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Systematic Review

Association of intraoperative hypotension with postoperative morbidity and mortality: systematic review and meta-analysis

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Abstract

Background: Intraoperative hypotension, with varying definitions in literature, may be associated with postoperative complications. The aim of this meta-analysis was to assess the association of intraoperative hypotension with postoperative morbidity and mortality.

Methods: MEDLINE, Embase and Cochrane databases were searched for studies published between January 1990 and August 2018. The primary endpoints were postoperative overall morbidity and mortality. Secondary endpoints were postoperative cardiac outcomes, acute kidney injury, stroke, delirium, surgical outcomes and combined outcomes. Subgroup analyses, sensitivity analyses and a meta-regression were performed to test the robustness of the results and to explore heterogeneity.

Results: The search identified 2931 studies, of which 29 were included in the meta-analysis, consisting of 130 862 patients. Intraoperative hypotension was associated with an increased risk of morbidity (odds ratio (OR) 2.08, 95 per cent confidence interval 1.56 to 2.77) and mortality (OR 1.94, 1.32 to 2.84). In the secondary analyses, intraoperative hypotension was associated with cardiac complications (OR 2.44, 1.52 to 3.93) and acute kidney injury (OR 2.69, 1.31 to 5.55). Overall heterogeneity was high, with an I^2 value of 88 per cent. When hypotension severity, outcome severity and study population variables were added to the meta-regression, heterogeneity was reduced to 50 per cent.

Conclusion: Intraoperative hypotension during non-cardiac surgery is associated with postoperative cardiac and renal morbidity, and mortality. A universally accepted standard definition of hypotension would facilitate further research into this topic.

Introduction

During surgery, most patients suffer from at least one episode of hypotension. The reported incidence varies, depending on the definition of intraoperative hypotension (IOH) used. IOH defined as a mean arterial pressure (MAP) below 65 mmHg occurred in approximately 65 per cent of operations, and IOH defined as a 20 per cent decrease in MAP from baseline occurred in 94 per cent[1]. More than 100 definitions of hypotension are mentioned in the literature, all using slightly different cut-off values, complicating research into IOH[1]. IOH is usually caused by the vasodilatory and cardiodepressive effects of anaesthetics or absolute hypovolaemia during surgery[2]. Older patients or patients undergoing major surgery are at particular risk of IOH[3].

Hypotension can reduce perfusion of vital organs and result in a mismatch of oxygen delivery and demand[4]. Clinical cohort studies[5,6] have shown an association of IOH with postoperative complications such as acute kidney injury (AKI) and myocardial infarction (MI). A systematic review[7] showed that optimizing perioperative haemodynamics using fluids and vasopressors lowered the incidence of postoperative AKI. However, not all studies have reported an association between IOH and postoperative morbidity[8–10].

A comprehensive review of studies on the effect of IOH on outcome in non-cardiac surgery is currently lacking. The primary aim of this meta-analysis was critically to appraise the association of IOH with postoperative morbidity and mortality in patients undergoing non-cardiac surgery. Secondary aims were to analyse its association with cardiac outcomes, AKI, stroke, delirium, surgical outcomes and combined outcomes.

Methods

This meta-analysis was performed following the MOOSE checklist[11], PRISMA guidelines[12], and methodology outlined in the Cochrane Handbook for systematic reviews[13]. This was a systematic review of risk, testing for the association of exposure with outcome. The study protocol was registered in the Prospero registry (number CRD42017079398). MEDLINE, Embase and Cochrane

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Library databases were searched, with guidance of a clinical librarian, between January 1990 and August 2018. Search terms contained both Medical Subject Headings (MeSH) terms and free text to define patient population (type of surgery), event (IOH), and postoperative outcomes (mortality and morbidity). The complete search strategy is available in *Appendix S1*. Titles, abstracts and full texts were screened independently by two reviewers for relevance, with use of the review program Rayyan[14]. Disagreements were discussed with a third reviewer. Reference lists of the selected articles were examined for additional eligible articles. Studies were included when IOH was incorporated as a predictive variable for postoperative mortality or organ damage in adult patients undergoing elective non-cardiac surgery. Exclusion criteria were non-availability of full texts or language other than English. In case of non-availability, authors were not contacted. Reviews and case reports were excluded. Finally, studies describing IOH in combination with low bispectral index and low minimum alveolar concentration, the so-called 'triple low state'[15,16], were excluded from the review as the effect of hypotension alone could not be studied.

Outcomes

The prespecified primary outcomes were overall morbidity and mortality. Prespecified secondary outcome measures were cardiac adverse outcomes, AKI, neurological outcomes (stroke), delirium, surgical complications such as surgical-site infection or anastomotic leakage, and combined outcomes.

Data extraction

Data were extracted using predefined tables for data collection. Data extraction was done in duplicate. Extracted data consisted of study design, patient characteristics, methods, definition of IOH, type of BP measurement (non-invasive or arterial), and postoperative patient outcomes.

Quality assessment

Critical appraisal was based on the Newcastle–Ottawa Scale (NOS) for cohort studies to assess the quality of non-randomized studies[17]. The NOS is a grading system with scores given for selection (maximum 4 points), comparability (maximum 2 points) and outcome (maximum 3 points), with a highest possible score of 9. Studies with a NOS score greater than 3 were included in the quantitative meta-analysis, to reduce possible bias introduced by low-quality studies.

Meta-analysis

The included studies were analysed in an overall meta-analysis. For each study, only one definition of IOH and one outcome in terms of morbidity or mortality were used in the analysis. Considering that both the predictive variable IOH and the outcome measures morbidity and mortality are dichotomous, data were extracted into 2×2 tables. When studies presented results using multiple definitions of IOH or multiple outcome variables, one of each was selected to be incorporated in the analysis. The selection procedure for the definitions of IOH and outcome variables was predefined and agreed upon by all reviewers without knowledge of the potential effect of their selection on the results.

First, an overview of all IOH definitions and outcomes used in the various articles was done. If more than one definition of hypotension was present in the study, the definition that was used most frequently in all studies was chosen. To illustrate, a MAP of 60 mmHg was used more frequently to define hypotension than a MAP of 50 mmHg, so that when a study reported both, results for MAP of 60 mmHg were extracted.

Second, the same method was applied to select and extract outcome variables. To illustrate, MI was reported more frequently than myocardial injury. Therefore, if a study reported results for both myocardial injury and MI, the MI data were extracted.

Studies were categorized based on postoperative outcomes in the following groups: mortality, cardiac, renal, stroke, delirium, and any postsurgical complication. The postsurgical complication category included all studies that did not fit into the other categories, and included surgical-site infection, postsurgical complications graded according to the Clavien–Dindo classification[18], anastomotic leakage, any postoperative complication and headache.

A random-effects meta-analysis was conducted, using inverse variance weighting to pool studies. Between-study variance (τ) was estimated using the Der Simonian–Laird method. The percentage of the variability in effect estimates between studies that was due to heterogeneity rather than sampling error (chance) was expressed as the I^2 value. To assess possible publication bias, a funnel plot was constructed and inspected visually. Egger's test was performed to test for asymmetry of the funnel plot.

Subgroup analysis

Subgroup analysis, based on severity of hypotension, was performed to evaluate whether the definition of hypotension influenced the association found. Hypotension severity was ranked considering both duration and depth of hypotension. A panel of anaesthetists was used to rank the 29 included definitions of hypotension, starting from the most severe definition. The same rank could be used for different definitions if these definitions were thought to be of equal severity (*Appendix S2*). All questionnaires were collected, recalculated and averaged into a 1–9 scale. Based on this scale, studies were divided into three groups: mild, moderate, and severe hypotension.

Sensitivity analyses

Sensitivity analyses were performed to test the robustness of the association found, with the aim of assessing whether the decisions made during the review process affected the overall odds ratio (OR). Pooled ORs in the sensitivity analyses were inspected visually to assess whether they showed the same direction of association as the result of the primary meta-analysis. If the OR of a sensitivity analysis aligned with that found in the primary meta-analysis, the overall result and conclusions were not influenced by including or excluding particular studies and were thus regarded as robust. Predefined factors for sensitivity analyses were: outcome severity, generalizability of the study population, and methodological quality of the studies.

The outcome severity of each included study was scored based on the Clavien–Dindo classification[18], which provides a validated grading system for the severity of postoperative complications. In this sensitivity analysis, the overall effect in studies with Clavien–Dindo grade IV and V was analysed.

To assess the influence of differences in study sample populations (generalizability) on the association between IOH and postoperative morbidity and mortality, the studies were divided based on the first question (S1) of the NOS scale: 'Representativeness of the exposed cohort'. Studies that were classified as generalizable were selected for the sensitivity analysis.

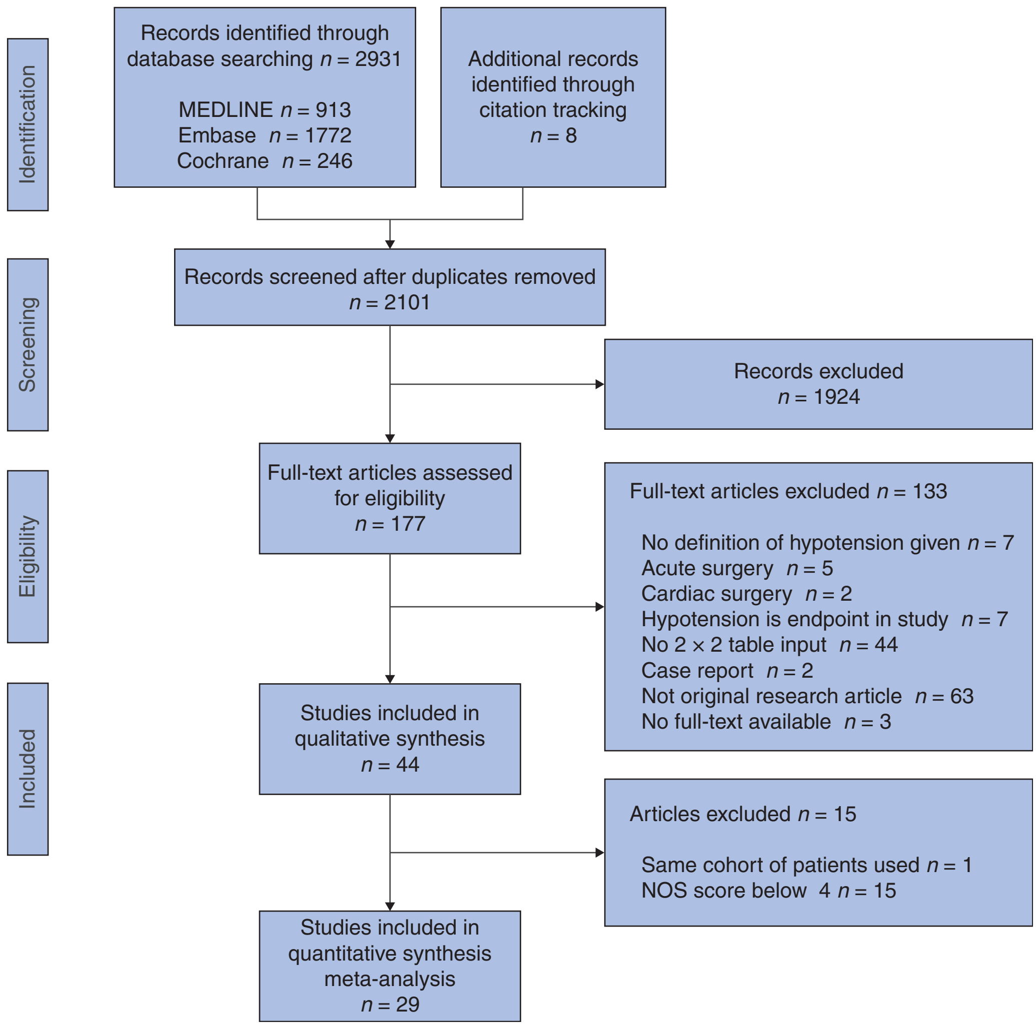

Fig. 1 **PRISMA diagram showing the selection of articles for review**

To assess the influence of study quality on the association between IOH and postoperative morbidity and mortality, studies were divided based on low (NOS score 4–5) or high (NOS score 6–8) study quality. For this sensitivity analysis, high-quality studies were selected. To test ultimately the robustness of the meta-analysis, the studies initially excluded because of low study quality (NOS score below 4) were included in the final sensitivity analysis.

Meta-regression

A meta-regression was performed to account for the heterogeneity in the effect of IOH on postoperative mortality and morbidity. Before the analysis, it was hypothesized that hypotension severity, outcome severity and the generalizability of the patient population accounted for (part of) the heterogeneity. As subgroups based on outcome (primary analysis) and subgroups based on outcome severity have overlapping properties, only outcome severity was included as a factor in the meta-regression. Hypotension severity was assessed as described above. The amount of heterogeneity in the meta-regression was estimated using the maximum likelihood method.

Data analysis was performed using the statistical program R[19,20]. The overall meta-analysis, sensitivity analyses, subgroup analysis and meta-regression were composed using the *meta* package in R.

Results

The initial search in MEDLINE, Embase and the Cochrane Library resulted in 2931 articles. Eight articles were found via citation tracking. Selection based on titles and abstracts resulted in 177 eligible articles. After screening of full texts, 133 articles were excluded. As a result, 44 articles were included in the qualitative synthesis (*Table S1*). Two articles[21,22] used the same cohort of patients; both reported a (similar) secondary analysis of the VISION cohort[23]. As this would introduce an overestimation of the weight of the VISION cohort, the article with the most severe outcome parameter[22] was included. Fourteen articles[24–37] were excluded based on low study quality based on the NOS scale (*Fig. 1*).

Study characteristics

In total, 29 studies[8–10,22,38–62] were included in the meta-analysis, a combined total of 130 862 patients. Mean(s.d.) age was 63(8) years, and 54 per cent of studied patients were men. Of the 29 studies, 25 studied morbidity and four studied mortality. Among the included morbidity studies, one[8] was a case–control study. This study used propensity score matching[63] in a large cohort, resulting in a high study quality. *Table 1* shows the quality of the studies included in the meta-analysis. The different definitions of IOH used are shown in *Fig. S1*.

Table 1 Quality of studies included in the meta-analysis according to the Newcastle–Ottawa Scale

Reference	Year	S1	S2	S3	S4	C	O1	O2	O3	Total NOS score
Babazade *et al.*[10]	2016	1	1	1	1	0	1	0	0	5
Bijker *et al.*[9]	2009	1	1	1	1	1	1	1	1	8
Brinkman *et al.*[38]	2015	0	1	1	1	0	1	0	0	4
Ellis *et al.*[39]	2018	0	1	1	1	0	1	1	1	6
Hallqvist *et al.*[40]	2017	1	1	1	1	0	1	1	1	7
Hallqvist *et al.*[41]	2016	1	1	0	0	0	1	1	1	5
Hirsch *et al.*[42]	2014	1	1	1	1	0	1	1	1	7
Hsieh *et al.*[8]	2016	1	1	1	0	1	1	1	1	7
Kheterpal *et al.*[43]	2009	1	1	1	0	0	0	1	0	4
Marcantonio *et al.*[44]	1998	1	1	1	1	0	1	1	1	7
Matsota *et al.*[45]	2016	1	1	1	1	0	1	0	0	5
McLean House *et al.*[46]	2016	1	1	1	0	0	1	1	0	5
Mizota *et al.*[47]	2017	1	1	1	1	1	1	1	1	8
Monk *et al.*[48]	2015	0	1	1	1	0	1	1	1	6
Patti *et al.*[49]	2011	1	1	0	0	0	1	1	0	4
Post *et al.*[50]	2012	1	1	1	1	0	1	1	0	6
Roshanov *et al.*[22]	2017	1	1	0	1	0	1	1	1	6
Sabate *et al.*[51]	2011	1	1	0	0	0	1	0	1	4
Santiago Lastra *et al.*[52]	2017	0	1	1	0	0	1	1	1	5
Sessler *et al.*[53]	2018	1	1	1	0	0	1	1	1	6
Sun *et al.*[54]	2015	1	1	1	1	0	1	0	0	5
Tallgren *et al.*[55]	2006	0	1	0	1	0	1	1	1	5
Thakar *et al.*[56]	2007	0	1	1	1	0	0	1	1	5
van Waes *et al.*[57]	2016	1	1	1	0	1	1	1	0	6
von Knorring *et al.*[58]	1992	0	1	1	1	0	0	1	1	5
White *et al.*[59]	2016	0	1	0	1	0	1	1	0	4
Xu *et al.*[60]	2015	0	1	1	1	0	1	1	1	6
Yu *et al.*[61]	2018	0	1	1	1	0	1	1	1	6
Ziser *et al.*[62]	1999	0	1	0	0	0	1	1	1	4

S1, representativeness of the exposed cohort; S2, selection of the non-exposed cohort; S3, ascertainment of exposure; S4, demonstrating that outcome of interest was not present at start of study; C, comparability of cohorts on the basis of the design or analysis; O1, assessment of outcome; O2, was follow-up long enough for outcomes to occur; O3, adequacy of follow-up of cohorts. NOS, Newcastle–Ottawa Scale.

Meta-analysis

The meta-analysis showed an overall significant association between IOH and postoperative morbidity and mortality (*Fig. 2*). Associations between IOH and postoperative complications were seen regarding cardiac outcomes (OR 2.44, 95 per cent confidence interval 1.52 to 3.93), AKI (OR 2.69, 1.31 to 5.55) and mortality (OR 1.94, 1.32 to 2.84). An association was found for IOH and the outcome subgroup 'any postsurgical complication' (OR 1.76, 1.04 to 2.98). There was no association between IOH and stroke (OR 0.81, 0.49 to 1.33) or delirium (OR 1.32, 0.47 to 3.71).

Heterogeneity

All studies assessed the effect of IOH on postoperative morbidity or mortality, but study designs varied. Heterogeneity between studies was high (I^2=88 per cent). Visual inspection of the funnel plot showed that, for both larger and smaller studies, negative as well as positive results were published. Egger's test to test for asymmetry in the funnel plot showed that there was no indication of publication bias ($P = 0.106$) (*Fig. 3*).

Subgroup analysis

Table S2 shows the hypotension severity ranking per study. Visual inspection showed that the ORs per subgroup increased with the severity of hypotension (*Fig. S2*). The subgroup of mild hypotension had an overall OR of 1.99 (95 per cent confidence interval 0.52 to 7.69), moderate hypotension had an overall OR of 1.59 (1.23 to 2.07), and severe hypotension had an OR of 2.62 (1.83 to 3.76).

Sensitivity analyses

All four sensitivity analyses indicated that the results of the meta-analysis were robust. *Table S2* gives the Clavien–Dindo grade per study outcome. *Fig. S3* shows that studies with a Clavien–Dindo grade III–V had a pooled association in the same direction as the overall pooled OR in the primary meta-analysis. *Figs S4* and *S5* show that the effect found in this meta-analysis remained when analysing solely studies classified as generalizable and when selecting only studies with the highest study quality.

Fig. S6 demonstrates that including studies with a very low study quality did not alter the overall results.

Meta-regression

Random-effects meta-regression revealed an association between the predefined factors and the amount of heterogeneity in the effect of IOH on postoperative morbidity and mortality. When the hypotension severity scale was included in the meta-regression, heterogeneity was reduced to 75 per cent ($P < 0.001$). *Fig. 4* depicts the association between severity of hypotension and outcome in a bubble plot. Adding the outcome severity scale as a second factor in this meta-regression reduced heterogeneity to 61 per cent ($P<0.001$). Finally, the generalizability of the studies was added to the meta-regression, further reducing the heterogeneity to 50 per cent (*Appendix S3*).

Discussion

IOH was associated with an increased risk of postoperative morbidity and mortality. This effect was most notable in studies with cardiac events, AKI and mortality as endpoints, indicating that these outcomes seem most susceptible to IOH.

These findings are in line with a recently published meta-analysis by Gu and colleagues[64], which showed that IOH alone (compared with the triple low state of IOH with low bispectral index and low minimum alveolar concentration) increased the risk of postoperative mortality and morbidity. However, these authors included only studies published to May 2016, excluding recently published articles. Moreover, they only extracted the results based on the most severe definition of hypotension, which might not provide the most clinically relevant effect estimation.

Wesselink and co-workers[65] performed a systematic review without meta-analysis, including all studies that reported on intraoperative outcome and hypotension, regardless of the possibility of extracting 2×2 tables. These authors reported that the association between IOH and outcome became stronger when the MAP was lower. However, various assumptions were made to translate the severity of different definitions of IOH, leading to debatable results.

Randomized trials are rare because it is difficult to maintain patients in predefined BP, and such trials are costly. Recently, the first RCT[66] studying the effect in 292 patients of IOH on a composite postoperative outcome of systemic inflammatory response syndrome and dysfunction of at least one organ system was published. This trial evaluated the effect of an individualized BP strategy, aiming at a systolic BP within 10 per cent of the patient's resting BP, compared with standard care. The authors reported a reduced risk of organ dysfunction with strict management of BP in patients undergoing abdominal surgery. In line with the results

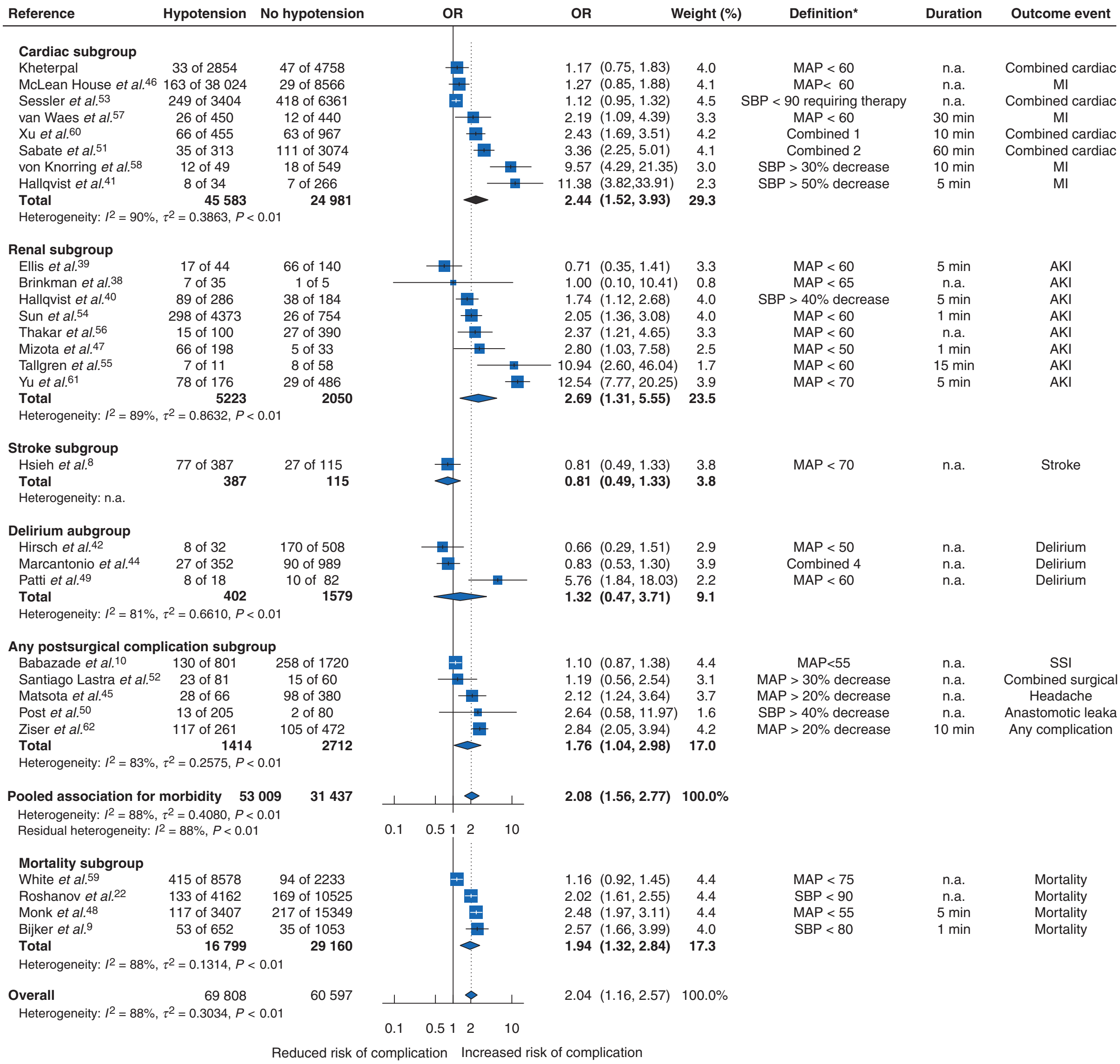

Fig. 2 Forest plot of all included studies

A random-effects model was used for all meta-analyses. Odds ratios (ORs) are shown with 95 per cent confidence intervals. *Units for mean arterial pressure (MAP) are mmHg. MI, myocardial infarction; SBP, systolic BP; SSI, surgical-site infection.

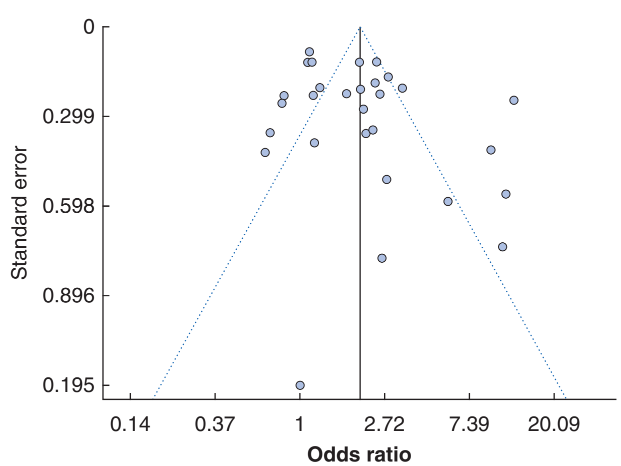

Fig. 3 Funnel plot of all included studies

Egger's test for funnel asymmetry: z=1.62, P=0.106.

of the present meta-analysis, their results stress the importance of the prevention of hypotension during surgery.

IOH was not associated with stroke in this meta-analysis, although only one article[8] reporting on stroke could be included, preventing definitive conclusions from being drawn. Furthermore, the *a priori* risk of postoperative stroke is extremely low, with a reported incidence of 0.1 per cent in non-cardiac, non-neurological surgery[8]. As such, the study might have been underpowered.

IOH was also not associated with delirum. However, a recently published RCT[66] found a significantly lower rate of altered consciousness level in the individualized BP group compared to standard care (5.4 per cent *versus* 15.9 per cent; P = 0.007).

This meta-analysis has provided an overview of the effect of IOH on multiple postoperative outcomes, aggregating all available evidence to date. Despite heterogeneity found between studies, the majority of studies show IOH to be associated with worse postoperative outcomes.

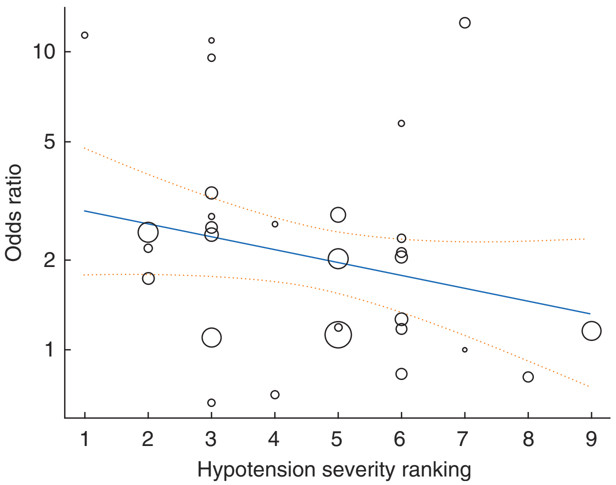

Fig. 4 Meta-regression: bubble plot visually demonstrating a relationship between severity of hypotension and odds ratios found in the 29 included studies

Each bubble represents the odds ratio for an included study. The size of each bubble corresponds with the study weight attributed in the meta-analysis. The regression line denotes the best fit with 95 per cent confidence intervals.

The debate about the importance of blood flow *versus* BP is long-lived. Both flow and pressure are required for adequate delivery of oxygen to tissues[67]. BP is a parameter measured during all operations; blood flow, on the other hand, is rarely measured.

Studies reporting on the effect of IOH on postoperative morbidity and mortality were included in the present review only if a 2×2 table could be constructed. This resulted in the exclusion of some large studies showing a positive association between IOH and outcomes[6,68]. Inclusion of these studies would probably have led to a stronger association between IOH and postoperative outcomes.

Despite this, the inclusion criteria resulted in a relatively large number of included studies and an extensive overall study population. Unfortunately, heterogeneity was high. Studies differed with respect to the chosen definitions of IOH and the reported postoperative outcomes. Definitions of IOH were based mostly on either absolute thresholds, such as MAP and systolic BP, or a relative threshold (a decrease in BP relative to patients' baseline BP). Different definitions of IOH may lead to different associations with adverse postoperative outcomes[1,65,69]. Currently, the intraoperative consensus statement[70] advises that MAP be maintained above the 60–70 mmHg threshold. A universally accepted threshold will facilitate easier comparison between studies in the future.

The sensitivity analyses performed in this study indicated a robust pooled effect of IOH on postoperative outcomes, and a large part of the heterogeneity found in the meta-analysis was explained by a combination of hypotension severity, outcome severity and study population. Despite the fact that articles published in languages other than English were not included in this meta-analysis, the funnel plot and Egger's test revealed no indication of publication bias.

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Supplementary material

Supplementary material is available at *BJS Open* online.

References

1. Bijker JB, van Klei WA, Kappen TH, van Wolfswinkel L, Moons KGM, Kalkman C. Incidence of intraoperative hypotension as a function of the chosen definition: literature definitions applied to a retrospective cohort using automated data collection. *Anesthesiology* 2007;107:213–220
2. Tritapepe L. Hypotension during surgery for high risk patients: cause or consequence of pathology? *Minerva Anestesiol* 2013;79:978–980
3. Cheung CC, Martyn A, Campbell N, Frost S, Gilbert K, Michota F *et al.* Predictors of intraoperative hypotension and bradycardia. *Am J Med* 2015;128:532–538
4. Harten J KJ. Perioperative optimisation. *Scot Med J* 2004;49:6–9
5. Sharma SK, McCauley J, Cottam D, Mattar SG, Holover S, Dallal R *et al.* Acute changes in renal function after laparoscopic gastric surgery for morbid obesity. *Surg Obes Relat Dis* 2006;2:389–392
6. Salmasi V, Maheshwari K, Yang D, Mascha EJ, Singh A, Sessler DI *et al.* Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after noncardiac surgery. *Anesthesiology* 2017;126:47–65
7. Brienza N, Giglio MT, Marucci M, Fiore T. Does perioperative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study. *Crit Care Med* 2009;37:2079–2090
8. Hsieh JK, Dalton JE, Yang D, Farag ES, Sessler DI, Kurz AM. The association between mild intraoperative hypotension and stroke in general surgery patients. *Anesth Analg* 2016;123:933–939
9. Bijker JB, van Klei WA, Vergouwe Y, Eleveld DJ, van Wolfswinkel L, Moons KGM *et al.* Intraoperative hypotension and 1-year mortality after noncardiac surgery. *Anesthesiology* 2009;111:1217–1226
10. Babazade RH, Yilmaz O, Nicole M, Stocchi L, Gorgun E, Kessler H *et al.* Association between intraoperative low blood pressure and development of surgical site infection after colorectal surgery. *Ann Surg* 2016;264:1058–1064
11. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA* 2000;283:2008–2012
12. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:2700
13. Higgins JPT, Green S (eds). Cochrane Handbook for Systematic Reviews of Interventions. Copenhagen: The *Cochrane Collaboration*, 2017

14. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. *Syst Rev* 2016;5:210
15. Kertai MD, White WD, Gan TJ. Cumulative duration of 'triple low' state of low blood pressure, low bispectral index, and low minimum alveolar concentration of volatile anesthesia is not associated with increased mortality. *Anesthesiology* 2014;121: 18–28
16. Sessler DI, Sigl JC, Kelley SD, Chamoun NG, Manberg PJ, Saager L *et al.* Hospital stay and mortality are increased in patients having a triple low of low blood pressure, low bispectral index, and low minimum alveolar concentration of volatile anesthesia. *Anesthesiology* 2012;116:1195–1203
17. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M *et al.* The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2017. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed 14 February 2019)
18. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;240:205–213
19. R Core Team, R *Foundation for Statistical Computing*. R: A Language and Environment for Statistical Computing. https://www.R-project.org/ (accessed 31 December 2018)
20. Stiglic G, Watson R, Cilar L. R you ready? Using the R programme for statistical analysis and graphics. *Res Nurs Health* 2019;42: 494–499
21. Abbott TEF, Pearse RM, Archbold RA, Ahmad T, Niebrzegowska E, Wragg A *et al.* A prospective international multicentre cohort study of intraoperative heart rate and systolic blood pressure and myocardial injury after noncardiac surgery: results of the VISION study. *Anesth Analg* 2018;126:1936–1945
22. Roshanov PS, Rochwerg B, Patel A, Salehian O, Duceppe E, Belley-Cote EP *et al.* Withholding *versus* continuing angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers before noncardiac surgery: an analysis of the vascular events in noncardiac surgery patients cohort evaluation prospective cohort. *Anesthesiology* 2017;126:16–27
23. Devereaux PJ, Biccard BM, Sigamani A, Xavier D, Chan MTV, Srinathan S *et al.* Association of postoperative high-sensitivity troponin levels with myocardial injury and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* 2017;317: 1642–1651
24. Charlson ME, MacKenzie CR, Gold JP, Ales KL, Topkins M, Shires GT. Risk for postoperative congestive heart failure. *Surg Gynecol Obstet* 1991;172:95–104
25. Pipanmekaporn T, Punjasawadwong Y, Charuluxananan S, Lapisatepun W, Bunburaphong P, Patumanond J *et al.* Incidence of and risk factors for cardiovascular complications after thoracic surgery for noncancerous lesions. *J Cardiothorac Vasc Anesth* 2014;28:960–965
26. Barone JE, Bull MB, Cussatti EH, Miller KD, Tucker JB. Perioperative myocardial infarction in low-risk patients undergoing noncardiac surgery is associated with intraoperative hypotension. *J Intensive Care Med* 2002;17:250–255
27. Sposato LA, Suarez A, Jauregui A, Riccio PM, Altounian M, Andreoli MG *et al.* Intraoperative hypotension, new onset atrial fibrillation, and adverse outcome after carotid endarterectomy. *J Neurol Sci* 2011;309:5–8
28. Yang L, Sun DF, Han J, Liu R, Wang LJ, Zhang ZZ *et al.* Effects of intraoperative hemodynamics on incidence of postoperative delirium in elderly patients: a retrospective study. *Med Sci Monit* 2016;22:1093–1100
29. Duane DT, Howard SJ, Kraayenbrink M. Incidence and predictors of bulbar palsy after surgery for acoustic neuroma. *J Neurosurg Anesthesiol* 1997;9:263–268
30. Guarino M, Stracciari A, Di Alessandro R, Borghi A, Gardella E, Pazzaglla P *et al.* A prospective study on the neurological complications after liver transplantation. *Gastroenterol Int* 1999;12: 140–145
31. Xu X, Ling Q, Wei Q, Wu J, Gao F, He ZL *et al.* An effective model for predicting acute kidney injury after liver transplantation. *Hepatobiliary Pancreat Dis Int* 2010;9:259–263
32. Li Q, Yao G, Ge Q, Yi M, Gao J, Xi Z. Relevant risk factors affecting time of ventilation during early postoperative period after orthotopic liver transplantation. *J Crit Care* 2010;25:221–224
33. Lauterio A, Di Sandro S, Gruttadauria S, Spada M, Di Benedetto F, Baccarani U *et al.* Donor safety in living donor liver donation: an Italian multicenter survey. *Liver Transpl* 2017;23:184–193
34. Chen Y, He L, Qu W, Zhang C. Predictors of intraoperative pressure injury in patients undergoing major hepatobiliary surgery. *J Wound Ostomy Continence Nurs* 2017;44:445–449
35. Balci MK, Vayvada M, Salturk C, Kutlu CA, Ari E. Incidence of early acute kidney injury in lung transplant patients: a single-center experience. *Transpl Proc* 2017;49:593–598
36. Chen X, Ding X, Shen B, Teng J, Zou J, Wang T *et al.* Incidence and outcomes of acute kidney injury in patients with hepatocellular carcinoma after liver transplantation. *J Cancer Res Clin Oncol* 2017;143:1337–1346
37. Vasivej T, Sathirapanya P, Kongkamol C. Incidence and risk factors of perioperative stroke in noncardiac, and nonaortic and its major branches surgery. *J Stroke Cerebrovasc Dis* 2016;25: 1172–1176
38. Brinkman R, HayGlass KT, Mutch WA, Funk DJ. Acute kidney injury in patients undergoing open abdominal aortic aneurysm repair: A pilot observational trial. *J Cardiothorac Vasc Anesth* 2015; 29:1212–1219
39. Ellis RJ, Del Vecchio SJ, Kalma B, Lim Ng K, Morais C, Francis RS *et al.* Association between preoperative hydration status and acute kidney injury in patients managed surgically for kidney tumours. *Int Urol Nephrol* 2018;50:1211–1217
40. Hallqvist L, Granath F, Huldt E, Bell M. Intraoperative hypotension is associated with acute kidney injury in noncardiac surgery. *Eur J Anaesthesiol* 2017;34:1–7
41. Hallqvist L, Martensson J, Granath F, Sahlen A, Bell M. Intraoperative hypotension is associated with myocardial damage in noncardiac surgery. *Eur J Anaesthesiol* 2016;33:450–456
42. Hirsch J, DePalma G, Tsai TT, Sands LP, Leung JM, Impact of intaoperative hypotension and blood pressure fluctuations on early postoperative delirium after non-cardiac surgery. *Br J Anaesth* 2015;115:418–426
43. Kheterpal S, O'Reilly M, Englesbe MJ *et al.* Preoperative and intraoperative predictors of cardiac adverse events after general, vascular and urological surgery. *Anesthesiology* 2009; 110:58–66
44. Marcantonio ER, Goldman L, Orav EJ, Cook EF, Lee TH. The association of intraoperative factors with the development of postoperative delirium. *Am J Med* 1998;105:380–384
45. Matsota PK, Christodoulopoulou TC, Batistaki CZ, Arvaniti CC, Voumvourakis KI, Kostopanagiotou GG. Factors associated with the presence of postoperative headache in elective surgery patients: a prospective single center cohort study. *J Anesth* 2017; 31:225–236
46. House McLean, Marolen KN, St Jacques PJ, McEvoy MD, Ehrenfeld JM. Surgical Apgar score is associated with

myocardial injury after noncardiac surgery. *J Clin Anesth* 2016;34:395–402

47. Mizota T, Hamada M, Matsukawa S, Seo H, Tanaka T, Segawa H. Relationship between intraoperative hypotension and acute kidney injury after living donor liver transplantation: A retrospective analysis. *J Cardiothoracic Vasc Anesth* 2017;31:582–589
48. Monk TG, Bronsert MR, Henderson WG *et al.* Association between intraoperative hypotension and hypertension and 30-day postoperative mortality in noncardiac surgery. *Anesthesiology* 2015;123:307–319
49. Patti R, Saitta M, Cusumano G, Termine G, Di Vita G. Risk factors for postoperative delirium after colorectal surgery for carcinoma. *Eur J Oncol Nurs* 2011;15:519–523
50. Post IL, Verheijen PM, Pronk A, Siccama I, Houweling PL. Intraoperative blood pressure changes as a risk factor for anastomotic leakage in colorectal surgery. *Int J Colorectal Dis* 2012;27:765–772
51. Sabate S, Mases A, Guilera N *et al.* Incidence and predictors of major perioperative adverse cardiac and cerebrovascular events in non-cardiac surgery. *Br J Anaesth* 2011;107:879–890
52. Santiago-Lastra Y, Mathis MR, Andraska E *et al.* Extended case duration and hypotension are associated with higher-grade postoperative complications after urinary diversion for non-oncological disease. *Urology* 2017;111:189–196
53. Sessler DI, Meyhoff CS, Zimmerman NM *et al.* Period-dependent associations between hypotension during and for four days after noncardiac surgery and a composite of myocardial infarction and death: a substudy of the POISE-2 Trial. *Anesthesiology* 2018;128:317–327
54. Sun LY, Wijeysundera DN, Tait GA, Beattie WS. Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. *Anesthesiology* 2015;123:515–523
55. Tallgren M, Niemi T, Poyhia R *et al.* Acute renal injury and dysfunction following elective abdominal aortic surgery. *Eur J Vasc Endovasc Surg* 2007;33:550–555
56. Thakar CV, Kharat V, Blanck S, Leonard AC. Acute kidney injury after gastric bypass surgery. *Clin J Am Soc Nephrol* 2007;2:426–430
57. van Waes JA, van Klei WA, Wijeysundera DN, van Wolfswinkel L, Lindsay TF, Beattie WS. Association between intraoperative hypotension and myocardial injury after vascular surgery. *Anesthesiology* 2015;124:35–44
58. von Knorring J, Lepantalo M, Lindgren L, Lindfors O. Cardiac arrhythmias and myocardial ischemia after thoracotomy for lung cancer. *Ann Thorac Surg* 1992;53:642–647
59. White SM, Moppet IK, Griffiths R *et al.* Secondary analysis of outcomes after 11 085 hip fracture operations from the prospective UK Anaesthesia Sprint Audit of Practice (ASAP-2). Anaesthesia 2016;71:506–514
60. Xu L, Yu C, Jiang J *et al.* Major adverse cardiac events in elderly patients with coronary artery disease undergoing noncardiac surgery: a multicenter prospective study in China. *Arch Gerontol Geriatr* 2015;61:503–509
61. Yu J, Keun Park H, Kwon H *et al.* Risk factors for acute kidney injury after percutaneous nephrolithotomy: implications of intraoperative hypotension. *Medicine (Baltimore)* 2018;97:e11580
62. Ziser A, Plevak DJ, Wiesner RH, Rakela J, Offord KP, Brown DL. Morbidity and mortality in cirrhotic patients undergoing anesthesia and surgery. *Anesthesiology* 1999;90:42–53
63. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011;46:399–424
64. Gu WJ, Hou BL, Kwong JSW, Tian X, Qian Y, Cui Y *et al.* Association between intraoperative hypotension and 30-day mortality, major adverse cardiac events, and acute kidney injury after non-cardiac surgery: a meta-analysis of cohort studies. *Int J Cardiol* 2018;258:68–73
65. Wesselink EM, Kappen TH, Torn HM, Slooter AJC, van Klei WA. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. *Br J Anaesth* 2018;121:706–721
66. Futier E, Lefrant JY, Guinot PG, Godet T, Lorne E, Cuvillon P *et al.* Effect of individualized *vs* standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery: a randomized clinical trial. *JAMA* 2017;318:1346–1357
67. Pinsky MR. Both perfusion pressure and flow are essential for adequate resuscitation. *Sepsis* 2000;4:143–146
68. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN *et al.* Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. *Anesthesiology* 2013;119:507–515
69. Vernooij LM, van Klei WA, Machina M, Pasma W, Beattie WS, Peelen LM. Different methods of modelling intraoperative hypotension and their association with postoperative complications in patients undergoing non-cardiac surgery. *Br J Anaesth* 2018;120:1080–1089
70. Sessler DI, Bloomstone JA, Aronson S, Berry C, Gan TJ, Kellum JA *et al.* Perioperative quality initiative consensus statement on intraoperative blood pressure, risk and outcomes for elective surgery. *Br J Anaesth* 2019;122:563–574