61) | <0.001 | 0.65 | (0.39, 1.07) | 0.09 |
| | LE with GA | 279 | 63 | 22.6 | 2.07 | (1.53, 2.80) | <0.001 | 1.47 | (0.96, 2.27) | 0.08 |

risk factor for death (OR, 4.97; 95% CI, 3.62–6.81) and stroke (OR, 2.14; 95% CI, 1.15–3.96), and was more common in β-blocked patients than in controls (15 *vs* 9.7%; $P<0.0001$).[13] β-blockers and neuraxial block have a lot in common: both ablate the stress response to surgery,[21–23] have been strongly advocated to improve outcomes[5 24] but potentially may increase the overall risk of negative outcomes in high-risk surgical patients.

However, there was no statistically significant effect of neuraxial block alone on clinically significant hypotension: only thoracic epidural block appeared to have an association when combined with general anaesthesia. In addition, there was minimal evidence for effect modification by randomized treatment (i.e. the risk of hypotension with neuraxial block was not exacerbated by β-blockers). The lower rate of hypotension in the spinal group may reflect the use of spinal anaesthesia in surgery where intermittent positive pressure ventilation and fluid shifts are less likely than during surgery requiring general anaesthesia (and especially thoracic epidural block). In addition, the awake patient may alert the anaesthetist early to compromised organ perfusion by complaining of nausea or dizziness.

The most likely explanation for these findings is the restricted definition of clinically significant hypotension in POISE, although we have no data to support this. Only systolic arterial pressures <90 mm Hg and requiring treatment were defined as clinically significant in POISE. We, therefore, may have missed important hypotension that was influenced by neuraxial block that was not <90 mm Hg, was not treated or both. This seems especially likely in the postoperative period. In addition, there is potential for unmeasured confounding in the hypotension analysis (i.e. other factors such as co-morbidities and associated treatments), the possibility of a Type II error (attributable to multiple comparisons), and the possibility that hypotension is not the mechanism by which neuraxial block may result in poor outcomes (although we can offer no alternative mechanism based on our results).

Wijeysundera and colleagues[25] used propensity scoring to construct a matched-paired retrospective cohort study derived from a 259 037-patient administrative database, and found a reduction in 30-day mortality (relative risk, 0.89; 95% CI, 0.81–0.98) in neuraxial block patients. Both datasets are observational with respect to treatment with neuraxial block, however the POISE data were prospectively collected in a clinical trial context, with clear data definitions and dedicated clinical research staff who could minimize missing and inaccurate data.[13] In contrast, administrative databases have unreliable and incomplete data collection and much greater risk of residual unmeasured confounding compared with prospectively collected data in a clinical trial.[26 27] Finally, ~60% of patients in Wijeysundera and colleagues' study were having lower limb joint surgery, likely to require lumbar rather than thoracic epidural block.

Overall, our data provided no compelling evidence that patients who receive neuraxial block have fewer major adverse cardiovascular outcomes than those who do not; in fact, our results suggest that the opposite could be true. These results have implications for future research. However, the wide variations in practice but overall declining use of postoperative epidural analgesia (partly because of the advent of minimally invasive surgery),[8 28] and the increasing difficulty of randomizing patients to this treatment,[8] mean that conducting very large randomized outcome trials will be challenging. Those anaesthetists who maintain strong convictions that thoracic epidurals in particular reduce death and major cardiovascular morbidity in high risk surgical patients should reassess these convictions in light of our results. This does not mean that thoracic epidurals are

contraindicated in high-risk patients, especially in those with compromised respiratory function or those in need of high-quality analgesia, just that epidurals should not be presented to patients as having definite beneficial effects on perioperative cardiovascular outcomes until definitive large randomized trial evidence is available.

The current analyses share several limitations with our previous nitrous oxide analysis[11] and other sub-group analyses of randomized trials that are designed *post hoc*. The POISE trial was not designed to test the effects of neuraxial block on the primary or secondary outcomes. The patients in the POISE trial were at high risk of cardiovascular complications (limiting generalizability to the whole non-cardiac surgery population and specifically patients without cardiovascular disease), not randomized to neuraxial block, and the use of these techniques was at the discretion of the attending anaesthetist. We did not measure respiratory complications and therefore cannot comment about any association of neuraxial block with these outcomes nor any association of respiratory complications with mortality. We had limited pre-randomization data reflecting the decision to use neuraxial block to include in the propensity analysis. This is one of the limitations of *post hoc* propensity methods and one of the disadvantages of these methods relative to randomized controlled trials. There are highly likely to be unmeasured and unknown factors that influenced the choice of neuraxial block that may provide an alternative explanation for our findings, especially those factors that were associated with high-risk patients and neuraxial block (such as risk for respiratory complications). Future studies should attempt to control or record this decision-making.

Interest in and experience with neuraxial block varies among anaesthestists and there are certainly institutional and regional differences. Decreases in the use of epidural block were observed after the MASTER trial was published, which showed no association between epidural block and serious postoperative cardiovascular adverse outcomes.[25 28] In addition, patients and surgeons have views about neuraxial block, with a recent pilot study for a large epidural trial reporting high rates of refusal in both groups.[8] In the present study, the only data point that captured these factors was the regional variation in the use of these techniques, and we included these in our propensity score.

We did not record the details of the neuraxial block (i.e. timing of initiation, site, success and extent of neuraxial block, agents used, and duration of neuraxial block). Future randomized trials need to control or record these factors. The success of neuraxial block may be vital to the outcome as failed neuraxial block is associated with worse outcomes than i.v. opioid analgesia,[29] and the extent of the block is correlated with the extent of sympathetic nervous system block.

Furthermore, exclusion of patients who were ineligible for neuraxial block was probably incomplete, because of inadequate data about the procedure and anaesthetist's decision-making, not only about the surgical site but also about the patient's co-morbidities, medications and preferences. The use of neuraxial block may influence clinical care in important ways that were not recorded, including delayed initiation of anticoagulants or anti-platelet agents, administration of platelets or coagulation factors before block placement or catheter removal, aggressive fluid administration or withholding of cardiovascular medications. Finally, we did not collect data on other aspects of anaesthesia or surgical care. Future studies should take these factors into account.

In conclusion, neuraxial block was associated with an increased risk of the composite outcome of cardiovascular death, non-fatal MI, and non-fatal cardiac arrest in patients at high risk of postoperative cardiovascular morbidity, but not stroke, death, or significant hypotension. Further, research is needed to determine if this association is causal or because of residual confounding.

## Supplementary material

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

## Declaration of interest

None declared.

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*Handling editor: L. Colvin*

### Reply from the authors

Editor—We thank Dr Scheffczik for her valuable contribution in response to our study.[1] Dr Scheffczik kindly explains the considerable causes for the lack of significant reduction in overall stroke rate. As Dr Scheffczik points out, we think that low numbers of patients and higher numbers with carotid diseases in the EAS group are important factors which could account for the non-significance of overall stroke rate. As Dr Scheffczik comments, we also think that the conversion rate from off-pump to on-pump is also an important factor regarding stroke rate. However, in our institution, the conversion rate was very low (0.5%), so we did not consider this factor. We agree with Dr Scheffczik that these results require confirmation preferably in a multicentre study.

## Declaration of interest

None declared.

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## Neuraxial block, death, and serious cardiovascular morbidity in the POISE trial

Editor— I believe I am not alone in finding the study by Leslie and colleagues[1] of high interest. Many of us have wondered if the choice of anaesthesia, general *vs* neuraxial, had a significant effect on the outcomes observed in the POISE trial.[2] Let us recall that the POISE trial randomized β-blocker naive patients to either extended-release metoprolol (given immediately before surgery) or placebo. Thus, one can easily imagine a scenario where patients who just received a large dose of metoprolol and underwent subsequent neuraxial block could have developed clinically significant hypotension, and perhaps even adverse outcomes, such as stroke. I hoped that the current study by Leslie and colleagues would answer the question, if there is a clinically relevant interaction between metoprolol, neuraxial anaesthesia, and outcomes. Unfortunately, the article does not provide these important data. Given the importance of an improved understanding regarding the interaction between β-blockers and neuraxial anaesthesia, would it be possible for the authors to provide the readership with two new Tables 2 and 3, stratified not just by neuraxial anaesthesia, but also by metoprolol administration? I understand that this request surmounts to a lot of extra work, but I believe it would offer very interesting insights.

## Declaration of interest

None declared.

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### Reply from the authors

Editor—We thank Dr Nagele for his interest in our paper[1] and his question regarding an interaction between metoprolol, neuraxial block, and outcomes. We are happy to provide this information for all outcomes of our main analysis. There was no evidence for interactions between neuraxial block and randomized treatment with respect to the primary outcome (cardiovascular death, non-fatal myocardial infarction, and non-fatal cardiac arrest within 30 days of randomization) [placebo odds ratio (OR), 1.17; 95% confidence interval (CI), 0.91–1.51; $P$=0.23; metoprolol OR, 1.32; CI, 1.00–1.74; $P$=0.05; $P$-value for interaction=0.54], myocardial infarction (placebo OR, 1.26; CI, 0.95–1.67; $P$=0.11; metoprolol OR, 1.40; CI, 1.02–1.94; $P$=0.04; $P$-value for interaction=0.62), or death (placebo OR, 0.80; CI, 0.51–1.25; $P$=0.32; metoprolol OR, 0.94; CI, 0.64–1.39; $P$=0.77; $P$-value for interaction=0.58). For clinically significant hypotension, the full results are: placebo OR, 1.29; CI, 1.03–1.61; $P$=0.02; metoprolol OR, 1.04; CI, 0.87–1.24; $P$=0.68; $P$-value for interaction=0.14. Numbers of strokes were too small to be submitted to this analysis.

## Declaration of interest

None declared.

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1 Leslie K, Myles P, Devereaux P, *et al.* Neuraxial block, death and serious cardiovascular morbidity in the POISE trial. *Br J Anaesth* 2013; **111**: 382–90

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## It is not the epidural that is dangerous, but the person who gives it

Editor—We want to thank Professor Leslie and colleagues[1] for their subanalyses of the POISE trial and their continuing efforts to contribute to the difficult and ongoing debate about the

possible effects of epidural analgesia on perioperative morbidity and mortality.

In their study, they focused on patients with a high risk for perioperative death, myocardial infarction (MI), stroke, and hypotension. The authors found that in this group, neuraxial block was associated with an increased risk of the composite outcome of cardiovascular death, non-fatal MI, and non-fatal cardiac arrest, but not stroke, death, or significant hypotension. While the incidence of hypotension in total was not significantly different, there was a highly significant difference in the incidence of hypotension in the subgroup of patients with thoracic and lumbar epidural analgesia. Hence, the authors concluded that perioperative hypotension caused by the epidural anaesthesia may have been an important factor contributing to these results.

Perioperative hypotension *per se* is an independent risk factor for perioperative complications like MI.[2–4] However, the specialist performing anaesthesia plays a key role in the prevention and treatment of severe hypotension. This was already shown decades ago in a study performed by Slogoff and Keats in 1985.[5] They observed a remarkable difference between the incidence of intraoperative hypotension and various anaesthetists, amply demonstrating that human factors strongly influence perioperative safety. There is no question that epidural analgesia is closely associated with arterial hypotension; however, this is easily treatable by co-loading with i.v. fluids or a vasopressor therapy.[6] All anaesthetists performing epidural analgesia should naturally pay close attention to hypotension and consider options for prevention and treatment, especially in patients with coronary artery disease. Sir Robert MacIntosh once said: 'It is not the drug that's dangerous—it is the man who gives it'. Adapted to epidural analgesia, one could say: 'It is not the epidural that's dangerous, but the person who gives it'.

As the accompanying editorial already points out, hypotension cannot be the sole explanation for the difference in the increased composite outcome of cardiovascular death, non-fatal MI, and non-fatal cardiac arrest in patients with neuraxial block. We would advise readers to exercise caution in the interpretation of the presented data. First, despite propensity score matching, these patients were not randomized to a neuraxial or a control group. Further confounding factors are multiple surgical settings in different countries worldwide, without any further detailed information. A lack of data exists with regard to how epidural or spinal anaesthesia was performed: the used epidural medications are unknown, for instance, if local anaesthetics or opioids or even both were used. The duration of postoperative epidural analgesia is unknown. Was epidural analgesia continued after surgery as a continuous, intermittent, or even in a patient-controlled modus? Furthermore, there seem to have been no restrictions with regard to further additional regional anaesthetic techniques. And what about failure of the epidural or spinal anaesthesia? The MASTER-trial already suggested a high number of premature terminations of epidural analgesia.[7 8] A non-working epidural may be associated with an even worse outcome for the patient, if not immediately reinserted or switched to an alternative analgesic method. This missing information makes the interpretation of this study difficult and may lead to more questions than answers for the readers.

As the authors already concluded, a systematic approach to assess the impact of epidural analgesia on morbiditiy and mortality is mandatory, taking into account the different surgical settings, different epidural medications, and time of follow-up. Data from a recently published meta-analysis should shed some light on this matter.[9]

## Declaration of interest

None declared.

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### Reply from the authors

Editor—We thank Pöpping and colleagues for their interest in our *post hoc* propensity-adjusted analysis of the association between neuraxial block and outcome in the POISE trial.[1] The finding of most concern from POISE was the association of β-block, hypotension, and serious adverse outcomes.[1] The results of our analysis suggest a similar concern, particularly regarding thoracic epidural anaesthesia. The possibility of residual confounding in our analysis, which was raised by Pöpping and colleagues, was extensively discussed in our