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Tight perioperative blood pressure management to reduce complications: a randomized pilot study

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ABSTRACT

- **Objective:** The pilot study is planned to evaluate a strategy feasible and practical to prevent perioperative hypotension for a full trial.
- **Design:** A prospective, single-centre, double-blinded, randomized-controlled pilot trial.
- **Setting:** We included patients in tertiary university hospital whereas our planned full trial will involve dozens of centers around the world.
- **Participants:** This trial included 80 adult patients scheduled for non-cardiac surgery.
- **Interventions:** In patients randomized to tight blood pressure (BP) control, intraoperative mean arterial pressure (MAP) was targeted to ≥85 mmHg maintained with norepinephrine infusion, and chronic antihypertensive medications was delayed until the third postoperative day. Routine BP management was with some expected intraoperative hypotension and immediately restart antihypertensive medications.
- **Primary and secondary outcome measures:** High-sensitivity troponin I and creatinine were evaluated preoperatively and daily for the initial three postoperative days. Primary outcomes were fraction of time, area under curve and time weighted average of intraoperative and postoperative hypotension. Secondary outcomes was the time antihypertensive medications were restarted after surgery.
- **Keywords:** Anesthesia, blood pressure, perioperative management, myocardial injury after non-cardiac surgery, myocardial infarction, acute kidney injury, delirium.
- **Results:** Forty patients in each group were analyzed.The median for intraoperative area of MAP >85 mmHg was 1303 [772-2419] mmHg*min in routine BP cases and 2425 [1926- 3545] mmHg*min in tight BP control. The area for intraoperative MAP <65 mmHg was 7 [0-40] mmHg*min with routine BP management, and 0 [0-0] mmHg*min with tight BP control. Antihypertensive medications were restarted 2 [1 to 3] days later in tight BP control cases. However, postoperative systolic pressures were similar.
- **Conclusions:** Tight BP management markedly increased intraoperative MAP and reduced the amount of hypotension. In contrast, delaying chronic antihypertensive medications had little effect on postoperative systolic pressure. The full trial appears feasible and remains necessary.

- **Trial registration:** www.clinicaltrials.gov (NCT04789733).

Strengths and limitations of this study

We achieved excellent separation of intraoperative mean arterial pressures from the preliminary results.
Tight BP management markedly increased intraoperative MAP and reduced the amount of hypotension and the full trial appears feasible and remains well warranted.
This was conducted in a single center whereas our planned full trial will involve dozens of centers around the world.
Our results demonstrating that BP management is feasible does not mean that it will prove practical at all trial sites.

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INTRODUCTION

Mortality in the 30 days after surgery is more than 100 times higher than intraoperative mortality.[1] Myocardial injury and associated vascular complications are among the leading causes of postoperative mortality.[2] Intraoperative hypotension is associated with myocardial injury after non-cardiac surgery (MINS) and myocardial infarction (MI), with the apparent harm threshold being a mean arterial pressure (MAP) ≈ 65 mmHg.[3, 4] Furthermore, postoperative hypotension is associated with myocardial infarction even after adjustment for intraoperative hypotension.[5]
The harm threshold for perioperative acute kidney injury (AKI) also appears to be a mean arterial pressure (MAP) near 65 mmHg.[6] Perioperative hypotension is also associated with delirium and cognitive decline,[7, 8] although inconsistently.[9] Furthermore, cumulative duration of MAP less than 50, 55, 60, 70, and 80 mmHg appear associated with increased odds of 30-day mortality after noncardiac surgery is reported in a retrospective cohort.[4] Hypotension prevention may therefore be a modifiable factor that reduces postoperative cardiovascular and perfusion related complications.
There is currently sparse evidence that the associations observed between hypotension and myocardial and renal injury are casual. A small randomized trial (n=292) reports that preventing intraoperative hypotension reduces the risk of major complications by 25%.[10] In contrast, a 458-patient randomized trial demonstrated no improvement with tight intraoperative blood pressure control.[11] Limited randomized data (n=199) also suggests that hypotension causes delirium.[12]
A robust trial remains necessary to characterize the potential benefits of reducing perioperative hypotension in high-risk patients. We therefore plan a multi-national randomized trial to test the primary hypothesis that perioperative hypotension prevention in high-risk patients reduces a composite of perfusion-related complications in the 30 days after major non-cardiac surgery. In anticipation of the full trial, we conducted a pre-planned pilot trial — reported here — designed to evaluate feasibility, especially the ability to target blood pressure per protocol.

METHODS AND ANALYSIS: PARTICIPANTS, INTERVENTION, AND OUTCOMES

Study design

This single-center trial was performed in China-Japan Union Hospital of Jilin University (Jilin, China). The study was approved by the Institutional Review Board (IRB #20201120) on November 30, 2020 and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at clinicaltrials.gov (NCT04789733, named as The GUARDIAN Pilot Trial, Principal investigator: K.L.).

Inclusion criteria

Major inclusion criteria were age ≥45 years; noncardiac surgery expected to last at least 2 hours; overnight hospitalization; ASA physical status 2-4; chronically taking at least one anti-hypertensive medication; and expected to have an arterial catheter.

Exclusion criteria

Participants were also required to have at least one of following risk factors: 1) history of peripheral arterial surgery; 2) history of coronary artery disease; 3) history of stroke or transient ischemic attack; 4) serum creatinine >175 μmol/L (>2.0 mg/dl); 5) diabetes requiring medication; 6) current smoking or 15 pack-year history of smoking tobacco; 7) scheduled for major vascular surgery; 8) body mass index ≥ 35 kg/m2; 9) preoperative high-sensitivity troponin T >14 ng/L or troponin I equivalent; or 10) B-type natriuretic protein (BNP) >80 ng/L or N-terminal B-type natriuretic protein (NT-proBNP) >100 ng/L.

Patients were excluded when they were scheduled for carotid artery surgery, intracranial surgery, partial or complete nephrectomy, pheochromocytoma surgery or liver transplantation. Patients were similarly excluded if they had a condition that precluded routine or tight blood pressure management or had end-stage renal disease. And finally, we also excluded patients with dementia or impairments that might compromise cognitive assessments.

Randomization and masking

Participants were randomly allocated using computer-generated assignments to tight or routine pressure management in a 1:1 ratio without stratification in a block size of four by an independent statistician (D.S.Y) using SAS 9.2 software (SAS Institute, USA). Allocation was concealed within sealed opaque envelopes until shortly before anesthesia induction.

Intervention

The original protocol is detailed in Supplemental Text Document. No changes were made before trial data were accessed. This manuscript adheres to the applicable CONSORT guidelines.

The pilot trial was designed to inform a future pivotal trial by considering two co-primary feasibility hypotheses. First that there is suitable statistical significant separation of intraoperative and postoperative blood pressure across two blood pressure management strategies (intraoperative MAP maintained ≥ 85 mmHg and postoperative tight pressure control versus routine care with some hypotension expected). And second, that restarting routine antihypertensive medications per protocol is feasible (restart delayed until the third postoperative day versus immediate restart). We also consider the exploratory efficacy hypothesis that perfusion-related complications and delirium are reduced by tight perioperative blood pressure control.

In patients assigned to tight pressure management, angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) were not given the morning of surgery. A norepinephrine peripherally intravenous infusion was adjusted to maintain intraoperative MAP ≥ 85 mmHg. General anesthesia was induced and maintained per routine , .Fluid administration and blood transfusion were also per clinical judgement. Resumption of chronic anti-hypertensive medications was delayed until the third postoperative day unless deemed necessary to treat hypertension or for another clinical indication.

In patients assigned to routine pressure management, routinely used ACEIs and ARBs were given the morning of surgery if deemed appropriate by the attending anesthesiologist. General anesthesia was induced and maintained per routine. Fluid administration and blood transfusion were also per clinical judgement. Intraoperative pressure management was per routine. As usual, chronic anti-hypertensive medication was restarted shortly after surgery unless contraindicated by hypotension.

Blinding

Randomization and group assignment were performed by an investigator (K.L) who did not participate in perioperative care or data collection. Anesthesiologists who were responsible for anesthetic management were not involved in trial follow up. Investigators (H.Z.T, L.W.Y) who performed postoperative follow-up and patients were masked to study group assignment. The trial was thus assessor blinded.

Data collection

The required data will be collected by trained research staff, recorded in paper based case report forms (CRFs) and then stored into Excel digital forms. Assessors will conduct the follow-up procedures in person.

Measurements

Intraoperative pressures from the required arterial catheter were automatically recorded in our electronic anesthesia records at 1-minute intervals. Typically, postoperative pressures were measured oscillometrically at 8-hour intervals.

For perfusion-related complications, we considered a collapsed (one or more) composite of myocardial injury, stroke, non-fatal cardiac arrest, Stage 2-3 acute kidney injury defined by the creatinine component of the Kidney Disease: Improving Global Outcomes (KIDGO) definition, deep or organ-space infection, sepsis, and all-cause mortality within 30 days of surgery. We required high-sensitivity troponin I and creatinine preoperatively and daily for

the initial three postoperative days.

Myocardial injury after non-cardiac surgery was defined as troponin I exceeding the local 99th percentile (0.04 ng/L).[13] Strokes were detected based on clinical symptoms and required radiographic evidence consistent with new-onset cerebral ischemic or hemorrhagic injury. Delirium was assessed between 7-10 AM and again between 5-8 PM by 3D-CAM for the initial four postoperative days while patients remain hospitalized,[14] with any positive assessment being considered evidence of delirium.

Primary outcomes

The first co-primary outcome was the fraction of time when intraoperative MAP was >85 mmHg, intraoperative area of MAP >85 mmHg, and intraoperative area of MAP <65 mmHg.

Secondary outcomes

The second co-primary outcome was postoperative blood pressure management, characterized by the time routine antihypertensive medications were restarted after surgery.

The secondary feasibility outcome measures were time-weighted average (TWA) intraoperative MAP, cumulative minimum MAP for 10 minutes, average postoperative systolic blood pressure (SBP), and mean of the lowest 3 postoperative SBPs. Post-hoc, we also defined the measures intraoperative area over MAP >80 mmHg and area of MAP <60 mmHg as additional secondary outcomes.

The exploratory efficacy outcome measures were: 1) perfusion-related complications within 30 days of surgery; and 2) postoperative delirium within the first 4 postoperative days.

Data and sample storage

All relevant clinical trial materials will be saved for at least 3 years after termination of the trial. The investigators and statistician have access to the whole data set.

Data monitoring

Due to the low-risk of the intervention, Data Monitoring Committee is not considered necessary in our study.

Protocol changes

No changes were made before trial data were accessed. Any important protocol modifications such as sample size will be communicated to relevant parties.

Power calculation

The study enrolled 40 patients in each treatment group. Design analysis for the study was done after patients were enrolled, but before data were accessed.

The fraction of time spent above 85 mmHg was assumed to be distributed as Beta (5, 5) and with the above sample size, the confidence interval half-width for estimating the mean would be 0.05 which was deemed to be sufficiently precise. The beta distribution was appropriate as the outcome was restricted to the closed interval between 0 and 1. The observed confidence

interval widths were 0.01.

Area of MAP <65 mmHg is typically heavily positively skewed. Using the same sample size as above, we assumed that area of MAP <65 mmHg would be distributed as Gamma (0.25, 0.1) which would give us a confidence interval half-width of 0.73. This was deemed to be sufficiently precise for estimation of the median area of MAP <65 mmHg. The observed CI half-widths were 8.6 [reference group] and 0 [treatment group].

Statistical analysis

Balance on baseline characteristics was assessed using absolute standardized difference (ASD), which is defined as the absolute difference in means, ranks, or proportions divided by the pooled standard deviation. Groups were considered to be imbalanced with respect to a baseline characteristic when ASD exceeded 0.44 [1.96*sqrt(1/n1 + 1/n2)].[15]

We primarily evaluated the effect of tight blood pressure control on the fraction of time when intraoperative MAP exceeded 85 mmHg using a t-test. Wilcoxon rank-sum tests were used to evaluate the effect of tight perioperative BP control on intraoperative area of MAP >85 mmHg, intraoperative area of MAP <65 mmHg, and time to restart routine antihypertensive medications after surgery.

We also evaluated the effect of tight blood pressure control on intraoperative area of MAP >80 mmHg, and intraoperative area of MAP <60 mmHg using Wilcoxon rank-sum tests. We used two-sided, two-sample t-tests to evaluate the effect of blood pressure control on time-weighted average intraoperative mean arterial pressure, cumulative minimum MAP for 10 minutes, time weighted average SBP, and mean of the lowest 3 postoperative SBPs. On an exploratory bases, we used log-binomial models to evaluate a collapsed composite of perfusion-related complications, and postoperative delirium.

All analyses were conducted using R 4.0.2.

Patient and public involvement

There was no patient involved.

Ethics and dissemination:

The protocol was approved by The Ethics Committee of the China-Japan Union Hospital of Jilin University, Changchun, China, (Chairperson Prof. Songyan Liu) on 28 June 2022. (Approval number: 20201120). The study was approved by the Institutional Review Board (IRB #20201120) on November 30, 2020 and written informed consent was obtained from all subjects participating in the trial.

Preliminary result

Between May 23, 2021, and September 29, 2021, 9618 cases were screened, and 393 were deemed eligible. Two-hundred and ninety cases were preferentially introduced and enrolled by another trial. A total of 103 patients were approached and 80 cases were consented. Forty patients were randomized to tight pressure management and 40 were randomized to routine pressure management. No patients withdrew before hospital discharge. Our CONSORT flow diagram is presented in Figure 1. Three patients assigned to tight pressure management were lost between discharge and the 1-month follow-up assessment. There were thus 80 patients

included in final analysis (K.S). The last patient follow-up was completed on November 1, 2021.

Patient demographic and baseline characteristics are presented in Table 1. Only diastolic blood pressure (DBP) and surgery type were imbalanced, with ASD >0.44.

Table 1. Baseline patient and demographic characteristics

Characteristic	Routine perioperative BP control	Tight perioperative BP management	ASD
	N=40	*N=40*	
Age	68(10)	67(10)	0.12
Height - cm	166(8)	165(8)	0.06
Weight - kg	66(12)	71(16)	0.28
SBP	142 (18)	148(21)	0.31
DBP	80 (10)	86(10)	0.67*
Surgery Type			0.66*
Abdominal	23 (58%)	18 (45%)	
Gynecologic	0 (0)	1 (2%)	
Neurosurgical	2 (5%)	6 (15%)	
Orthopedic	6 (15%)	3 (8%)	
Thoracic	7 (18%)	12 (30%)	
Thoracic and abdominal	1 (2%)	0 (0)	
Urology	1 (2%)	0 (0)	
Smokers	8 (20%)	6 (15%)	0.13

Data are presented as means (SD)s or n (%) as appropriate.
*ASD – Absolute Standardized Difference; *ASD > 0.44 indicates imbalance.*

The mean(SD) fraction of time with intraoperative MAP exceeding 85 mmHg (i.e., time when MAP >85 mmHg divided by total surgery duration) was 0.52(0.25) in patients assigned to routine blood pressure management and 0.87(0.15) in those assigned to tight control. The estimated absolute difference in the mean fraction of time between tight and routine blood pressure management was 0.35 [0.26 to 0.44].

The median intraoperative area of MAP >85 mmHg was 1303 [772-2419] mmHg*min in patients assigned to routine perioperative BP control and 2425 [1926- 3545] mmHg*min in those assigned to tight perioperative BP management (Figure 2). Tight blood pressure control increased area of MAP >85 mmHg by 1102 [596 to 1608] mmHg*min. Similarly, for intraoperative area of MAP <65 mmHg, the median was 7 [0-40] mmHg*min with routine pressure management, and 0 [0-0] mmHg*min with tight control (Figure 3). Tight pressure

control thus reduced exposure to MAP <65 mmHg by 6 [2 to 15] mmHg*min. In the routine pressure management group, 40% (n = 16) of the patients experienced hypotension (any time below 65 mmHg) with a median duration of 6 [2-9] minutes compared to 10% (n = 4) in the tight blood pressure control group, with a median durat-ion of 5 [4-6] minutes (Figure 4).

The median intraoperative area of MAP >80 mmHg was 1917 [1249- 3169] mmHg*min in patients assigned to routine BP control and 3355 [2549-4417] mmHg*min in the patients assigned to tight BP control. The area of MAP >80 mmHg was thus 1335 [667 to 1928] mmHg*min greater in patients assigned to tight pressure control. For intraoperative area of MAP <60 mmHg, the median was 0 [0-6] mmHg*min with routine pressure management and 0 [0-0] mmHg*min with tight pressure control, for an estimated treatment effect of 0 [0 to 0] (Table 2).

Table 2. Summary of analysis results.

Outcome	**Routine BP Management*** ***N = 40***	**Tight Perioperative BP Control*** ***N = 40***	**Estimated treatment effect [95% CI]**
Primary Outcomes			
Fraction of intraoperative period with MAP >85 mmHg	0.52(0.25)	0.87(0.15)	0.35 [0.26 to 0.44]**
Area of intraoperative MAP >85 mmHg (mmHg*min)	1303 [772-2419]	2425 [1926- 3545]	1102 [596 to 1608]***
Area of intraoperative MAP ≤65 mmHg (mmHg*min)	7 [0-40]	0 [0-0]	-6 [-15 to -2]***
Time to restart antihypertensive medications (days)	1 [1-1]	4 [3-4]	2 [1 to 3]***
Secondary Outcomes			
Area of intraoperative MAP >80 mmHg (mmHg*min)	1917 [1249- 3169]	3355 [2549-4417]	1335 [667 to 1928]**
Area of intraoperative MAP ≤60 mmHg (mmHg*min)	0 [0-6]	0 [0-0]	0 [0 to 0]**
Time-weighted average intraoperative MAP (mmHg)	89(9)	101(8)	12 [8 to 16]***

Minimum intraoperative MAP sustained for 10 cumulative minutes (mmHg)	71(9)	85(9)	14 [11 to 18]***
Mean postoperative systolic pressure (mmHg)	133(15)	138(13)	5 [-1 to 11]***
Mean of 3 lowest postoperative systolic pressures [mmHg]	122(14)	127(14)	5 [-1 to11]***

*Data presented as means (SD) or medians [IQR]
** Difference in means and 95% CI
*** Hodges Lehmann shift estimator

The difference in the intraoperative TWA MAP between tight and routine pressure management was 12 [8 to 16] mmHg, and the difference in cumulative intraoperative minimum MAP sustained for 10 minutes was 14 [11 to 18] mmHg. (Supplemental Figure 1; Table 2).

Antihypertensive medications were restarted 2 [1 to 3] days later in patients assigned to tight blood pressure control. The difference in postoperative mean SBP between tight and routine pressure management was 5 [-1 to 11] mmHg, and the difference in mean of the lowest 3 postoperative SBP measurements was also 5 [-1 to 11] mmHg (Supplemental Figure 2; Table 2).

The incidence of perfusion related complications was 12% in both groups and the relative risk was estimated to be 1.0 [0.3 to 3.3]. No delirium was detected in either group. No severe adverse events were attributed to the study.

DISCUSSION

Intraoperative blood pressure management was excellent in patients assigned to tight control titrated with norepinephrine intravenous infusion, and MAP exceeded the target of 85 mmHg 87% of the time. Furthermore, the average of the lowest mean arterial pressures sustained for ten minutes in the tight group was 85 mmHg, indicating that mean arterial pressures in these patients was only rarely and transiently less than 85 mmHg. Intraoperative pressures also exceeded 85 mmHg about half the time in patients assigned to routine management which is unsurprising since hypertension was an inclusion criterion for the trial.

Because patients cannot be randomized to hypotension, the more important question is the extent to which pressures were <65 mmHg, which is thought to be the intraoperative harm threshold, with routine management.3 Unsurprisingly, there was almost no hypotension in patients assigned to tight control whereas the median area <65 mmHg was 7 mmHg*min in those with routine management. Furthermore, the lowest mean arterial pressures sustained for ten minutes in patients assigned to routine management was 71(9) mmHg, and about 40% had lowest sustained pressures ≤65 mmHg. There were thus distinct differences in mean arterial pressures in the two management groups, with one having virtually no hypotension and the other often experiencing mean pressures ≤65 mmHg.

Antihypertensive management was successful with the mean restart day being 1 with routine management and 4 with tight management, corresponding to a difference of 2 [95% CI: 1 to 3] days which is a clinically meaningful difference. However, antihypertensive management had little effect on postoperative systolic pressures, with the lowest three measurements differing by only 5 mmHg. Furthermore, the average lowest measurements exceeded 120 mmHg which is well above proposed postoperative harm threshold defined either by a mean arterial pressure of 75 mmHg[16] or a systolic pressure of 90 mmHg.[5]

Previous studies report considerably more postoperative hypotension than we observed. For example, Liem reported that 2 cumulative hours below threshold of 60 mmHg occurred in 8% patients and 4 continuous hours less than 75 mmHg occurred in 48% patients.[16] Khanna and colleagues similarly reported that 63% of patients experienced a MAP ≤75 mmHg within 48 hours after surgery, and that 22% experienced MAP ≤65 mmHg.[17] However, there were two important differences between our trial and previous observational reports. The first is that both previous reports were based on continuous noninvasive blood pressure monitoring rather than oscillometric assessments at 8-hour intervals. Continuous monitoring will obviously detect more hypotension than intermittent monitoring. Furthermore, continuous non-invasive monitors are not well validated and may at times generate false low values. More frequent postoperative measurements would be helpful in a full trial. The second important difference between current and previous results is that enrollment in our pilot trial was restricted to patients taking anti-hypertensive medications, and thus having a diagnosis of hypertension. It is understandable that hypertensive patients would have less hypotension than a general surgical population.

Only 10 of 80 patients experienced our composite outcome of major perfusion-related complications, evenly split between the treatment groups. With so few events, the (lack of) difference between the groups is noninformative. Curiously, no delirium was observed in our 80 patients. The incidence of delirium after non-cardiac surgery varies widely, but is probably now lower than previously reported.[18, 19] Delirium incidence also clearly depends strongly on age, with the incidence increasing markedly in patients older than 65 years.[9] The average age in our patients was 67 years which is relatively young which may have contributed to lack of observed delirium.

The major limitation of our trial is that it was conducted in a single center whereas our planned full trial will involve dozens of centers around the world. Our results demonstrating that intraoperative pressure and postoperative antihypertensive management is feasible does not mean that it will prove practical at all trial sites. Because the trial was only powered for feasibility and pressure management, the incidence of hard outcomes (based on only ten events) is essentially non-informative.

Conclusion

In summary, we achieved excellent separation of intraoperative mean arterial pressures. Similarly, we were able to control restarting antihypertensive medications per protocol — although doing so had relatively little effect on postoperative systolic pressures. Furthermore, the requirement that all patients have chronic hypertension resulted in relatively high intraoperative and postoperative pressures. Consequently, we amended the protocol for the full trial to include patients without chronic hypertension. The full trial appears feasible and

remains well warranted.

Contributorship statement

Kai Li was principal investigator and helped design the protocol, applied for ethics approval, registered the trial, assigned groups, and drafted the manuscript. Zhouting Hu and Wangyu Li helped collect data. Karan Shah was responsible for data analysis. Daniel I. Sessler designed the protocol and provided overall trial guidance. All authors reviewed and revised the manuscript.

Competing interests

Dr. Sessler is a consultant for Edwards Lifesciences (Irvine, California), Mercury Medical (Cleveland, Ohio), and Pacira Biosciences (Parsippany, New Jersey). He serves on advisory boards and has equity interests in Calorint (Philadelphia, Philadelphia), Transtronics (Philadelphia, Philadelphia), the Health Data Analytics Institute (Boston, Massachusetts), Medasense (Tel Aviv, Israel), Serenno (Tel Aviv, Israel), Sensifree (Cupertino, California), Perceptive Medical (Newport Beach, California), and Neuroindex (Tel Aviv, Israel). He serves on the board of the Foundation for Anesthesia Education and Research (Schaumburg, Illinois). The other authors declare no competing interests.

Funding

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Data sharing statement

The investigators and statistician have access to the whole data set.

Ethics approval

The protocol was approved by The Ethics Committee of the China-Japan Union Hospital of Jilin University, Changchun, China, (Chairperson Prof. Songyan Liu) on 28 June 2022. (Approval number: 20201120).

Patient consent for publication.

Consent obtained directly from patient(s).

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Figure Legends

Figure 1. CONSORT flow diagram. Patient flow through stages of the trial.

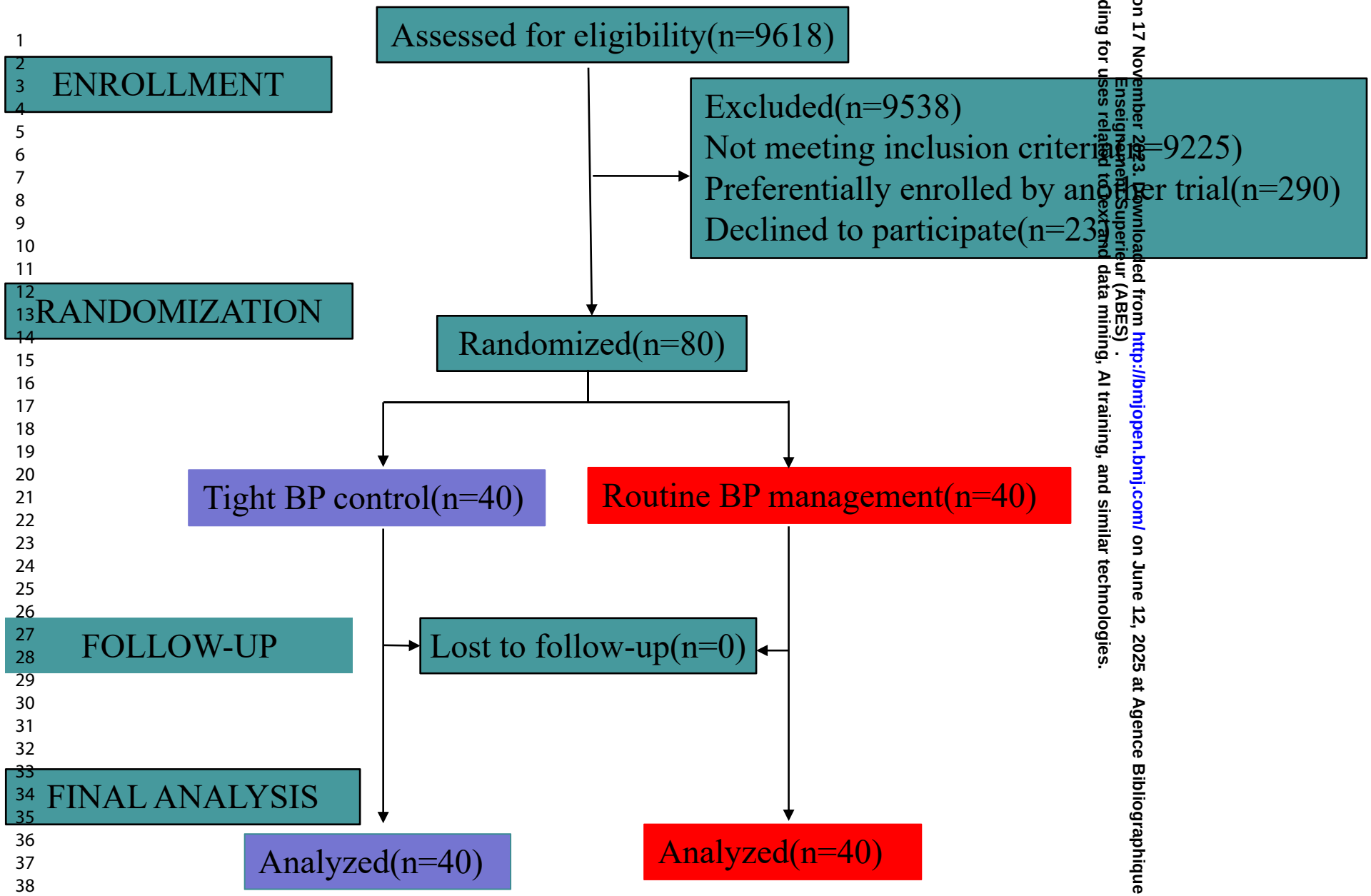
Figure 2. Area of intraoperative MAP >85 mmHg by blood pressure management group. The lower and upper edges of the box correspond to 25th and 75th percentile respectively, with the central line representing the median; whiskers extend to 1.5 times the interquartile range from the edges of the box; data beyond the whiskers are outliers and plotted individually.

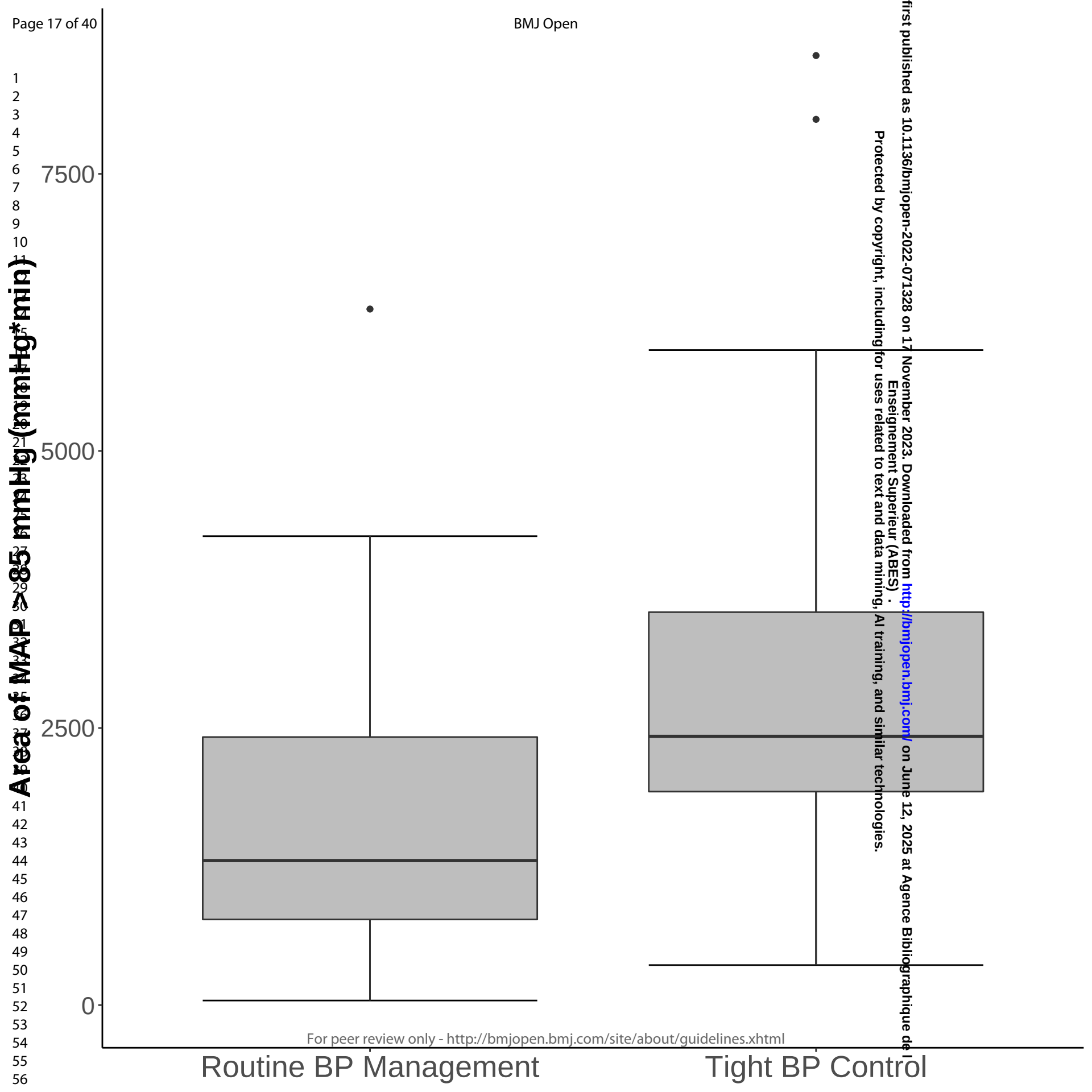
Figure 3. Area of intraoperative MAP <65 mmHg by blood pressure management group. The lower and upper edges of the box correspond to 25th and 75th percentile respectively, with the central line representing the median; whiskers extend to 1.5 times the interquartile range from the edges of the box; data beyond the whiskers are outliers and plotted individually.

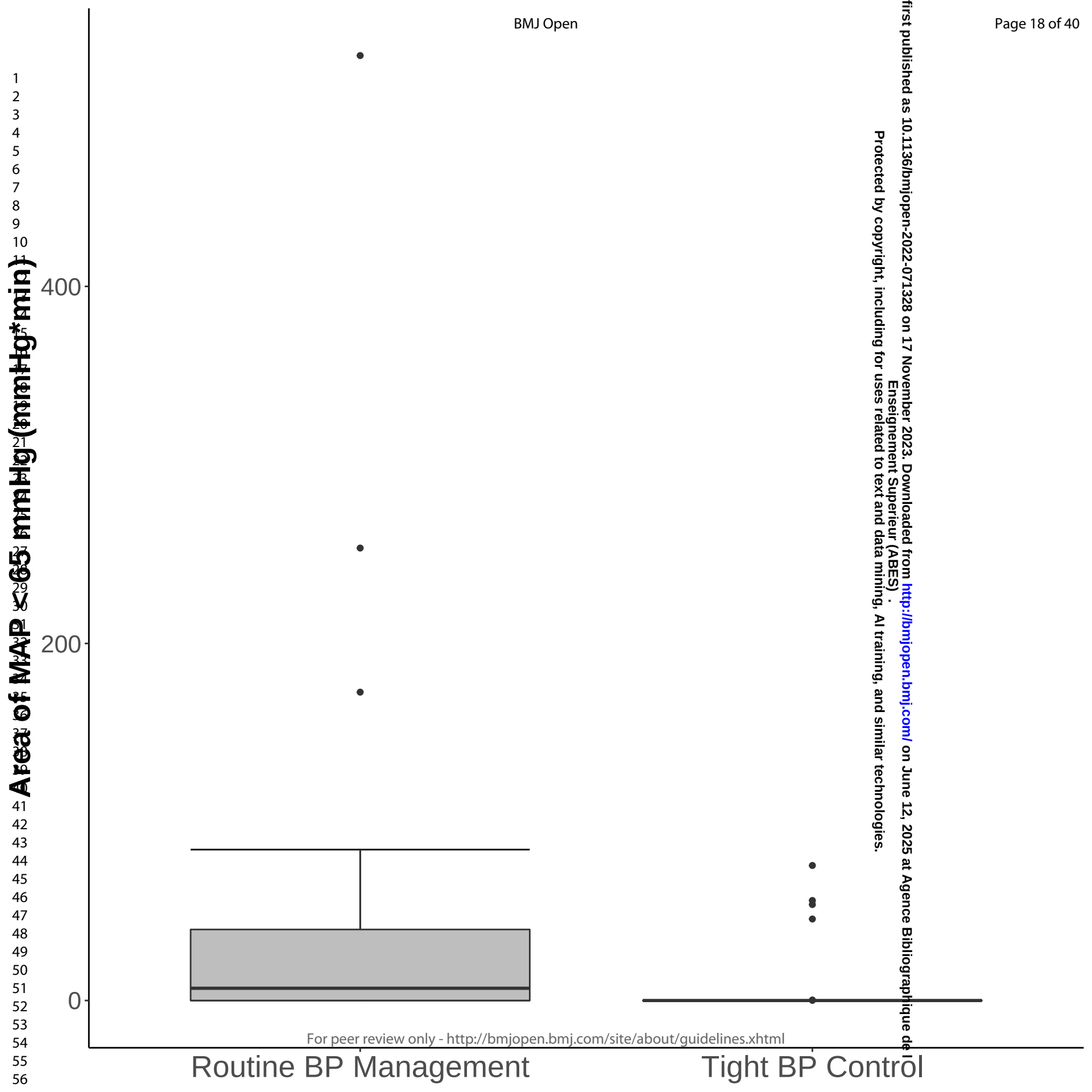
Figure 4. Time spent below 65 mmHg by blood pressure management group. Patients who never went below 65mmHg not shown.

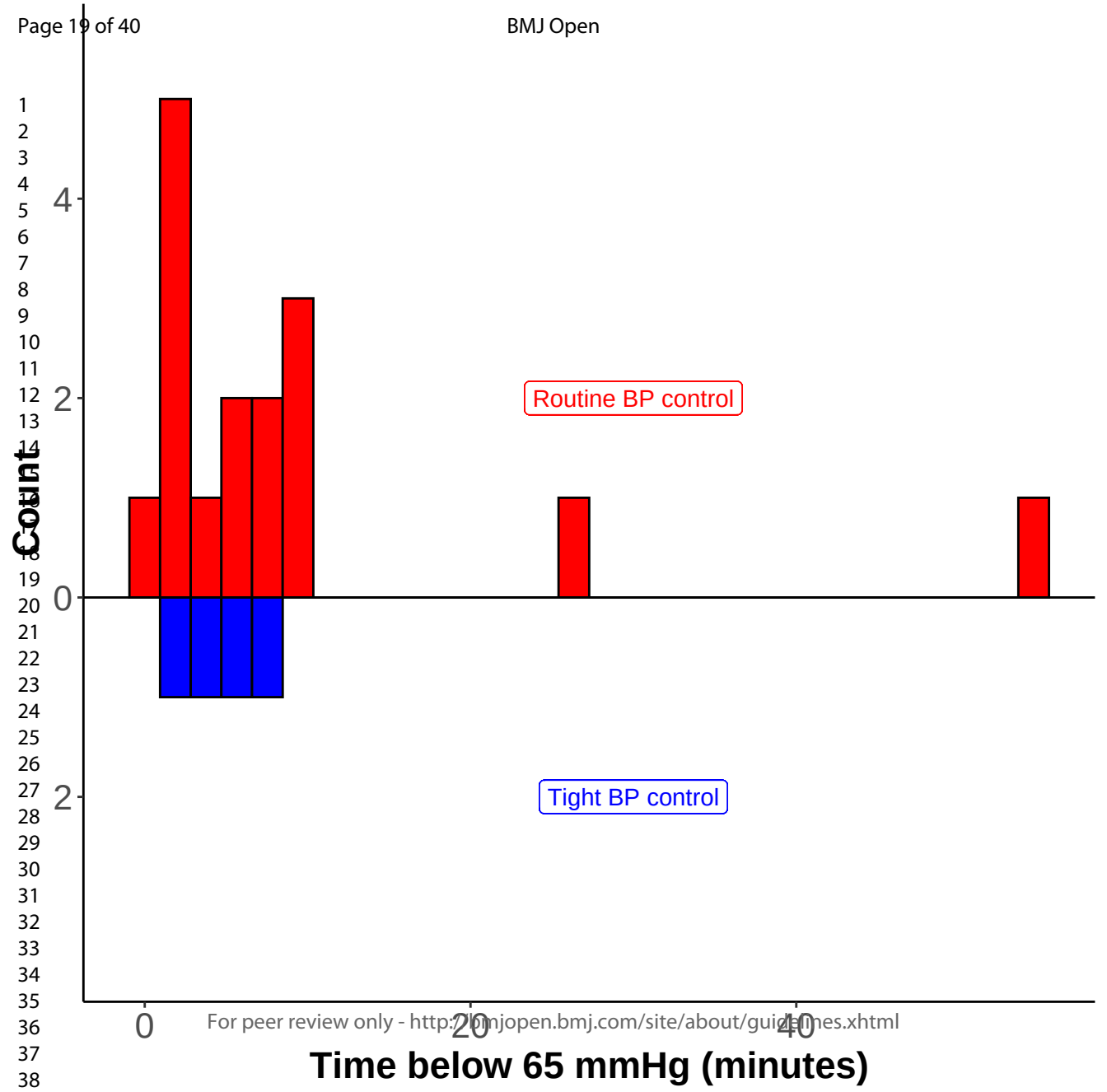
Supplemental Figure 1. Cumulative lowest intraoperative MAP sustained for 10 minutes by treatment group. The lower and upper edges of the box correspond to 25th and 75th percentile respectively, with the central line representing the median; whiskers extend to 1.5 times the interquartile range from the edges of the box; all data points are plotted individually and superimposed on the boxplot.

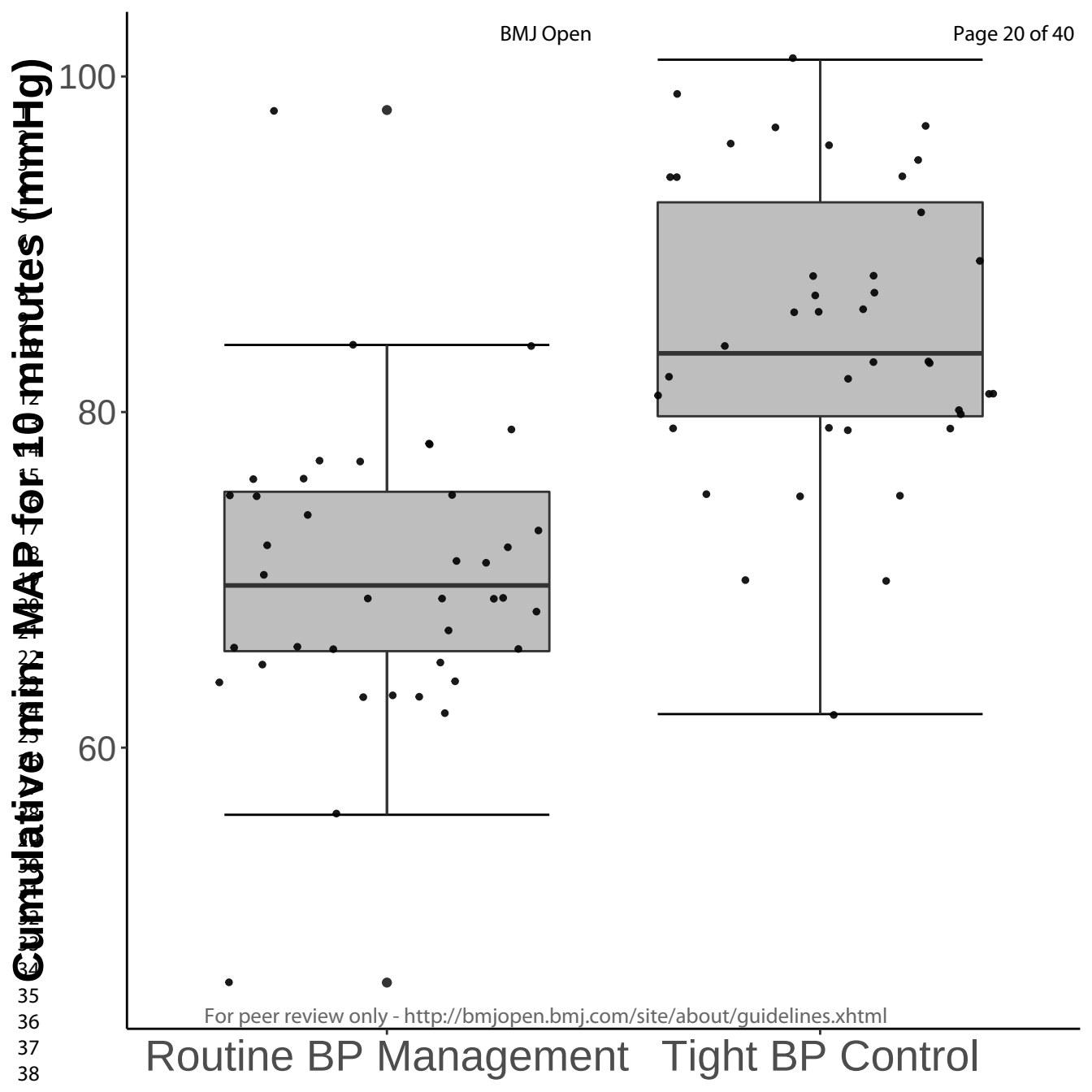
Supplemental Figure 2. Mean of lowest 3 postoperative systolic blood pressure measurements by treatment group. The lower and upper edges of the box correspond to 25th and 75th percentile respectively, with the central line representing the median; whiskers extend to 1.5 times the interquartile range from the edges of the box; all data points are plotted individually and superimposed on the boxplot.

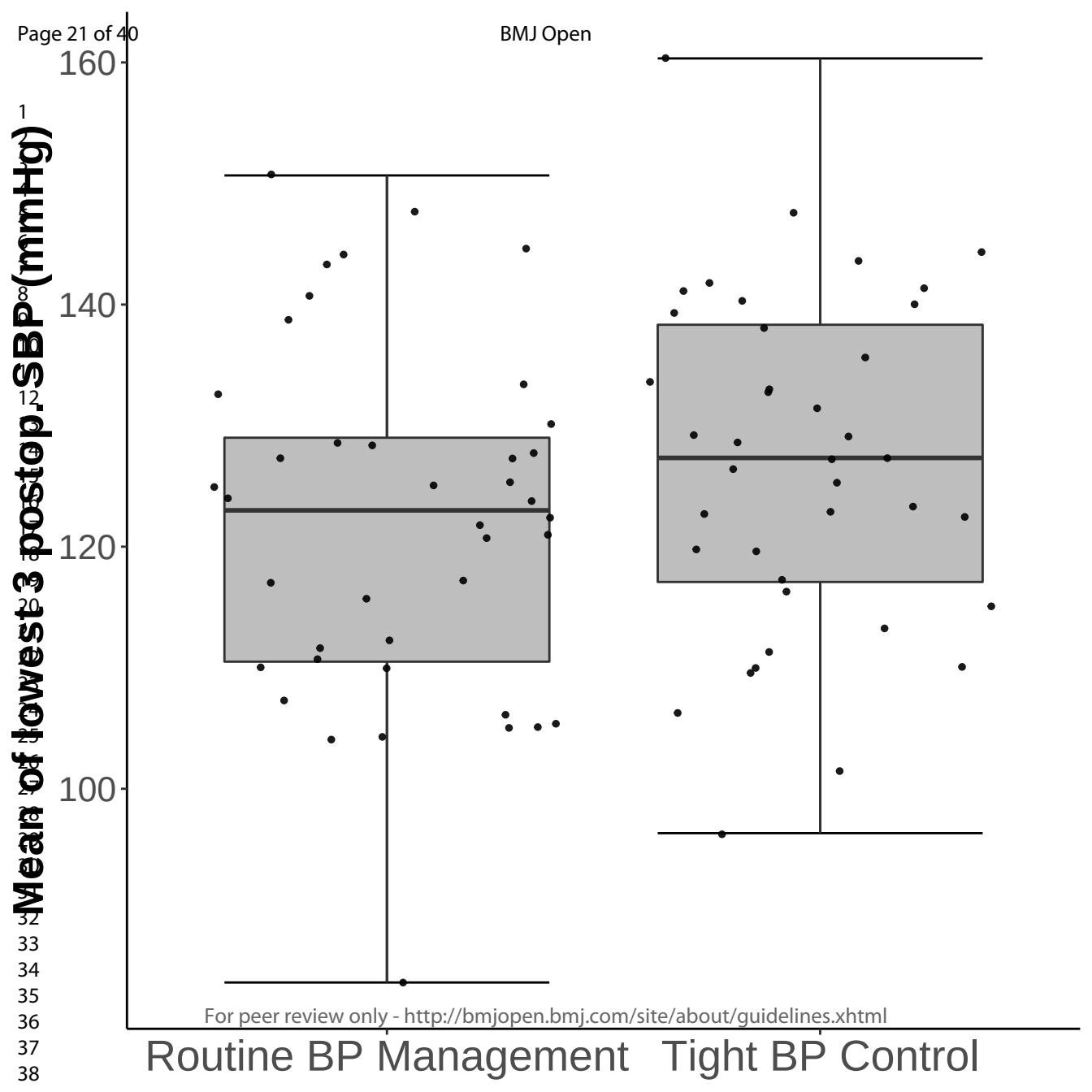












Pilot of "tight perioperative blood pressure management to reduce serious cardiovascular, renal, and cognitive complications"

The GUARDIAN Pilot Trial

Single-center prospective randomized pilot trial

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Guided by

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Summary

We are planing to propose a robust international randomized trial in 6,254 patients to test the primary hypothesis that perioperative tight blood pressure management reduces a composite of major perfusion-related complications (myocardial injury, stroke, non-fatal cardiac arrest, Stage 2-3 acute kidney injury, deep or organ-space infection, sepsis, and death) in the 30 days after major non-cardiac surgery.

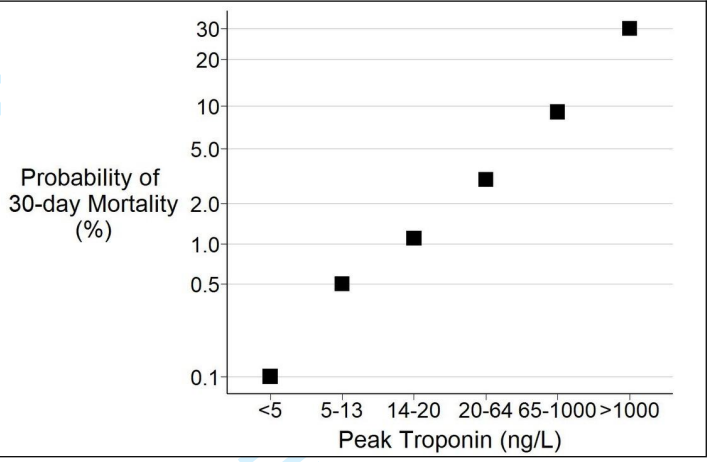
In anticipation of the full trial, we will conduct the pre-planned pilot trial designed to evaluate feasibility, especially the ability to target blood pressure per protocol. The pilot trial of 80 cases will be designed to inform a future pivotal trial by considering two co-primary feasibility hypotheses. First that there is suitable separation of intraoperative and postoperative blood pressure across two blood pressure management strategies (intraoperative MAP maintained ≥85 mmHg and postoperative tight pressure control *versus* routine care with some hypotension expected). And second, that restarting routine antihypertensive medications per protocol is feasible (restart delayed until the third postoperative day *versus* immediate restart). We also consider the exploratory efficacy hypothesis that perfusion-related complications and delirium are reduced by tight perioperative blood pressure control.

Introduction

When patients having major surgery reach the post-anaesthesia care unit, families naturally assume that they have survived the most dangerous part of the perioperative experience. Their assumption is wrong. Mortality in the 30 days after surgery is 1,000 times higher than intraoperative mortality.[1,2] In fact, if the month after surgery were considered a disease, it would be the third leading cause of death in the United States.[3] Most postoperative mortality occurs during the initial hospitalization, that is, under direct medical care in our highest-level facilities. The two most common and comparable causes of 30-day mortality after non-cardiac surgery are major bleeding which cannot easily be prevented, and myocardial injury which possibly can be; sepsis is a distant third.[4]

Myocardial injury after non-cardiac surgery (MINS) is defined by troponin elevation of presumably ischemic origin, and is highly associated with 30-day[5] (Fig. 1) and one-year[6] mortality. Myocardial infarction (MI), per 4th Universal Definition, is defined by troponin elevation *and* either symptoms or signs of myocardial ischemia.[7] More than 90% of MINS and MI occur within the initial two postoperative days.[8] Both are strongly associated with many *unmodifiable* baseline characteristics including age, diabetes, and cardiovascular history. In large randomized trials (n=7,000-10,000), we have shown that MI cannot be safely prevented by beta blockers,[9] avoiding nitrous oxide,[10] clonidine,[11] or aspirin.[12] In a recent large trial, one patient in seven who had MINS suffered re-infarction within 17 postoperative months.[13]

Fig. 1. 30-day mortality as a function of postoperative peak high-sensitivity troponin T. Mortality increases markedly from 0.1% at a troponin T concentration <5 ng/L to 30% mortality when troponin T exceeds 1,000 ng/L. Data from The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators: Association between complications and death within 30 days after noncardiac surgery. Can Med Assoc J 2019; 191: E830-E7



Intraoperative hypotension is associated with MINS and MI, with the harm threshold being a mean arterial pressure (MAP) ≈65 mmHg (Fig. 2).[14,15] The harm threshold for acute kidney injury (AKI) is similar,[14,16,17] and 40% of Stage 2 AKI persists or is worse 1-2 years after surgery (Turan, Anesthesiology, in press). We and others have also shown that postoperative hypotension is associated with myocardial infarction, *independent of intraoperative hypotension* (Fig. 3).[18,19]

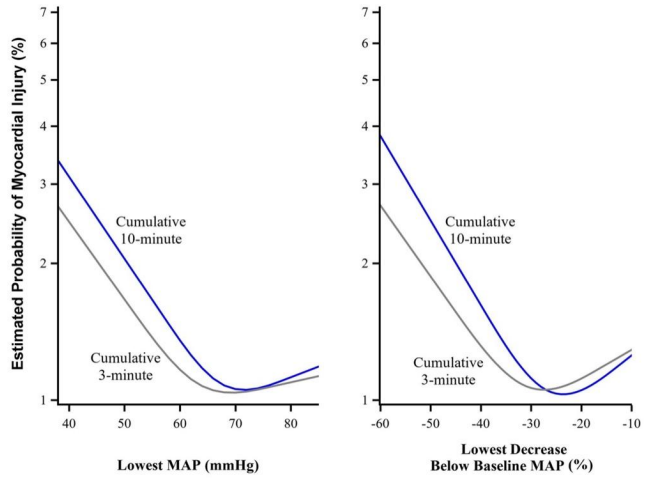


Fig. 2. Lowest mean arterial pressure (MAP) thresholds for myocardial injury after non-cardiac surgery. The left graph shows the relationship between the lowest cumulative absolute mean arterial pressure maintained for 3 and 10 minutes and myocardial injury. The right graph shows the relationship between the lowest cumulative relative mean arterial pressure maintained for 3 and 10 minutes and myocardial injury. Both graphs are multivariable logistic regressions adjusted for baseline characteristics and smoothed by restricted cubic spline with three degrees and knots at 10th, 50th, and 90th percentiles of given exposure variable. From Salmasi, et al: Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after non-cardiac surgery: A retrospective cohort analysis. Anesthesiology 2017; 126: 47-65.

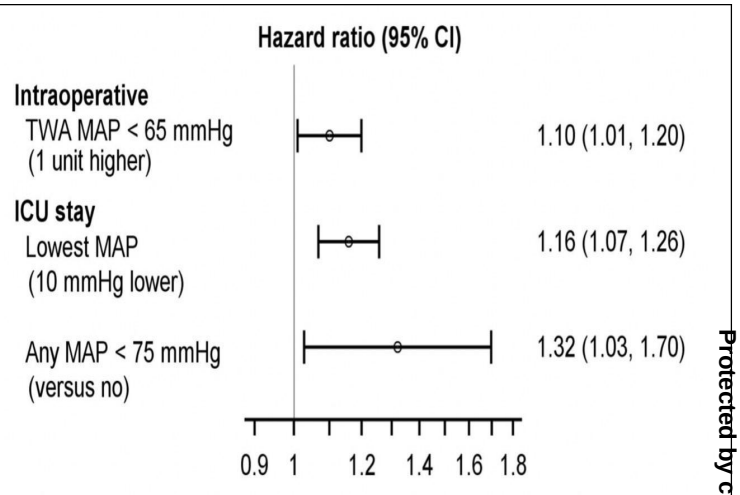


Fig. 3. Odds ratios of average relative effect on the primary composite of 30-day myocardial infarction and mortality for three perioperative periods: intraoperative, remaining day of surgery, and the initial four PODs of hospitalization. CIs for multiple comparisons were adjusted by Bonferroni correction. Correspondingly, P < 0.017 (0.05/3) was considered to be significant for the average relative effect. The circles present the odds ratios, and the bars present the CIs. POD = postoperative day. From Sessler 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: 317-27

There is currently sparse evidence that the associations are casual. But a small fragile randomized trial (n=292) shows that preventing intraoperative hypotension reduces the risk of major complications by 25%.[20] Perioperative hypotension is also associated with stroke,[9,21-24] although inconsistently.[25] Blood pressure — specifically hypotension prevention — is therefore a modifiable factor that may reduce cardiovascular complications.

Delirium is a common complication of cardiac surgery and is associated with morbidity and mortality.[26-32] The reported incidence of delirium after major non-cardiac surgery is typically about 10%, and increases markedly as age increases beyond 65 years. The pathophysiology of delirium is multifactorial but surely includes inadequate brain perfusion that results when mean arterial pressure is less than the lower limit of autoregulation.[33-35] Consistent with this theory, hypotension is associated with delirium and cognitive decline,[28,36,37] although inconsistently.[27,38,39] Limited randomized data (n=199) indicate that hypotension causes delirium.[40] Patients who have delirium after surgery are far more likely than others to develop long-term cognitive impairment,[41] although it remains unknown whether the association is causal. Hypotension may also provoke overt or (far more commonly) covert strokes which is strongly linked to delirium.[42]

No robust randomized trial has been published.

Specific Aims

Mortality in the 30 days after surgery is surprisingly common, and usually occurs during the initial hospitalization. Major bleeding and cardiovascular complications are the most common causes of 30-day postoperative mortality. Cardiovascular complications are independently associated with intraoperative and postoperative hypotension. Cognitive impairment, both acute delirium and long-term, are common after major surgery. There is increasing evidence that perioperative hypotension may contribute to brain injury. However, there is currently only sparse and fragile randomized evidence indicating that intraoperative hypotension prevention reduces cardiovascular risk and/or cognitive impairment in non-cardiac surgical patients. We are planing to propose a robust international randomized trial in 6,254 patients to test the primary hypothesis that perioperative tight blood pressure management reduces a composite of major perfusion-related complications (myocardial injury, stroke, non-fatal cardiac arrest, Stage 2-3 acute kidney injury, deep or organ-space infection, sepsis, and death) in the 30 days after major non-cardiac surgery.

In anticipation of the full trial, we will conduct the pre-planned pilot trial designed to evaluate feasibility, especially the ability to target blood pressure per protocol.

Aims

First, we will test whether there is suitable separation of intraoperative and postoperative blood pressure across two blood pressure management strategies (intraoperative MAP maintained ≥85 mmHg and postoperative tight pressure control versus routine care with some hypotension expected).

Second, that restarting routine antihypertensive medications per protocol should be feasible (restart delayed until the third postoperative day versus immediate restart).

We also consider the exploratory efficacy hypothesis that perfusion-related complications and delirium are reduced by tight perioperative blood pressure control.

Methods

The trial will be conducted with IRB approval and written patient consent will be obtained. There will be no restriction on sex, or ethnicity. All qualifying patients will be asked to consider the trial. The trial is restricted to patients ≥45 years old because cardiovascular outcomes are rare in younger patients, but there is no upper age restriction. The trial will be registered on ClinicalTrial.gov before enrollment.Pilot patients will be enrolled before normal enrollment.A full statistical analysis plan will be developed before any data are evaluated. Reporting will be consistent with the CONSORT guidelines.

Subject selection

Consenting patients will be **eligible** if they are:

1. Scheduled for major noncardiac surgery expected to last at least 2 hours;
2. Having general endotracheal anesthesia;
3. Expected to require at least overnight hospitalization;
4. Are designated ASA physical status 2-4;
5. Chronically taking at least one anti-hypertensive medication;
6. Expected to have direct blood pressure monitoring with an arterial catheter;
7. At least 45 years old;
8. Cared for by clinicians willing to follow the protocol;
9. Subject to at least one of the following risk factors:
    a. History of peripheral arterial surgery;
    b. History of coronary artery disease;
    c. History of stroke or transient ischemic attack;
    d. Serum creatinine >175 µmal/L (>2.0 mg/dl);
    e. Diabetes requiring medication;
    f. Current smoking or 15 pack-year history of smoking tobacco
    g. Scheduled for major vascular surgery
    h. Body mass index ≥35 kg/m^2;
    i. Preoperative high-sensitivity troponin T >14 ng/L or troponin I equivalent
    j. B-type natriuretic protein (BNP) >80 ng/ml or N-terminal B-type natriuretic protein (NT-ProBNP) >200 ng/ml.

Patients will be **ineligible** if they:

1. Are scheduled for carotid artery surgery;
2. Are scheduled for intracranial surgery;
3. Are scheduled for partial or complete nephrectomy
4. Are scheduled for pheochromocytoma surgery;
5. Are scheduled for liver transplantation;
6. Have a condition that precludes routine or tight blood pressure management such as surgeon request for relative hypotension or relatively high pressure required for carotid artery surgery;
7. Have end-stage renal disease requiring dialysis or estimated glomerular filtration rate (eGFR) <30 ml/min;
8. Have a documented history of dementia;
9. Have language, vision, or hearing impairments that may compromise cognitive assessments;

Protocol

Consenting patients who take either ACEIs or ARBs will be asked not to take the medications on the morning of surgery, and instead bring them with them to the hospital. Qualifying patients will be randomly allocated using computer-generated assignments 1:1 ratio without stratification in a block of four. Allocation will be concealed within sealed opaque envelopes until shortly before anesthesia induction. Allocation will thus remain concealed until the last practical moment. Randomization will be implemented by clinicians in collaboration with research personnel. Arterial catheter transducers will be positioned at the level of the right atrium, and adjusted as necessary if

patient position is changed. A fast-flush square-wave test will be performed shortly after catheter insertion to confirm that dynamic characteristics of the pressure monitoring system are appropriate.[10]

The treatments will be:1) norepinephrine infusion to maintain intraoperative MAP ≥85 mmHg, delayed resumption of chronic antihypertensive medications, and a target ward systolic pressure of at least 120 mmHg (tight pressure management); or, 2) routine intraoperative blood pressure management and prompt resumption of chronic antihypertensive medications (routine pressure management)

Tight pressure management: In patients assigned to tight pressure management, angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) will not be given the morning of surgery. Clinicians will be encouraged to insert the required arterial catheter before anesthetic induction because much hypotension occurs shortly after anesthetic induction.[46] A norepinephrine infusion (in the preferred local concentration) will be prepared, connected to an intravenous catheter, and activated at a low rate. Norepinephrine can be safely given through a central catheter or peripherally. In a recent study of 14,328 patients, there were only 5 extravasation events and not a single patient experienced local tissue injury.[47] It can be substituted if norepinephrine is contraindicated or impractical.

General anesthesia will be induced with propofol which will be given in repeated small boluses in an effort to keep intraoperative MAP ≥85 mmHg. Simultaneously, the vasopressor infusion will be adjusted with the same goal. Anesthetic dose, fluid administration, and vasopressor administration will be adjusted with the goal of maintaining intraoperative MAP ≥85 mmHg.

Resumption of chronic anti-hypertensive medications will be delayed until the third postoperative day unless deemed necessary to treat hypertension or for some other clear indication (e.g., preventing atrial fibrillation in a chronic beta-blocker user) because >90% of MINS occurs within 48 hours after surgery. When necessary to treat hypertension, chronic antihypertensive or new medications can be used per clinician preference. Clinicians will make what efforts they can to maintain postoperative systolic pressure of at least 120 mmHg during the initial three postoperative days by maintaining adequate hydration, using inotropic and chronotropic drugs, and vasopressor as necessary. This protocol specifies the blood pressure target, but leaves implementation to clinical judgement.

Routine pressure management: In patients assigned to routine pressure management, ACEIs and ARBs can be given the morning of surgery if deemed appropriate by the attending anesthesiologist. The arterial catheter will be inserted before or after induction of anesthesia per clinician preference. General anesthesia will be induced and maintained per routine. Intraoperative pressure management will be per routine. As usual, chronic anti-hypertensive medications will be restarted shortly after surgery unless contraindicated by hypotension.

In both groups, other aspects of anesthetic management will be at the discretion of the responsible anesthesiologist, including the types and volumes of various fluids. Volatile or intravenous anesthesia is permitted. There is increasing evidence that deep anesthesia promotes delirium and long-term cognitive dysfunction (Evered, in review).[49] Therefore, processed EEG monitoring, such as the Bispectral Index (BIS) or Patient State Index (PSI), should be used. If BIS is

the method, a value of 50 should be targeted from soon after induction until shortly before emergence. If another EEG system is used, a comparable hypnotic depth should be targeted.

There will be no limitation on ancillary vasoactive, chronotropic, and inotropic drugs. Clinicians will be free to use advanced hemodynamic monitoring (e.g., FlowTrac, esophageal Doppler, etc.). Blood products will be given per routine. Similarly, postoperative analgesic management will be per routine and clinician preference. Neuraxial and peripheral nerve blocks are permitted, but epidural catheters should not be activated until surgery is nearly finished.

Because patients must be fairly sick to qualify for Pilot GUARDIAN, some will go to directly from surgery to critical care units, or much less often, become unstable and require transfer from a routine ward to an ICU. In either case, every effort will be to maintain randomized treatments and blood pressure targets.

In all cases, good judgement will predominate. Clinicians should always act in their patients best interests, irrespective of the GUARDIAN protocol.

Measurements

Baseline

Baseline demographic and morphometric characteristics will be recorded, including height, weight, and sex. Routine anesthetic variables will be recorded including volatile anesthetic partial pressure, Fluid type and volume, estimated blood loss, and transfusions. Cardiovascular risks will be recorded, including hypertension requiring treatment, diabetes requiring oral medications or insulin, history of previous myocardial infarction, congestive heart failure, chronic obstructive pulmonary disease, current smoking status, and pack-years of smoking history. Cardiovascular medications will be similarly recorded by category, including beta blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and statins. Types of surgery will be characterized as orthopedic, laparoscopic, open abdominal, neurosurgical (including spine), thoracic, urologic, gynecologic, vascular, and other. Timing will be characterized as elective, urgent, or emergent.

Baseline laboratory values (within 30 days before surgery) will be recorded on an as-available basis, including albumin, BNP, and NT-ProBNP. Baseline electrocardiogram and echocardiogram interpretations will also be recorded as available, as will hemoglobin and creatinine other than specified below.

Perioperative

Blood pressure is our primary exposure and will therefore be carefully recorded. The most recent pressure from a clinic assessment will be used. Our institution have electronic anesthesia records that will automatically record systolic, mean, and diastolic pressures from the required arterial catheter at no less than 1-minute intervals. When possible, we will obtain electronic data which are efficient, denser, and more reliable than manual recording. But where necessary, intraoperative blood pressures will be recorded manually at 5-minute intervals. Ward blood pressure will normally be recorded by nurses at 8-hour-intervals. Any pressures obtained for clinical purposes will be recorded for use in the trial.Additional ward pressures might also be obtained. However, all blood pressures during the initial three postoperative days will be retrieved and included in the trial database. We will restrict recording to this period because >90% of postoperative myocardial injury occurs within the

initial two postoperative days. High-risk patients may require ICU admission. Blood pressure is measured frequently in critical care units, and all available pressures will be recorded.

We will require **creatinine** preoperatively (within 30 days), and on the initial three postoperative days while patients remain hospitalized. Additional values obtained for clinical reasons will be recorded during the initial 30 postoperative days. Hemoglobin will be recorded on an as-available basis for the initial three postoperative days.

Blood for generations 4 or 5 **troponin** T, or troponin I will be recorded preoperatively up to 30 days before surgery, and on the first three postoperative days so long as patients remain hospitalized.[8] Additional troponin samples will also be obtained if patients have shortness of breath or experience chest, neck, or arm pain. Blood troponin concentrations exceeding thresholds (depending on individual types of troponin tests) should prompt cardiology consultation, an electrocardiogram, and when practical an echocardiogram.

Myocardial injury will be diagnosed by objective screening based on preoperative and first three postoperative day troponin I values crossing specific thresholds for MINS so long as patients remain hospitalized. Abnormal troponin concentrations will be evaluated as clinically indicated with ECG, echocardiography, and clinical symptoms; the resulting values will be recorded, as will other cardiovascular interventions such as angioplasty. MINS will be diagnosed by troponin exceeding thresholds apparently of ischemic origin (e.g., no other obvious cause for artifactual elevation). Myocardial infarction will also be centrally adjudicated and require *both* MINS and at least one symptom (e.g., chest pain or shortness of breath) or sign (e.g. ECG or echocardiogram abnormality).

We will consider all patients who had an elevated serum troponin concentration anytime during the first 30 days after surgery and determine the presence of any ischemic features (*i.e.*, whether patients fulfilled the universal definition of myocardial infarction),[50] whether there was a non-ischemic etiology that could explain the elevated troponin measurement, and whether the myocardial injury appears to have occurred during or after surgery (*i.e.*, no evidence to support it was due to a preoperative event).

Myocardial injury after non-cardiac surgery will be defined as having values exceeding local 99th percentile for troponin I. Patients meeting diagnostic criteria for MINS will be evaluated for myocardial infarction with an electrocardiogram, echocardiogram (when possible), and a cardiac consultation. Non-fatal cardiac arrest and mortality will be determined from case-reports and medical records. Strokes will be detected based on clinical symptoms, and require radiographic evidence, consistent with new-onset cerebral ischemic or hemorrhagic injury.

Delirium will be assessed 7-10 AM and 5-8 PM for the initial four postoperative days while patients remain hospitalized because this approach will detect nearly all postoperative delirium (Fig. 4). Delirium will not be evaluated the evening after surgery because confusion might result from residual anesthetic effects. We will use the 3D-CAM which is based on a three-minute questionnaire, and has a sensitivity of 95% (95% CI, 84, 99), and specificity of 94% (CI: 90, 97) compared with formal psychometric evaluation.[51] The test works well in patients with dementia.[51] CAM-ICU, which is also well validated, will be substituted when patients are intubated.[52] Delirium will be assessed by investigators trained in the methods. Any positive CAM test will be considered evidence of delirium which will analyzed dichotomously.

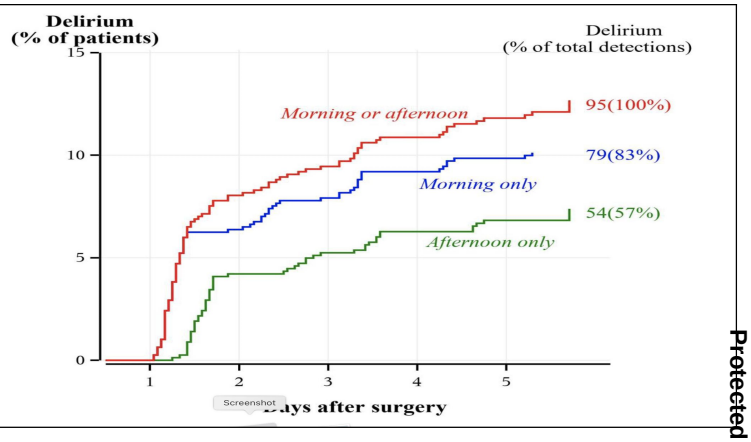


Fig. 4. Detection of delirium with CAM-ICU as a function of assessment times over postoperative days 1-5. Nearly all delirium was detected with twice daily assessments for the initial four postoperative days. From Hamadnalla, et al, in review.

Acute kidney injury. Postoperative Acute Kidney Injury will be defined by Kidney Disease Improving Global Guidelines (KDIGO) Clinical Practice Guidelines.110 By convention in perioperative studies, urine output will not be considered since it is rarely available.111 Specifically, patients will be considered to have Stage 1 acute kidney injury (risk) if the postoperative serum creatinine increases at 1.5-1.9-fold or by more than 0.3 mg/dl (≥26.5 µmol/L) within a 48-hour period. Stage 2 will be defined by a 2.0-2.9-fold increase in creatinine, and Stage 3 will be defined by a 3-fold increase in creatinine or an increase from baseline by ≥4 mg/dl (≥353.6 µmol/L) or initiation of renal replacement therapy.We will compare the preoperative creatinine concentration closest to surgery to the highest postoperative concentration measured within 7 days. Only Stages 2 and 3 will be considered for the primary perioperative composite.

Outcomes and clinically meaningful differences

The first co-primary feasibility outcomes are the fraction of time when intraoperative MAP >85 mmHg, intraoperative area of MAP >85 mmHg, and intraoperative area of MAP <65 mmHg. The area of MAP below (above) a threshold refers to the cumulative sum of areas for the MAP-time curve below (above) the specified threshold.

The second co-primary feasibility outcome is postoperative blood pressure management, characterized by the time routine antihypertensive medications restarted after surgery.

The secondary feasibility outcome measures are time-weighted average (TWA) intraoperative MAP, cumulative minimum MAP for 10 minutes, average postoperative systolic blood pressure (SBP), and mean of the lowest 3 postoperative SBPs.

The exploratory efficacy outcome measures are: 1) perfusion-related complications within 30 days of surgery; and 2) postoperative delirium within the first 4 postoperative days.

Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose: is life-threatening; or requires inpatient hospitalization or prolongation of existing hospitalization; or results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect; or is a medically important event.

Suspected unexpected serious adverse reactions (SUSARs) are events that meet the following criteria: 1) suspected to be causally associated with blood pressure management, anesthetic induction agent, or vasopressor; 2) unexpected if the nature, severity, or outcome of the reaction(s) is

not consistent with the reference information (i.e., product monograph for trial drugs); 3) serious (as defined above for an SAE); and 4) not a defined efficacy.

Efficacy and safety outcomes will be recorded separately and not as SAEs, except if, because of the course or severity or any other feature of such events, the investigator, according to his/her best medical judgment, considers these events as exceptional in this medical condition.

Hospitalizations, which were planned before inclusion in the study (e.g., elective or scheduled surgery or other interventions), will not be regarded as SAEs. This pertains also to hospitalizations which are part of the normal treatment or monitoring of the studied disease or another disease present before inclusion in the study (e.g., patient returning to the hospital for chemotherapy), and which did not result in a worsening of the disease.

All SAEs need to be reported within 48 hours of knowledge of the event to the Project Office. For such events, research personnel will complete an SAE CRF in the database. The Project Office will then inform regulatory authorities in a timely manner, as necessary, according to the applicable regulations.

The DMC will provide oversight of patients' safety throughout the trial by reviewing aggregate data (including all reported study outcome events and SAEs) by treatment group at regular intervals throughout the duration of the trial and as defined in the DMC Charter.

Data Analysis

Primary, secondary, and exploratory outcomes will be analyzed on a modified intent-to-treat basis by randomized group assignments. Specifically, we will include all randomized patients who have surgery, even if the operation is changed to one that would not otherwise qualify for Pilot GUARDIAN.

Balance on baseline characteristics will be assessed using absolute standardized difference (ASD), which is defined as the absolute difference in means, ranks, or proportions divided by the pooled standard deviation. Groups are considered to be imbalanced with respect to a baseline characteristic when ASD exceeded 0.44 [$1.96*\text{sqrt}(1/n_1 + 1/n_2)$].

We primarily evaluate the effect of tight blood pressure control on the fraction of time when intraoperative MAP exceeded 85 mmHg using a t-test. Wilcoxon rank-sum tests will be used to evaluate the effect of tight perioperative BP control on intraoperative area of MAP >85 mmHg, intraoperative area of MAP <65 mmHg, and time to restart routine antihypertensive medications after surgery.

Sample Size Considerations

The study will enroll 40 patients in each treatment group. Design analysis for the study will be done after data collection but before we conducted the analysis.

The fraction of time spent above 85 mmHg is assumed to be distributed as Beta (5, 5) and with the above sample size, the confidence interval half-width for estimating the mean would be 0.05 which is deemed to be sufficiently precise. The beta distribution is appropriate as the outcome is restricted to the closed interval between 0 and 1. The observed confidence interval widths are 0.01.

Schedule of Procedures

	BP	anti-HP medicine	Creatinine	Troponin I+ECG(Positive)	3D-CAM/ICU-CAM	Perfusion-related complications	Mortality
Baseline(<30d)	Y	Y	Y	Y			
DOS	IBP+MAP≥85/IBP	Y/N	Y	Y			
POD1	Y	Y/N	Y	Y	Twice		
POD2	Y	Y/N	Y	Y	Twice		
POD3	Y	Y			Twice		
POD4		Y			Twice		
Ward request	Y	Y	Y	Y			
Discharged						Y	Y
POD30-35						Y	Y

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吉林大学中日联谊医院科研伦理委员会
涉及人的生物医学研究伦理审批件

（2020 年）临审（20201120）

项目名称	严格围术期血压管理减少心血管意外、肾衰、认知障碍-GUARDIAN 研究的预实验 Pilot of "tight perioperative blood pressure management to reduce serious cardiovascular, renal, and cognitive complications"		
申请科室	麻醉科	项目负责人	李凯
工作证号	603972	身份证号	410205198210062011
联系方式	13596195176	类别	干预性研究
研究目的	为我院与美国克利夫兰诊所临床预后中心共同发起的国际多中心研究，提供参照，验证研究方案的可行性，组间区分性；初步探讨严格围术期血压管理对减少心血管意外、肾衰、认知障碍的作用		

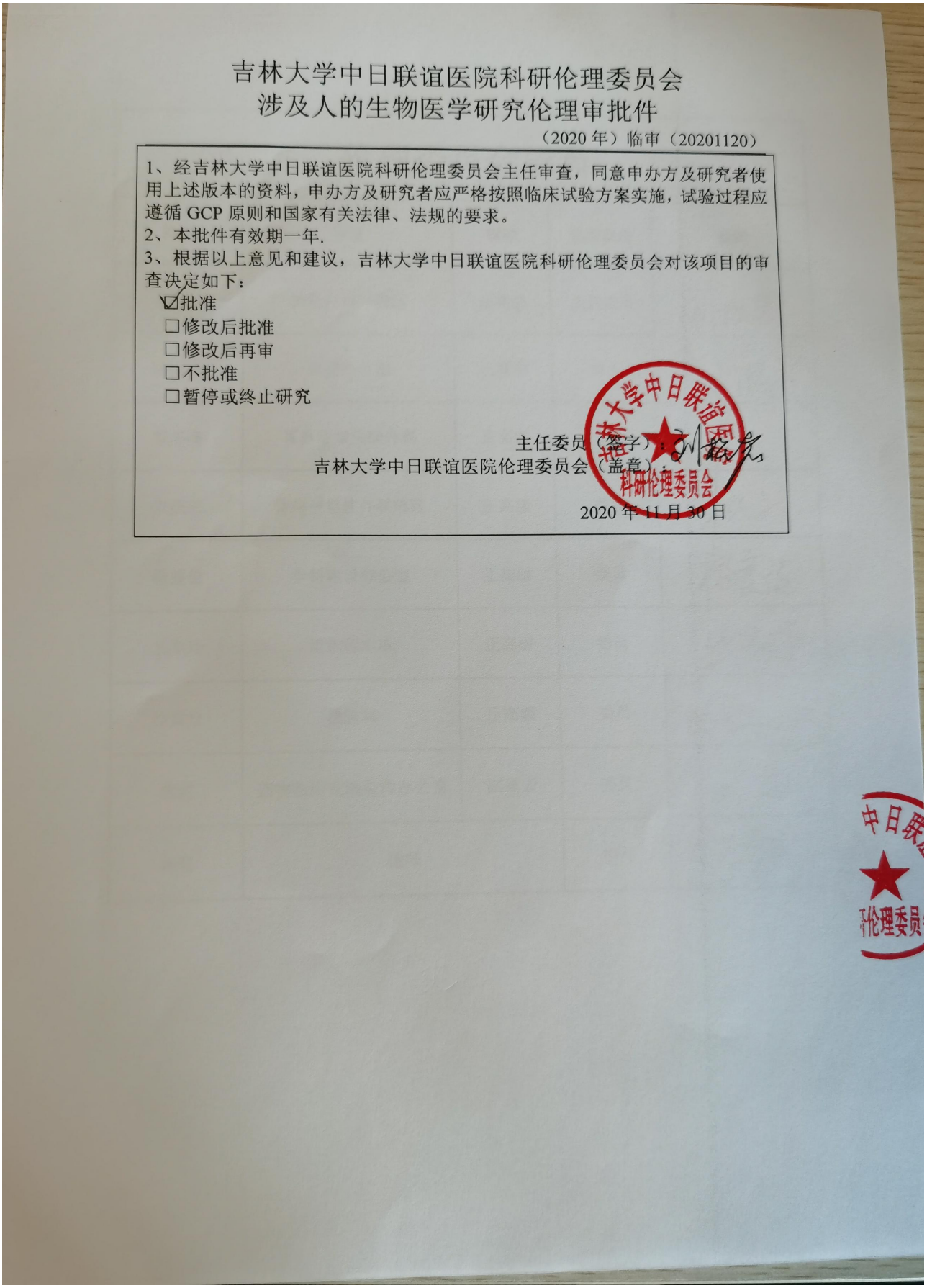
主要审查文件（含版本号）如下：

1 研究者发起的临床研究申请表受理申请表
2 临床研究方案（版本号：V1.0，版本日期：2020 年 11 月 01 日）
3 知情同意书及其他书面资料（版本号：1.0，版本日期：2020 年 11 月 01 日）
4 研究者简历、临床试验项目组成人员清单
5 研究者资质认证

研究者声明：(Inspection contents)	1、真实性：本表格内所写内容真实有效，若非真实，责任由申请人本人自负。 2、利益冲突：在此研究中不存在经济上、物质上、以及社会关系方面的利益冲突。倘若在研究开展过程中发现目前尚未知晓的利益冲突，我将及时向伦理委员会报告。 1. Authenticity: The content written in this form is true and valid. If it is not true, the responsibility is my own responsibility. 2. Conflict of interest: there is no conflict of interest in economic, material, or social relations in this research. If there is a conflict of interest that is not yet known during the research, I will report to the ethics committee in time.

申请人签名(Signature of applicant)	李凯	日期(date)：2020 年(year)11 月(month)30 日(day)

同意	作必要的修正后同意	作必要的修正后重审	不同意	终止或暂停该试验	弃权	回避
7 票	票	票	票	票	票	票



吉林大学中日联谊医院科研伦理委员会
涉及人的生物医学研究伦理审批件

（2020 年）临审（20201120）

1、经吉林大学中日联谊医院科研伦理委员会主任审查，同意申办方及研究者使用上述版本的资料，申办方及研究者应严格按照临床试验方案实施，试验过程应遵循 GCP 原则和国家有关法律、法规的要求。

2、本批件有效期一年.

3、根据以上意见和建议，吉林大学中日联谊医院科研伦理委员会对该项目的审查决定如下：

☑批准

☐修改后批准

☐修改后再审

☐不批准

☐暂停或终止研究

主任委员（签字）：

吉林大学中日联谊医院伦理委员会（盖章）：

2020 年 11 月 30 日

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	2
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance, see CONSORT for abstracts)	2-3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	3-4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	4
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4-5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	-
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	4
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	4
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	4
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	5

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	5
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6-7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	6-7
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	7
	13b	For each group, losses and exclusions after randomisation, together with reasons	7
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7
	14b	Why the trial ended or was stopped	-
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	7-8
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	8-10
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	9-10
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	9-10
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	-
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	11
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	10-11
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	10-11
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	4
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	13

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Tight perioperative blood pressure management to reduce complications: a randomized feasibility trial

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Tight perioperative blood pressure management to reduce complications: a randomized feasibility trial

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ABSTRACT

- **Objective:** Evaluate feasibility of a trial of perioperative hypotension and serious complications.
- **Design:** A patient and assessor blinded randomized feasibility trial.
- **Setting:** We included patients in tertiary university hospital.
- **Participants:** We enrolled 80 adults scheduled for major non-cardiac surgery.
- **Interventions:** In patients randomized to tight blood pressure control, intraoperative mean arterial pressure (MAP) was targeted to ≥85 mmHg maintained with norepinephrine infusion, and restarting chronic antihypertensive medications was delayed until the third postoperative day. In the reference group, intraoperative blood pressure was managed per routine and antihypertensive medications were restarted immediately after surgery.
- **Primary and secondary outcome measures:** Our first co-primary outcome was the fraction of time when intraoperative MAP was >85 mmHg, intraoperative area of MAP >85 mmHg, and intraoperative area of MAP <65 mmHg. The second co-primary outcome was time until antihypertensive medications were restarted after surgery. . Secondary outcomes were time-weighted average (TWA) intraoperative MAP, cumulative minimum MAP for 10 minutes, average postoperative systolic blood pressure (SBP), and mean of the lowest 3 postoperative SBPs.
- **Results:** Forty patients in each group were analyzed. The median for intraoperative area of MAP >85 mmHg was 1303 [772-2419] mmHg*min in routine BP cases and 2425 [1926- 3545] mmHg*min in tight BP control. The area for intraoperative MAP <65 mmHg was 7 [0-40] mmHg*min with routine BP management, and 0 [0-0] mmHg*min with tight BP control. Antihypertensive medications were restarted 2 [1 to 3] days later in tight BP control cases. However, postoperative systolic pressures were similar.
- **Conclusions:** Tight BP management markedly increased intraoperative MAP and reduced the amount of hypotension. In contrast, delaying chronic antihypertensive medications had little effect on postoperative systolic pressure. The full trial appears feasible and remains necessary but should not include postoperative antihypertensive

management.

- **Trial registration:** www.clinicaltrials.gov (NCT04789733).
- **Keywords:** Anesthesia, blood pressure, perioperative management, myocardial injury after non-cardiac surgery, myocardial infarction, acute kidney injury, delirium.

Strengths and limitations of this study

• The protocol was practical, and intraoperative pressure management was excellent separated.
• However, we failed to manipulate postoperative blood pressure by changing when antihypertensive medications were restarted.
• Feasibility in one site does not mean that it will prove practical at all trial sites.

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INTRODUCTION

Mortality in the 30 days after surgery is more than 100 times higher than intraoperative mortality.[1] Myocardial injury and associated vascular complications are among the leading causes of postoperative mortality.[2] Intraoperative hypotension is associated with myocardial injury after non-cardiac surgery (MINS) and myocardial infarction (MI), with the apparent harm threshold being a mean arterial pressure (MAP) ≈ 65 mmHg.[3, 4] Furthermore, postoperative hypotension is associated with myocardial infarction even after adjustment for intraoperative hypotension.[5]

The harm threshold for perioperative acute kidney injury (AKI) also appears to be a mean arterial pressure (MAP) near 65 mmHg.[6] Perioperative hypotension is also associated with delirium and cognitive decline,[7, 8] although inconsistently.[9] Furthermore, cumulative duration of MAP less than 50, 55, 60, 70, and 80 mmHg appear associated with increased odds of 30-day mortality after noncardiac surgery is reported in a retrospective cohort.[4] Hypotension prevention may therefore be a modifiable factor that reduces postoperative cardiovascular and perfusion related complications.

There is currently sparse evidence that the associations observed between hypotension and myocardial and renal injury are casual. A small randomized trial (n=292) reports that preventing intraoperative hypotension reduces the risk of major complications by 25%.[10] In contrast, a 458-patient randomized trial demonstrated no improvement with tight intraoperative blood pressure control.[11] Limited randomized data (n=199) also suggests that hypotension causes delirium.[12]

A robust trial remains necessary to characterize the potential benefits of reducing perioperative hypotension in high-risk patients. We therefore plan a multi-national randomized trial to test the primary hypothesis that perioperative hypotension prevention in high-risk patients reduces a composite of perfusion-related complications in the 30 days after major non-cardiac surgery. In anticipation of the full trial, we conducted a pre-planned feasibility trial — reported here — designed to evaluate feasibility, especially the ability to target blood pressure per protocol.

METHODS AND ANALYSIS: PARTICIPANTS, INTERVENTION, AND OUTCOMES

Study design

This single-center trial was performed in China-Japan Union Hospital of Jilin University (Jilin, China). The study was approved by the Institutional Review Board (IRB #20201120) on November 30, 2020 and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at clinicaltrials.gov (NCT04789733, named as The GUARDIAN Pilot Trial, Principal investigator: K.L.).

Inclusion criteria

Major inclusion criteria were age ≥45 years; noncardiac surgery expected to last at least 2 hours; overnight hospitalization; ASA physical status 2-4; chronically taking at least one anti-hypertensive medication; and expected to have an arterial catheter before anaesthesia induction. Participants were also required to have at least one of following risk factors: 1) history of peripheral arterial surgery; 2) history of coronary artery disease; 3) history of stroke or transient ischemic attack; 4) serum creatinine >175 μmol/L (>2.0 mg/dl); 5) diabetes requiring medication; 6) current smoking or 15 pack-year history of smoking tobacco; 7) scheduled for major vascular surgery; 8) body mass index ≥ 35 kg/m^2; 9) preoperative high-sensitivity troponin T >14 ng/L or troponin I equivalent; or 10) B-type natriuretic protein (BNP) >80 ng/L or N-terminal B-type natriuretic protein (NT-proBNP) >100 ng/L.

Exclusion criteria

Patients were excluded when they were scheduled for carotid artery surgery, intracranial surgery, partial or complete nephrectomy, pheochromocytoma surgery or liver transplantation. Patients were similarly excluded if they had a condition that precluded routine or tight blood pressure management or had end-stage renal disease. And finally, we also excluded patients with dementia or impairments that might compromise cognitive assessments.

Randomization and masking

Participants were randomly allocated using computer-generated assignments to tight or routine pressure management in a 1:1 ratio without stratification in a block size of four by an independent statistician (D.S.Y) using SAS 9.2 software (SAS Institute, USA). Allocation was concealed within sealed opaque envelopes until shortly before anesthesia induction.

Intervention

The original protocol is detailed in Supplemental Text Document. No changes were made before trial data were accessed. This manuscript adheres to the applicable CONSORT guidelines.

Our feasibility trial was designed to inform a future pivotal trial by considering two co-primary feasibility hypotheses. First that there is suitable statistically significant and clinically meaningful separation of intraoperative and postoperative blood pressure across two blood pressure management strategies (intraoperative MAP maintained ≥ 85 mmHg and postoperative tight pressure control versus routine care with some hypotension expected). And second, that restarting routine antihypertensive medications per protocol is feasible (restart delayed until the third postoperative day versus immediate restart). We also consider the exploratory efficacy hypothesis that perfusion-related complications and delirium are reduced by tight perioperative blood pressure control.

In patients assigned to tight pressure management, angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) were not given the morning of surgery. A norepinephrine peripherally intravenous infusion was adjusted to maintain intraoperative MAP ≥85 mmHg. Either intermittent bolus 4-8 ug noradrenaline at 2 mg/500 ml or a continuous

infusion noradrenaline 3-10 ml/h of a 2 mg/50 ml solution was used per clinical routine in our institution. General anesthesia was induced and maintained per routine as intraoperative bispectral index value of 40-60. Fluid administration and blood transfusion were also per clinical judgement. Resumption of chronic anti-hypertensive medications was delayed until the third postoperative day unless deemed necessary to treat hypertension or for another clinical indication.

In patients assigned to routine pressure management, routinely used ACEIs and ARBs were given the morning of surgery if deemed appropriate by the attending anesthesiologist. Vasopressors, as above, were used per the attending clinician's discretion. General anesthesia was induced and maintained per routine as intraoperative bispectral index of 40-60. Fluid administration and blood transfusion were also per clinical judgement. Intraoperative pressure management was per routine. As usual, chronic anti-hypertensive medication was restarted shortly after surgery unless contraindicated by hypotension.

Blinding

Randomization and group assignment were performed by an investigator (K.L) who did not participate in perioperative care or data collection. Anesthesiologists who were responsible for anesthetic management were not involved in trial follow up. Investigators(Z.T.H, W.Y.L)who performed postoperative follow-up and patients were masked to study group assignment. The trial was thus assessor and patients blinded.

Data collection

The required data was collected by trained research staff, recorded in paper based case report forms (CRFs) and then stored into Excel digital forms. Assessors will conduct the follow-up procedures in person.

Measurements

Intraoperative pressures from the required arterial catheter were automatically recorded in our electronic anesthesia records at 1-minute intervals before anesthesia induction. Typically, postoperative pressures were measured oscillometrically at 8-hour intervals in surgical ward.
For perfusion-related complications, we considered a collapsed (one or more) composite of myocardial injury, stroke, non-fatal cardiac arrest, Stage 2-3 acute kidney injury defined by the creatinine component of the Kidney Disease: Improving Global Outcomes (KIDGO) definition, deep or organ-space infection, sepsis, and all-cause mortality within 30 days of surgery. We required high-sensitivity troponin I and creatinine preoperatively and daily for the initial three postoperative days.

Myocardial injury after non-cardiac surgery was defined as troponin I exceeding the local 99th percentile (0.04 ng/mL).[13] Strokes were detected based on clinical symptoms and required radiographic evidence consistent with new-onset cerebral ischemic or hemorrhagic injury. Delirium was assessed between 7-10 AM and again between 5-8 PM by 3D-CAM for the initial four postoperative days while patients remain hospitalized,[14] with any positive assessment being considered evidence of delirium.

Primary outcomes

The first co-primary outcome was the fraction of time when intraoperative MAP was >85 mmHg, intraoperative area of MAP >85 mmHg, and intraoperative area of MAP <65 mmHg. The second co-primary outcome was postoperative blood pressure management, characterized by the time routine antihypertensive medications were restarted after surgery.

Secondary outcomes

The secondary feasibility outcome measures were time-weighted average (TWA) intraoperative MAP, cumulative minimum MAP for 10 minutes, average postoperative systolic blood pressure (SBP), and mean of the lowest 3 postoperative SBPs. Cumulative minimum MAP for 10 minutes was calculated as the lowest MAP, at or below which a patient's MAP was sustained for at least 10 minutes during the surgery. Post-hoc, we also defined the measures intraoperative area over MAP >80 mmHg and area of MAP <60 mmHg as additional secondary outcomes.

The exploratory efficacy outcome measures were: 1) perfusion-related complications within 30 days of surgery; and 2) postoperative delirium within the first 4 postoperative days.

Data and sample storage

All relevant clinical trial materials will be saved for at least 3 years after termination of the trial. The investigators and statistician have access to the entire data set.

Data monitoring

The trial was coordinated by an Executive Committee, but there was not an external Data and Safety Monitoring Board.

Protocol changes

No protocol changes were made during the trial or before trial data were accessed.

Power calculation

The study enrolled 40 patients in each treatment group. The statistical analysis plan was finalized after patients were enrolled, but before data were accessed.

The fraction of time spent above 85 mmHg was not expected to be normally distributed and instead, assumed to have a Beta(5,5) distribution. Using the above sample size, the confidence interval half-width for estimating the mean would be 0.05, which was deemed to be sufficiently precise. The observed confidence interval widths were 0.01.

Area of MAP <65 mmHg is typically heavily skewed and not normally distributed. Using the same sample size as above, we assumed that area of MAP <65 mmHg would be distributed as Gamma (0.25, 0.1) which would give us a confidence interval half-width of 0.73. This was deemed to be sufficiently precise for estimation of the mean area of MAP <65 mmHg. The observed CI half-widths were 8.6 [reference group] and 0 [treatment group].

Statistical analysis

Balance on baseline characteristics was assessed using absolute standardized difference (ASD), which is defined as the absolute difference in means, ranks, or proportions divided by the pooled standard deviation. Groups were considered to be imbalanced with respect to a baseline characteristic when ASD exceeded 0.44 [1.96*sqrt(1/n1 + 1/n2)].[15]

We primarily evaluated the effect of tight blood pressure control on the fraction of time when intraoperative MAP exceeded 85 mmHg using a t-test. Wilcoxon rank-sum tests were used to evaluate the effect of tight perioperative BP control on intraoperative area of MAP >85 mmHg, intraoperative area of MAP <65 mmHg, and time to restart routine antihypertensive medications after surgery.

We also evaluated the effect of tight blood pressure control on intraoperative area of MAP >80 mmHg, and intraoperative area of MAP <60 mmHg using Wilcoxon rank-sum tests. We used two-sided, two-sample t-tests to evaluate the effect of blood pressure control on time-weighted average intraoperative mean arterial pressure, cumulative minimum MAP for 10 minutes, time weighted average SBP, and mean of the lowest 3 postoperative SBPs. On an exploratory bases, we used log-binomial models to evaluate a collapsed composite of perfusion-related complications, and postoperative delirium.

All analyses were conducted using R 4.0.2.

Patient and public involvement

There was no public or patient involvement.

Ethics and dissemination:

The protocol was approved by The Ethics Committee of the China-Japan Union Hospital of Jilin University, Changchun, China, (Chairperson Prof. Songyan Liu) on November 30, 2020 (Approval number: 20201120).and written informed consent was obtained from all subjects participating in the trial.

Results

Between May 23, 2021, and September 29, 2021, 9618 cases were screened, and 393 were deemed eligible. Two-hundred and ninety cases were preferentially enrolled by another trial. A total of 103 patients were approached, and 80 consented. Forty patients were randomized to tight pressure management and 40 were randomized to routine pressure management. No patients withdrew before hospital discharge. Our CONSORT flow diagram is presented in Figure 1. Three patients assigned to tight pressure management were lost between discharge and the 1-month follow-up assessment. There were thus 80 patients included in the primary analysis, and 77 in the 1-month analysis. The last patient follow-up was completed on November 1, 2021.

Patient demographic and baseline characteristics are presented in Table 1. Only diastolic blood pressure (DBP) and surgery type were imbalanced, with ASD >0.44. The median [Q1, Q3] blood loss was 175 [100, 300] ml in the tight perioperative BP control group and 50 [50, 200]

ml in the routine BP management group.

Table 1.Patient baseline and demographic characteristics

Characteristic	Routine perioperative BP control	Tight perioperative BP management	ASD
	N=40	*N=40*	
Age	68 (10)	67 (10)	0.12
Height - cm	166 (8)	165 (8)	0.06
Weight - kg	66 (12)	71 (16)	0.28
SBP	142 (18)	148 (21)	0.31
DBP	80 (10)	86 (10)	0.67*
Surgery length (hours)	2.56 [2, 4]	2.25 [1.7, 2.8]	0.26
Surgery Type			0.66*
Abdominal	23 (58%)	18 (45%)	
Gynecologic	0 (0)	1 (2%)	
Neurosurgical	2 (5%)	6 (15%)	
Orthopedic	6 (15%)	3 (8%)	
Thoracic	7 (18%)	12 (30%)	
Thoracic and abdominal	1 (2%)	0 (0)	
Urology	1 (2%)	0 (0)	
Smokers	8 (20%)	6 (15%)	0.13

Data are presented as mean (SD), median [Q1, Q3] or n (%) as appropriate.
*ASD – Absolute Standardized Difference; *ASD > 0.44 indicates imbalance.*

The mean (SD) fraction of time with intraoperative MAP exceeding 85 mmHg (i.e., time when MAP >85 mmHg divided by total surgery duration) was 0.52(0.25) in patients assigned to routine blood pressure management and 0.87(0.15) in those assigned to tight control. The estimated absolute difference in the mean fraction of time between tight and routine blood pressure management was 0.35 [95% CI: 0.26, 0.44].

The median [Q1-Q3] intraoperative area of MAP >85 mmHg was 1303 [772-2419] mmHg*min in patients assigned to routine perioperative BP control and 2425 [1926- 3545] mmHg*min in those assigned to tight perioperative BP management (Figure 2). Tight blood pressure control increased area of MAP >85 mmHg by 1102 [95% CI: 596, 1608] mmHg*min. Similarly, for intraoperative area of MAP <65 mmHg, the median [Q1-Q3] was 7 [0-40] mmHg*min with routine pressure management, and 0 [0-0] mmHg*min with tight control (Figure 3). Tight pressure control thus reduced exposure to MAP <65 mmHg by 6 [95% CI: 2, 15] mmHg*min.

In the routine pressure management group, 40% (n = 16) of the patients experienced hypotension (any time below 65 mmHg) with a median [Q1-Q3] duration of 6 [2-9] minutes compared to 10% (n = 4) in the tight blood pressure control group, with a median duration of 5 [4-6] minutes (Supplemental Figure 1).

The median [Q1, Q3] intraoperative area of MAP >80 mmHg was 1917 [1249-3169] mmHg*min in patients assigned to routine BP control and 3355 [2549-4417] mmHg*min in the patients assigned to tight BP control. The area of MAP >80 mmHg was thus 1335 [95% CI: 667, 1928] mmHg*min greater in patients assigned to tight pressure control. For intraoperative area of MAP <60 mmHg, the median was 0 [0-6] mmHg*min with routine pressure management and 0 [0-0] mmHg*min with tight pressure control, for an estimated treatment effect of 0 [95% CI: 0, 0] (Table 2).

Table 2. Summary of analysis results.

Outcome	**Routine BP Management*** ***N = 40***	**Tight Perioperative BP Control*** ***N = 40***	**Estimated treatment effect [95% CI]**
Primary Outcomes			
Fraction of intraoperative period with MAP >85 mmHg	0.52 (0.25)	0.87 (0.15)	0.35 [0.26 to 0.44]**
Area of intraoperative MAP >85 mmHg (mmHg*min)	1303 [772-2419]	2425 [1926- 3545]	1102 [596 to 1608]***
Area of intraoperative MAP ≤65 mmHg (mmHg*min)	7 [0-40]	0 [0-0]	-6 [-15 to -2]***
Time to restart antihypertensive medications (days)	1 [1-1]	4 [3-4]	2 [1 to 3]***
Secondary Outcomes			
Area of intraoperative MAP >80 mmHg (mmHg*min)	1917 [1249- 3169]	3355 [2549-4417]	1335 [667 to 1928]**
Area of intraoperative MAP ≤60 mmHg (mmHg*min)	0 [0-6]	0 [0-0]	0 [0 to 0]**
Time-weighted average	89(9)	101(8)	12 [8 to 16]***

intraoperative MAP (mmHg)			
Minimum intraoperative MAP sustained for 10 cumulative minutes (mmHg)	71(9)	85(9)	14 [11 to 18]***
Mean postoperative systolic pressure (mmHg)	133(15)	138(13)	5 [-1 to 11]***
Mean of 3 lowest postoperative systolic pressures [mmHg]	122(14)	127(14)	5 [-1 to11]***

*Data presented as means (SD) or medians [IQR]
** Difference in means and 95% CI
*** Hodges Lehmann shift estimator

The mean difference in the intraoperative TWA MAP between tight and routine pressure management was 12 [95% CI: 8 to 16] mmHg, and the difference in cumulative intraoperative minimum MAP sustained for 10 minutes was 14 [95% CI: 11 to 18] mmHg. (Supplemental Figure 2; Table 2).

Antihypertensive medications were restarted 2 [95% CI: 1 to 3] days later in patients assigned to tight blood pressure control. The difference [95% CI] in postoperative mean SBP between tight and routine pressure management was 5 [-1 to 11] mmHg, and the difference in mean of the lowest 3 postoperative SBP measurements was also 5 [-1 to 11] mmHg (Supplemental Figure 3; Table 2).

The incidence of perfusion related complications was 12% in both groups and the relative risk was estimated to be 1.0 [0.3 to 3.3]. No delirium was detected in either group. No severe adverse events were attributed to the study.

DISCUSSION

Intraoperative blood pressure management was well maintained in patients assigned to tight control titrated with norepinephrine intravenous infusion, and MAP exceeded the target of 85 mmHg in 87% of the time. Furthermore, the average of the lowest mean arterial pressures sustained for ten minutes in the tight group was 85 mmHg, indicating that mean arterial pressures in these patients was only rarely and transiently less than 85 mmHg. Intraoperative pressures also exceeded 85 mmHg about half the time in patients assigned to routine management which is unsurprising since hypertension was an inclusion criterion for the trial.

Because patients cannot be randomized to hypotension, the more important question is the extent to which pressures were <65 mmHg, which is thought to be the intraoperative harm threshold, with routine management. There was almost no hypotension in patients assigned to tight control whereas the median area <65 mmHg was 7 mmHg*min in those with routine management. Furthermore, the lowest mean arterial pressures sustained for ten minutes in

patients assigned to routine management was 71 (9) mmHg, and about 40% of patients had lowest sustained pressures ≤65 mmHg. There were thus distinct differences in mean arterial pressures in the two management groups, with one having virtually no hypotension and the other often experiencing mean pressures ≤65 mmHg.

Antihypertensive management was successful with the mean restart day being 1 with routine management and 4 with tight management, corresponding to a difference of 2 [95% CI: 1 to 3] days which is a clinically meaningful difference. However, antihypertensive management had little effect on postoperative systolic pressures, with the lowest three measurements differing by only 5 mmHg. Furthermore, the average lowest measurements exceeded 120 mmHg which is well above proposed postoperative harm threshold defined either by a mean arterial pressure of 75 mmHg[16] or a systolic pressure of 90 mmHg.[5] These results suggest that antihypertensive management should not be included in the full trial.

Previous studies report considerably more postoperative hypotension than we observed. For example, Liem reported that 2 cumulative hours below threshold of 60 mmHg occurred in 8% patients and 4 continuous hours less than 75 mmHg occurred in 48% patients.[16] Khanna and colleagues similarly reported that 63% of patients experienced a MAP ≤75 mmHg within 48 hours after surgery, and that 22% experienced MAP ≤65 mmHg.[17] However, there were two important differences between our trial and previous observational reports. The first is that both previous reports were based on continuous noninvasive blood pressure monitoring rather than oscillometric assessments at 8-hour intervals. Continuous monitoring will obviously detect more hypotension than intermittent monitoring. Furthermore, continuous non-invasive monitors are not well validated and may at times generate false low values. More frequent postoperative measurements would be helpful in a full trial. The second important difference between current and previous results is that enrollment in our feasibility trial was restricted to patients taking anti-hypertensive medications, and thus having a diagnosis of hypertension. It is understandable that hypertensive patients would have less hypotension than a general surgical population.

Only 10 of 80 patients experienced our composite outcome of major perfusion-related complications, evenly split between the treatment groups. With so few events, the (lack of) difference between the groups is noninformative. Curiously, no delirium was observed in our 80 patients. The incidence of delirium after noncardiac surgery varies widely, but is probably now lower than previously reported.[18, 19] Delirium incidence also clearly depends strongly on age, with the incidence increasing markedly in patients older than 65 years.[9] The average age in our patients was 67 years which is relatively young which may have contributed to lack of observed delirium.

The major limitation of our trial is that it was conducted in a single center whereas our planned full trial will involve dozens of centers around the world. Our results demonstrating that intraoperative pressure and postoperative antihypertensive management is feasible does not mean that it will prove practical at all trial sites. Because the trial was only powered for feasibility and pressure management, the incidence of hard outcomes (based on only ten events)

is essentially non-informative.

Conclusion

We achieved substantial separation of intraoperative mean arterial pressures. Similarly, we were able to control restarting antihypertensive medications per protocol — although doing so had relatively little effect on postoperative systolic pressures. Furthermore, the requirement that all patients have chronic hypertension resulted in relatively high intraoperative and postoperative pressures. Consequently, we amended the protocol for the full trial to include patients without chronic hypertension and no longer specify posotoperative antihypertensive management. The full trial appears feasible and remains well warranted.

Contributorship statement

Kai Li was principal investigator and helped design the protocol, applied for ethics approval, registered the trial, assigned groups, and drafted the manuscript. Zhouting Hu and Wangyu Li helped collect data. Karan Shah was responsible for data analysis. Daniel I. Sessler designed the protocol and provided overall trial guidance. All authors reviewed and revised the manuscript.

Competing interests

Dr. Sessler is a consultant for Edwards Lifesciences (Irvine, California). He serves on advisory boards and has equity interests in Calorint (Philadelphia, Philadelphia), TransQtronics (Philadelphia, Philadelphia), the Health Data Analytics Institute (Boston, Massachusetts), Medasense (Tel Aviv, Israel), Serenno (Tel Aviv, Israel), and Perceptive Medical (Newport Beach, California). The other authors declare no competing interests.

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Data sharing statement

The investigators and statistician have access to the whole data set. Data will be shared collaboratively with external parties with approval of the Executive Committee and appropriate data-use agreements.

Ethics approval

The protocol was approved by The Ethics Committee of the China-Japan Union Hospital of Jilin University, Changchun, China, (Chairperson Prof. Songyan Liu) on November 30, 2020 .. (Approval number: 20201120).

Patient consent for publication.

Consent obtained directly from patient(s).

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Figure Legends

Figure 1. CONSORT flow diagram. Patient flow through stages of the trial.

Figure 2. Area of intraoperative MAP >85 mmHg by blood pressure management group. The lower and upper edges of the box correspond to 25th and 75th percentile respectively, with the central line representing the median; whiskers extend to 1.5 times the interquartile range from the edges of the box; data beyond the whiskers are outliers and plotted individually.

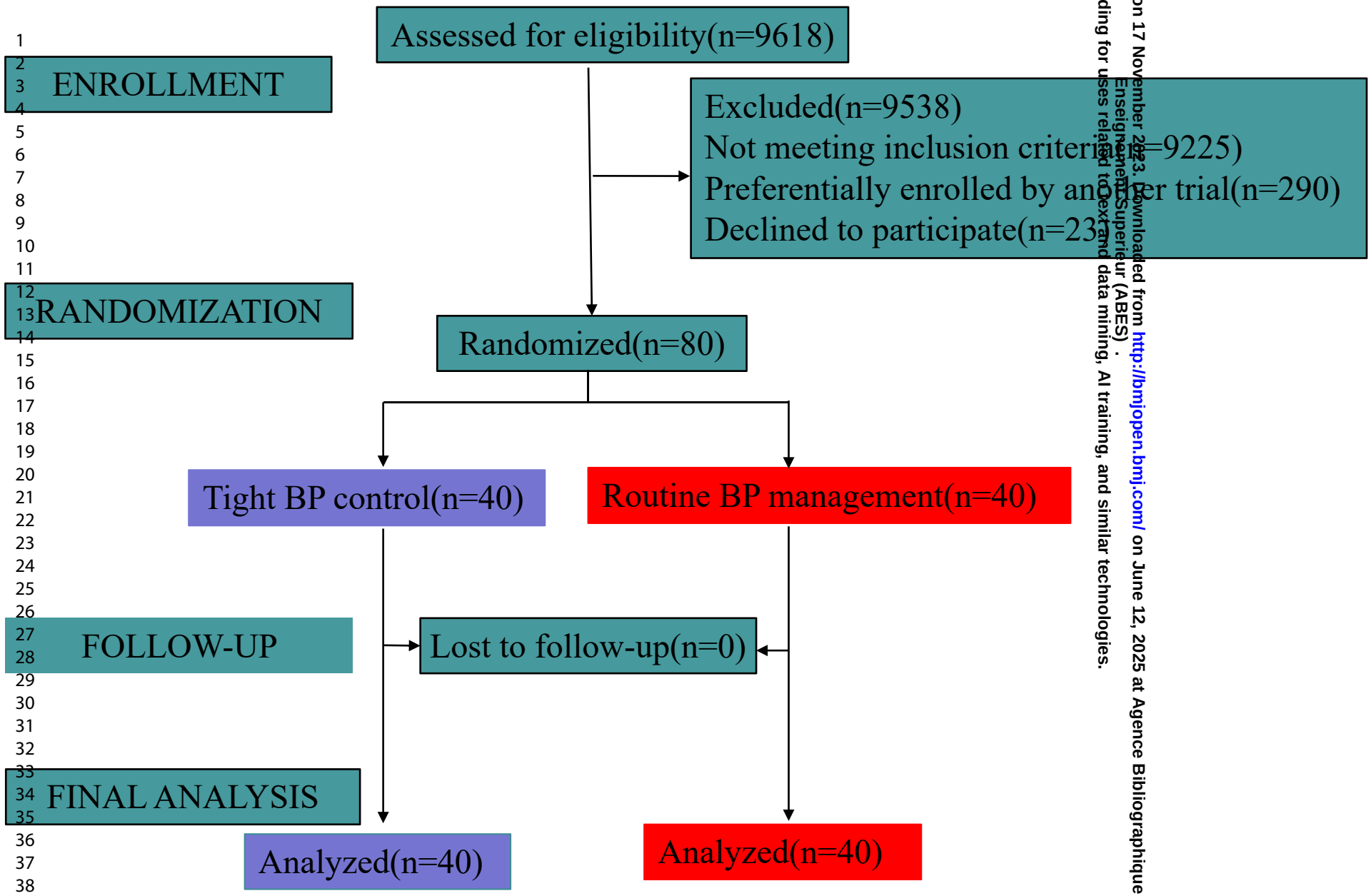
Figure 3. Area of intraoperative MAP <65 mmHg by blood pressure management group. The lower and upper edges of the box correspond to 25th and 75th percentile respectively, with the central line representing the median; whiskers extend to 1.5 times the interquartile range from the edges of the box; data beyond the whiskers are outliers and plotted individually.

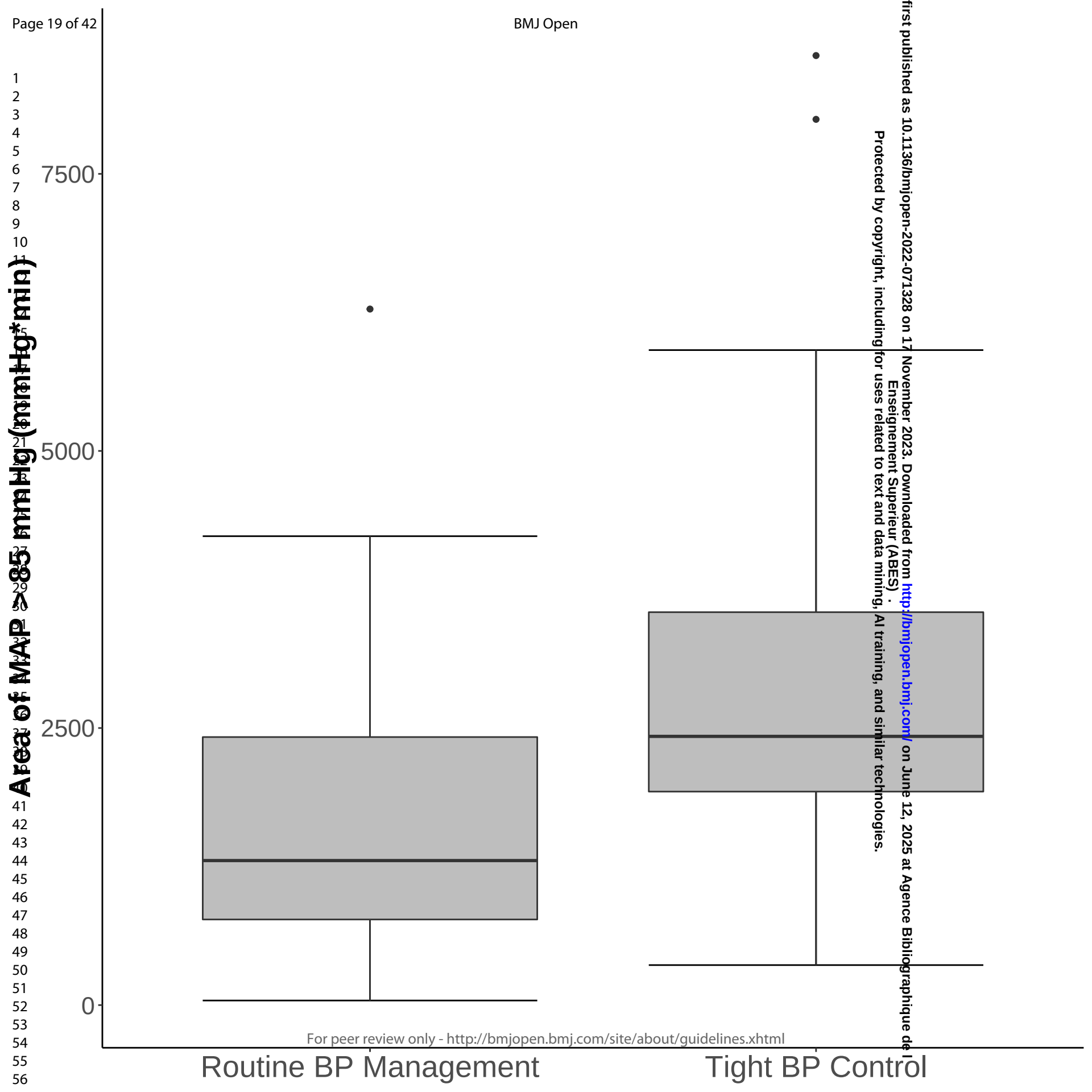
Supplemental Figure 1. Time spent below 65 mmHg by blood pressure management group. Patients who never went below 65mmHg not shown.

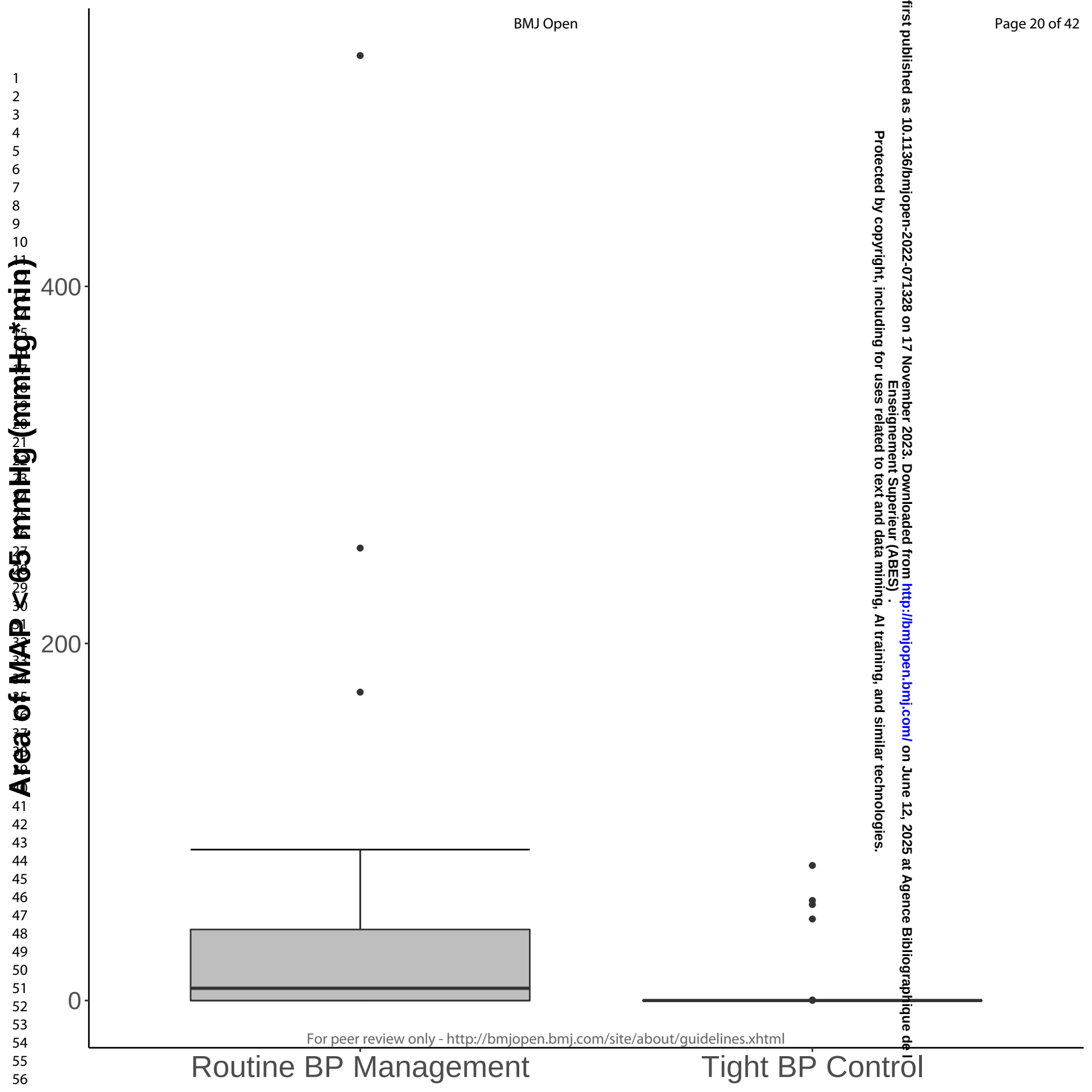
Supplemental Figure 2. Cumulative lowest intraoperative MAP sustained for 10 minutes by treatment group. The lower and upper edges of the box correspond to 25th and 75th percentile respectively, with the central line representing the median; whiskers extend to 1.5 times the interquartile range from the edges of the box; all data points are plotted individually and superimposed on the boxplot.

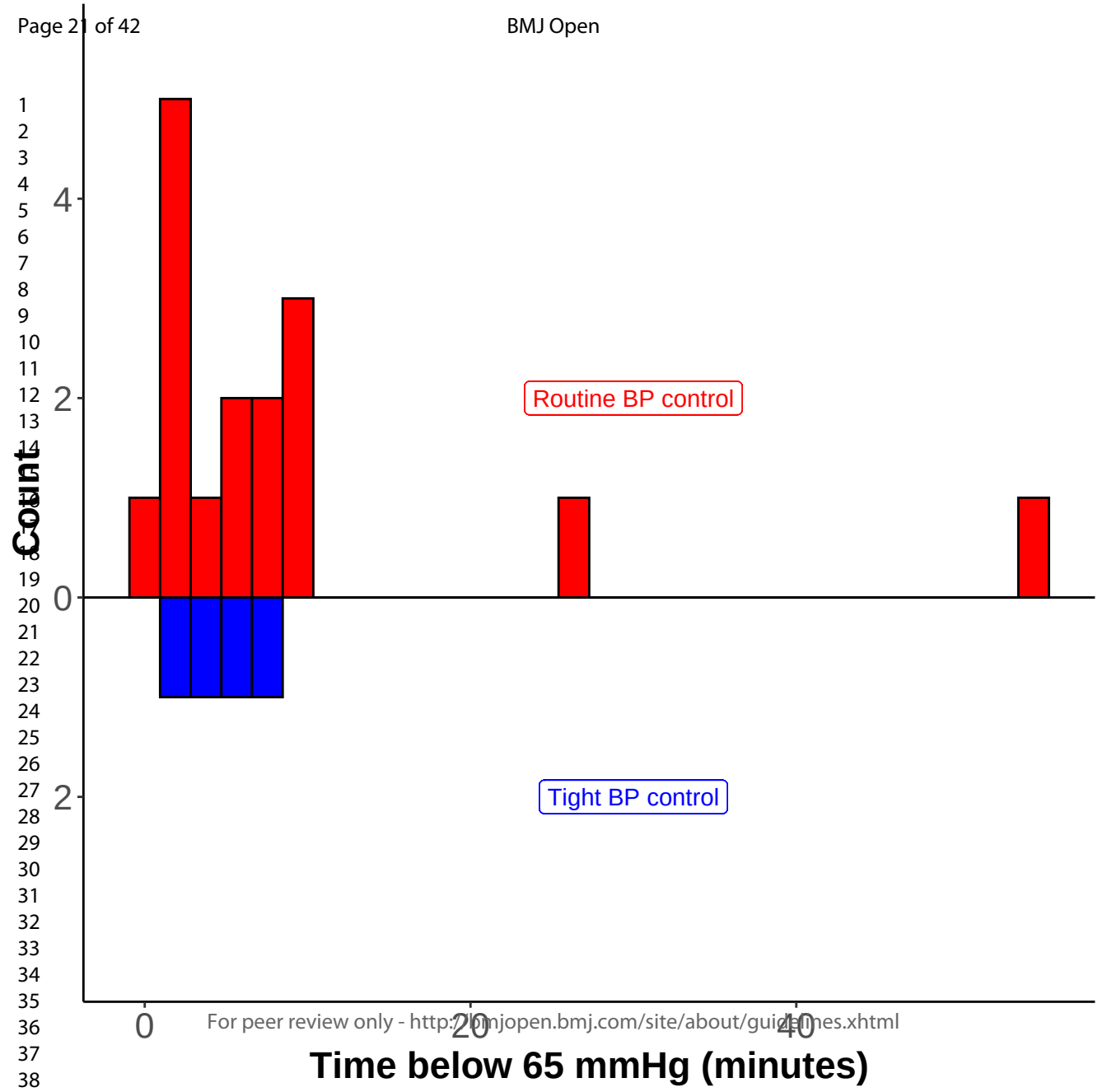
Supplemental Figure 3. Mean of lowest 3 postoperative systolic blood pressure measurements by treatment group. The lower and upper edges of the box correspond to 25th and 75th

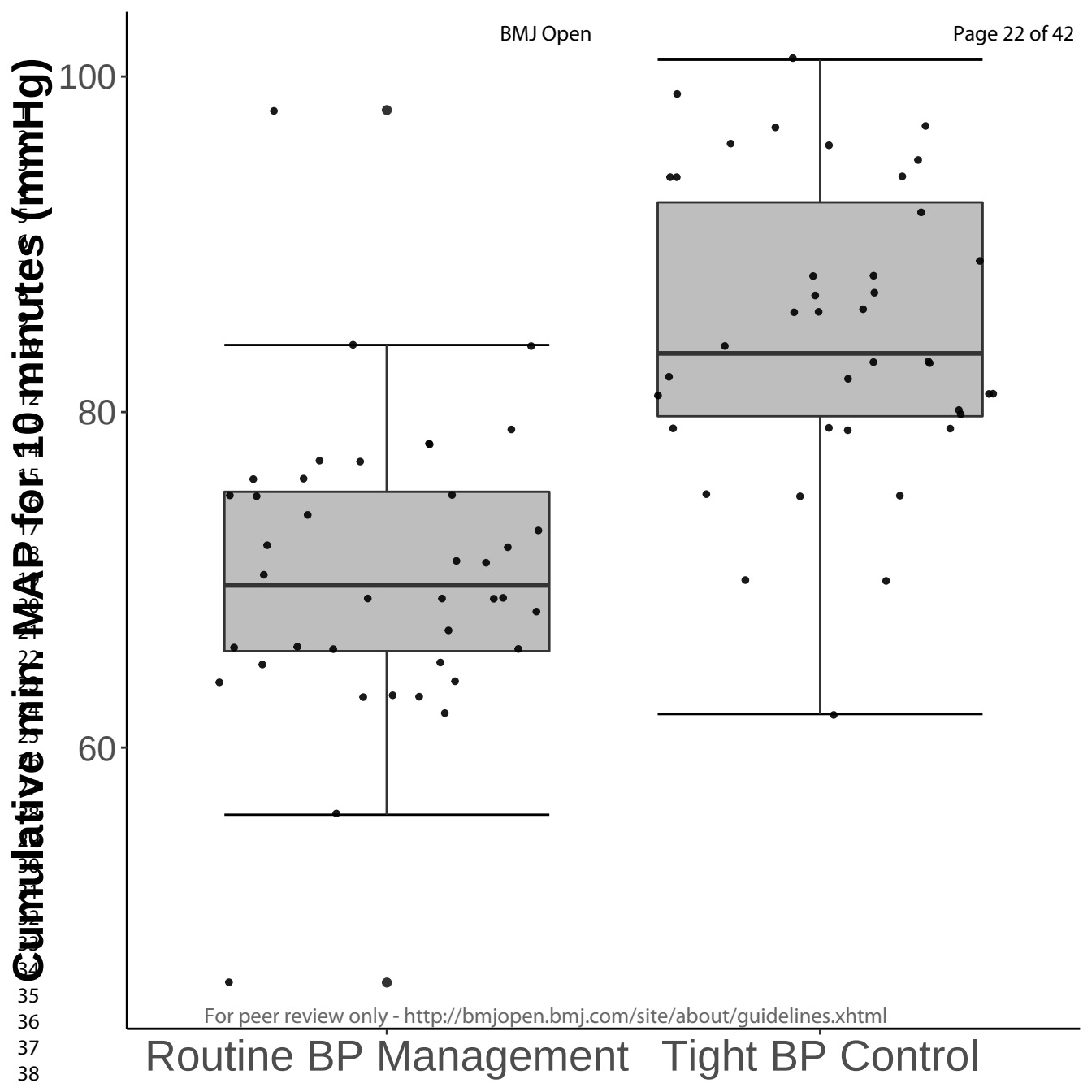
percentile respectively, with the central line representing the median; whiskers extend to 1.5 times the interquartile range from the edges of the box; all data points are plotted individually and superimposed on the boxplot.

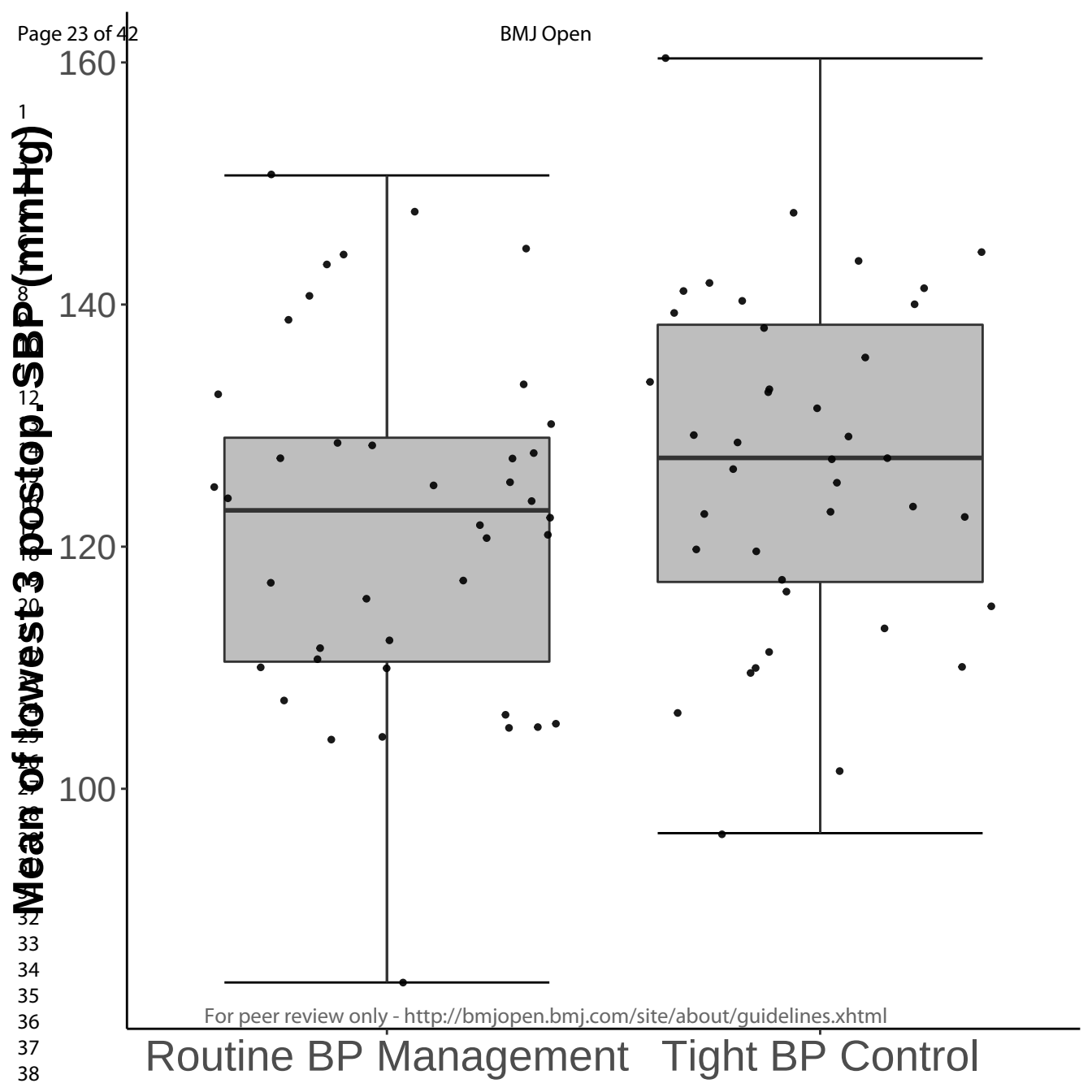












Pilot of "tight perioperative blood pressure management to reduce serious cardiovascular, renal, and cognitive complications"

The GUARDIAN Pilot Trial

Single-center prospective randomized pilot trial

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Guided by

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Summary

We are planing to propose a robust international randomized trial in 6,254 patients to test the primary hypothesis that perioperative tight blood pressure management reduces a composite of major perfusion-related complications (myocardial injury, stroke, non-fatal cardiac arrest, Stage 2-3 acute kidney injury, deep or organ-space infection, sepsis, and death) in the 30 days after major non-cardiac surgery.

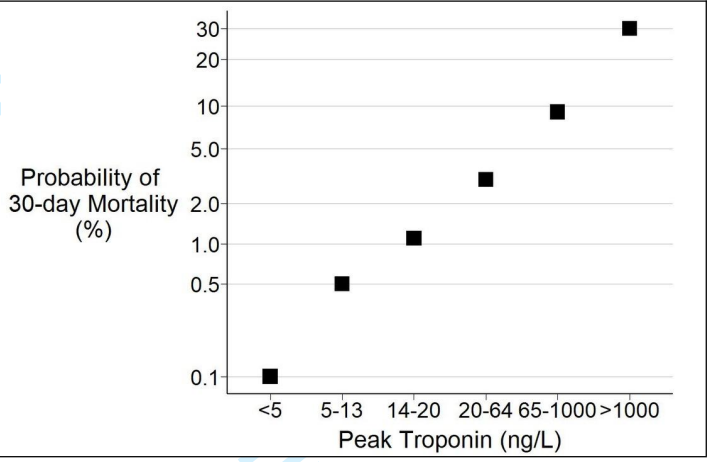
In anticipation of the full trial, we will conduct the pre-planned pilot trial designed to evaluate feasibility, especially the ability to target blood pressure per protocol. The pilot trial of 80 cases will be designed to inform a future pivotal trial by considering two co-primary feasibility hypotheses. First that there is suitable separation of intraoperative and postoperative blood pressure across two blood pressure management strategies (intraoperative MAP maintained ≥85 mmHg and postoperative tight pressure control *versus* routine care with some hypotension expected). And second, that restarting routine antihypertensive medications per protocol is feasible (restart delayed until the third postoperative day *versus* immediate restart). We also consider the exploratory efficacy hypothesis that perfusion-related complications and delirium are reduced by tight perioperative blood pressure control.

Introduction

When patients having major surgery reach the post-anaesthesia care unit, families naturally assume that they have survived the most dangerous part of the perioperative experience. Their assumption is wrong. Mortality in the 30 days after surgery is 1,000 times higher than intraoperative mortality.[1,2] In fact, if the month after surgery were considered a disease, it would be the third leading cause of death in the United States.[3] Most postoperative mortality occurs during the initial hospitalization, that is, under direct medical care in our highest-level facilities. The two most common and comparable causes of 30-day mortality after non-cardiac surgery are major bleeding which cannot easily be prevented, and myocardial injury which possibly can be; sepsis is a distant third.[4]

Myocardial injury after non-cardiac surgery (MINS) is defined by troponin elevation of presumably ischemic origin, and is highly associated with 30-day[5] (Fig. 1) and one-year[6] mortality. Myocardial infarction (MI), per 4th Universal Definition, is defined by troponin elevation *and* either symptoms or signs of myocardial ischemia.[7] More than 90% of MINS and MI occur within the initial two postoperative days.[8] Both are strongly associated with many *unmodifiable* baseline characteristics including age, diabetes, and cardiovascular history. In large randomized trials (n=7,000-10,000), we have shown that MI cannot be safely prevented by beta blockers,[9] avoiding nitrous oxide,[10] clonidine,[11] or aspirin.[12] In a recent large trial, one patient in seven who had MINS suffered re-infarction within 17 postoperative months.[13]

Fig. 1. 30-day mortality as a function of postoperative peak high-sensitivity troponin T. Mortality increases markedly from 0.1% at a troponin T concentration <5 ng/L to 30% mortality when troponin T exceeds 1,000 ng/L. Data from The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators: Association between complications and death within 30 days after noncardiac surgery. Can Med Assoc J 2019; 191: E830-E7



Intraoperative hypotension is associated with MINS and MI, with the harm threshold being a mean arterial pressure (MAP) ≈65 mmHg (Fig. 2).[14,15] The harm threshold for acute kidney injury (AKI) is similar,[14,16,17] and 40% of Stage 2 AKI persists or is worse 1-2 years after surgery (Turan, Anesthesiology, in press). We and others have also shown that postoperative hypotension is associated with myocardial infarction, *independent of intraoperative hypotension* (Fig. 3).[18,19]

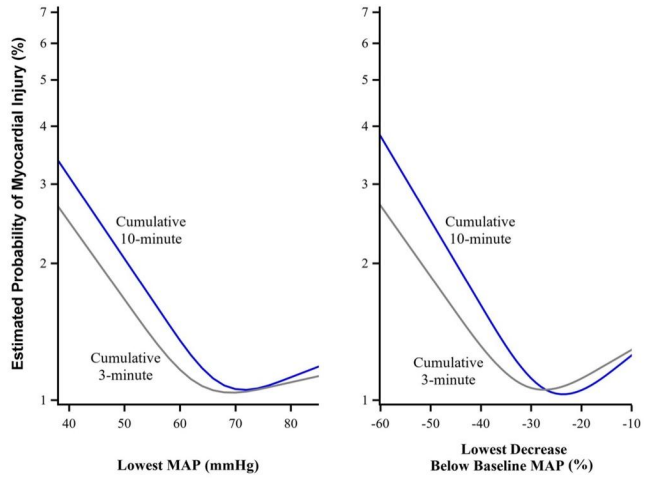


Fig. 2. Lowest mean arterial pressure (MAP) thresholds for myocardial injury after non-cardiac surgery. The left graph shows the relationship between the lowest cumulative absolute mean arterial pressure maintained for 3 and 10 minutes and myocardial injury. The right graph shows the relationship between the lowest cumulative relative mean arterial pressure maintained for 3 and 10 minutes and myocardial injury. Both graphs are multivariable logistic regressions adjusted for baseline characteristics and smoothed by restricted cubic spline with three degrees and knots at 10th, 50th, and 90th percentiles of given exposure variable. From Salmasi, et al: Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after non-cardiac surgery: A retrospective cohort analysis. Anesthesiology 2017; 126: 47-65.

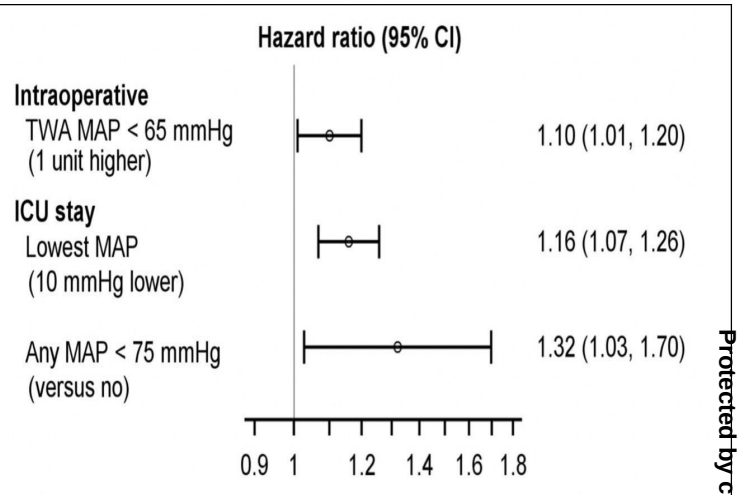


Fig. 3. Odds ratios of average relative effect on the primary composite of 30-day myocardial infarction and mortality for three perioperative periods: intraoperative, remaining day of surgery, and the initial four PODs of hospitalization. CIs for multiple comparisons were adjusted by Bonferroni correction. Correspondingly, P < 0.017 (0.05/3) was considered to be significant for the average relative effect. The circles present the odds ratios, and the bars present the CIs. POD = postoperative day. From Sessler 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: 317-27

There is currently sparse evidence that the associations are casual. But a small fragile randomized trial (n=292) shows that preventing intraoperative hypotension reduces the risk of major complications by 25%.[20] Perioperative hypotension is also associated with stroke,[9,21-24] although inconsistently.[25] Blood pressure — specifically hypotension prevention — is therefore a modifiable factor that may reduce cardiovascular complications.

Delirium is a common complication of cardiac surgery and is associated with morbidity and mortality.[26-32] The reported incidence of delirium after major non-cardiac surgery is typically about 10%, and increases markedly as age increases beyond 65 years. The pathophysiology of delirium is multifactorial but surely includes inadequate brain perfusion that results when mean arterial pressure is less than the lower limit of autoregulation.[33-35] Consistent with this theory, hypotension is associated with delirium and cognitive decline,[28,36,37] although inconsistently.[27,38,39] Limited randomized data (n=199) indicate that hypotension causes delirium.[40] Patients who have delirium after surgery are far more likely than others to develop long-term cognitive impairment,[41] although it remains unknown whether the association is causal. Hypotension may also provoke overt or (far more commonly) covert strokes which is strongly linked to delirium.[42]

No robust randomized trial has been published.

Specific Aims

Mortality in the 30 days after surgery is surprisingly common, and usually occurs during the initial hospitalization. Major bleeding and cardiovascular complications are the most common causes of 30-day postoperative mortality. Cardiovascular complications are independently associated with intraoperative and postoperative hypotension. Cognitive impairment, both acute delirium and long-term, are common after major surgery. There is increasing evidence that perioperative hypotension may contribute to brain injury. However, there is currently only sparse and fragile randomized evidence indicating that intraoperative hypotension prevention reduces cardiovascular risk and/or cognitive impairment in non-cardiac surgical patients. We are planing to propose a robust international randomized trial in 6,254 patients to test the primary hypothesis that perioperative tight blood pressure management reduces a composite of major perfusion-related complications (myocardial injury, stroke, non-fatal cardiac arrest, Stage 2-3 acute kidney injury, deep or organ-space infection, sepsis, and death) in the 30 days after major non-cardiac surgery.

In anticipation of the full trial, we will conduct the pre-planned pilot trial designed to evaluate feasibility, especially the ability to target blood pressure per protocol.

Aims

First, we will test whether there is suitable separation of intraoperative and postoperative blood pressure across two blood pressure management strategies (intraoperative MAP maintained ≥85 mmHg and postoperative tight pressure control versus routine care with some hypotension expected).

Second, that restarting routine antihypertensive medications per protocol should be feasible (restart delayed until the third postoperative day versus immediate restart).

We also consider the exploratory efficacy hypothesis that perfusion-related complications and delirium are reduced by tight perioperative blood pressure control.

Methods

The trial will be conducted with IRB approval and written patient consent will be obtained. There will be no restriction on sex, or ethnicity. All qualifying patients will be asked to consider the trial. The trial is restricted to patients ≥45 years old because cardiovascular outcomes are rare in younger patients, but there is no upper age restriction. The trial will be registered on ClinicalTrial.gov before enrollment.Pilot patients will be enrolled before normal enrollment.A full statistical analysis plan will be developed before any data are evaluated. Reporting will be consistent with the CONSORT guidelines.

Subject selection

Consenting patients will be **eligible** if they are:

1. Scheduled for major noncardiac surgery expected to last at least 2 hours;
2. Having general endotracheal anesthesia;
3. Expected to require at least overnight hospitalization;
4. Are designated ASA physical status 2-4;
5. Chronically taking at least one anti-hypertensive medication;
6. Expected to have direct blood pressure monitoring with an arterial catheter;
7. At least 45 years old;
8. Cared for by clinicians willing to follow the protocol;
9. Subject to at least one of the following risk factors:
    a. History of peripheral arterial surgery;
    b. History of coronary artery disease;
    c. History of stroke or transient ischemic attack;
    d. Serum creatinine >175 µmal/L (>2.0 mg/dl);
    e. Diabetes requiring medication;
    f. Current smoking or 15 pack-year history of smoking tobacco
    g. Scheduled for major vascular surgery
    h. Body mass index ≥35 kg/m^2;
    i. Preoperative high-sensitivity troponin T >14 ng/L or troponin I equivalent
    j. B-type natriuretic protein (BNP) >80 ng/ml or N-terminal B-type natriuretic protein (NT-ProBNP) >200 ng/ml.

Patients will be **ineligible** if they:

1. Are scheduled for carotid artery surgery;
2. Are scheduled for intracranial surgery;
3. Are scheduled for partial or complete nephrectomy
4. Are scheduled for pheochromocytoma surgery;
5. Are scheduled for liver transplantation;
6. Have a condition that precludes routine or tight blood pressure management such as surgeon request for relative hypotension or relatively high pressure required for carotid artery surgery;
7. Have end-stage renal disease requiring dialysis or estimated glomerular filtration rate (eGFR) <30 ml/min;
8. Have a documented history of dementia;
9. Have language, vision, or hearing impairments that may compromise cognitive assessments;

Protocol

Consenting patients who take either ACEIs or ARBs will be asked not to take the medications on the morning of surgery, and instead bring them with them to the hospital. Qualifying patients will be randomly allocated using computer-generated assignments 1:1 ratio without stratification in a block of four. Allocation will be concealed within sealed opaque envelopes until shortly before anesthesia induction. Allocation will thus remain concealed until the last practical moment. Randomization will be implemented by clinicians in collaboration with research personnel. Arterial catheter transducers will be positioned at the level of the right atrium, and adjusted as necessary if

patient position is changed. A fast-flush square-wave test will be performed shortly after catheter insertion to confirm that dynamic characteristics of the pressure monitoring system are appropriate.[10]

The treatments will be:1) norepinephrine infusion to maintain intraoperative MAP ≥85 mmHg, delayed resumption of chronic antihypertensive medications, and a target ward systolic pressure of at least 120 mmHg (tight pressure management); or, 2) routine intraoperative blood pressure management and prompt resumption of chronic antihypertensive medications (routine pressure management)

Tight pressure management: In patients assigned to tight pressure management, angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) will not be given the morning of surgery. Clinicians will be encouraged to insert the required arterial catheter before anesthetic induction because much hypotension occurs shortly after anesthetic induction.[46] A norepinephrine infusion (in the preferred local concentration) will be prepared, connected to an intravenous catheter, and activated at a low rate. Norepinephrine can be safely given through a central catheter or peripherally. In a recent study of 14,328 patients, there were only 5 extravasation events and not a single patient experienced local tissue injury.[47] It can be substituted if norepinephrine is contraindicated or impractical.

General anesthesia will be induced with propofol which will be given in repeated small boluses in an effort to keep intraoperative MAP ≥85 mmHg. Simultaneously, the vasopressor infusion will be adjusted with the same goal. Anesthetic dose, fluid administration, and vasopressor administration will be adjusted with the goal of maintaining intraoperative MAP ≥85 mmHg.

Resumption of chronic anti-hypertensive medications will be delayed until the third postoperative day unless deemed necessary to treat hypertension or for some other clear indication (e.g., preventing atrial fibrillation in a chronic beta-blocker user) because >90% of MINS occurs within 48 hours after surgery. When necessary to treat hypertension, chronic antihypertensive or new medications can be used per clinician preference. Clinicians will make what efforts they can to maintain postoperative systolic pressure of at least 120 mmHg during the initial three postoperative days by maintaining adequate hydration, using inotropic and chronotropic drugs, and vasopressor as necessary. This protocol specifies the blood pressure target, but leaves implementation to clinical judgement.

Routine pressure management: In patients assigned to routine pressure management, ACEIs and ARBs can be given the morning of surgery if deemed appropriate by the attending anesthesiologist. The arterial catheter will be inserted before or after induction of anesthesia per clinician preference. General anesthesia will be induced and maintained per routine. Intraoperative pressure management will be per routine. As usual, chronic anti-hypertensive medications will be restarted shortly after surgery unless contraindicated by hypotension.

In both groups, other aspects of anesthetic management will be at the discretion of the responsible anesthesiologist, including the types and volumes of various fluids. Volatile or intravenous anesthesia is permitted. There is increasing evidence that deep anesthesia promotes delirium and long-term cognitive dysfunction (Evered, in review).[49] Therefore, processed EEG monitoring, such as the Bispectral Index (BIS) or Patient State Index (PSI), should be used. If BIS is

the method, a value of 50 should be targeted from soon after induction until shortly before emergence. If another EEG system is used, a comparable hypnotic depth should be targeted.

There will be no limitation on ancillary vasoactive, chronotropic, and inotropic drugs. Clinicians will be free to use advanced hemodynamic monitoring (e.g., FlowTrac, esophageal Doppler, etc.). Blood products will be given per routine. Similarly, postoperative analgesic management will be per routine and clinician preference. Neuraxial and peripheral nerve blocks are permitted, but epidural catheters should not be activated until surgery is nearly finished.

Because patients must be fairly sick to qualify for Pilot GUARDIAN, some will go to directly from surgery to critical care units, or much less often, become unstable and require transfer from a routine ward to an ICU. In either case, every effort will be to maintain randomized treatments and blood pressure targets.

In all cases, good judgement will predominate. Clinicians should always act in their patients best interests, irrespective of the GUARDIAN protocol.

Measurements

Baseline

Baseline demographic and morphometric characteristics will be recorded, including height, weight, and sex. Routine anesthetic variables will be recorded including volatile anesthetic partial pressure, Fluid type and volume, estimated blood loss, and transfusions. Cardiovascular risks will be recorded, including hypertension requiring treatment, diabetes requiring oral medications or insulin, history of previous myocardial infarction, congestive heart failure, chronic obstructive pulmonary disease, current smoking status, and pack-years of smoking history. Cardiovascular medications will be similarly recorded by category, including beta blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and statins. Types of surgery will be characterized as orthopedic, laparoscopic, open abdominal, neurosurgical (including spine), thoracic, urologic, gynecologic, vascular, and other. Timing will be characterized as elective, urgent, or emergent.

Baseline laboratory values (within 30 days before surgery) will be recorded on an as-available basis, including albumin, BNP, and NT-ProBNP. Baseline electrocardiogram and echocardiogram interpretations will also be recorded as available, as will hemoglobin and creatinine other than specified below.

Perioperative

Blood pressure is our primary exposure and will therefore be carefully recorded. The most recent pressure from a clinic assessment will be used. Our institution have electronic anesthesia records that will automatically record systolic, mean, and diastolic pressures from the required arterial catheter at no less than 1-minute intervals. When possible, we will obtain electronic data which are efficient, denser, and more reliable than manual recording. But where necessary, intraoperative blood pressures will be recorded manually at 5-minute intervals. Ward blood pressure will normally be recorded by nurses at 8-hour-intervals. Any pressures obtained for clinical purposes will be recorded for use in the trial.Additional ward pressures might also be obtained. However, all blood pressures during the initial three postoperative days will be retrieved and included in the trial database. We will restrict recording to this period because >90% of postoperative myocardial injury occurs within the

initial two postoperative days. High-risk patients may require ICU admission. Blood pressure is measured frequently in critical care units, and all available pressures will be recorded.

We will require **creatinine** preoperatively (within 30 days), and on the initial three postoperative days while patients remain hospitalized. Additional values obtained for clinical reasons will be recorded during the initial 30 postoperative days. Hemoglobin will be recorded on an as-available basis for the initial three postoperative days.

Blood for generations 4 or 5 **troponin** T, or troponin I will be recorded preoperatively up to 30 days before surgery, and on the first three postoperative days so long as patients remain hospitalized.[8] Additional troponin samples will also be obtained if patients have shortness of breath or experience chest, neck, or arm pain. Blood troponin concentrations exceeding thresholds (depending on individual types of troponin tests) should prompt cardiology consultation, an electrocardiogram, and when practical an echocardiogram.

Myocardial injury will be diagnosed by objective screening based on preoperative and first three postoperative day troponin I values crossing specific thresholds for MINS so long as patients remain hospitalized. Abnormal troponin concentrations will be evaluated as clinically indicated with ECG, echocardiography, and clinical symptoms; the resulting values will be recorded, as will other cardiovascular interventions such as angioplasty. MINS will be diagnosed by troponin exceeding thresholds apparently of ischemic origin (e.g., no other obvious cause for artifactual elevation). Myocardial infarction will also be centrally adjudicated and require *both* MINS and at least one symptom (e.g., chest pain or shortness of breath) or sign (e.g. ECG or echocardiogram abnormality).

We will consider all patients who had an elevated serum troponin concentration anytime during the first 30 days after surgery and determine the presence of any ischemic features (*i.e.*, whether patients fulfilled the universal definition of myocardial infarction),[50] whether there was a non-ischemic etiology that could explain the elevated troponin measurement, and whether the myocardial injury appears to have occurred during or after surgery (*i.e.*, no evidence to support it was due to a preoperative event).

Myocardial injury after non-cardiac surgery will be defined as having values exceeding local 99th percentile for troponin I. Patients meeting diagnostic criteria for MINS will be evaluated for myocardial infarction with an electrocardiogram, echocardiogram (when possible), and a cardiac consultation. Non-fatal cardiac arrest and mortality will be determined from case-reports and medical records. Strokes will be detected based on clinical symptoms, and require radiographic evidence, consistent with new-onset cerebral ischemic or hemorrhagic injury.

Delirium will be assessed 7-10 AM and 5-8 PM for the initial four postoperative days while patients remain hospitalized because this approach will detect nearly all postoperative delirium (Fig. 4). Delirium will not be evaluated the evening after surgery because confusion might result from residual anesthetic effects. We will use the 3D-CAM which is based on a three-minute questionnaire, and has a sensitivity of 95% (95% CI, 84, 99), and specificity of 94% (CI: 90, 97) compared with formal psychometric evaluation.[51] The test works well in patients with dementia.[51] CAM-ICU, which is also well validated, will be substituted when patients are intubated.[52] Delirium will be assessed by investigators trained in the methods. Any positive CAM test will be considered evidence of delirium which will analyzed dichotomously.

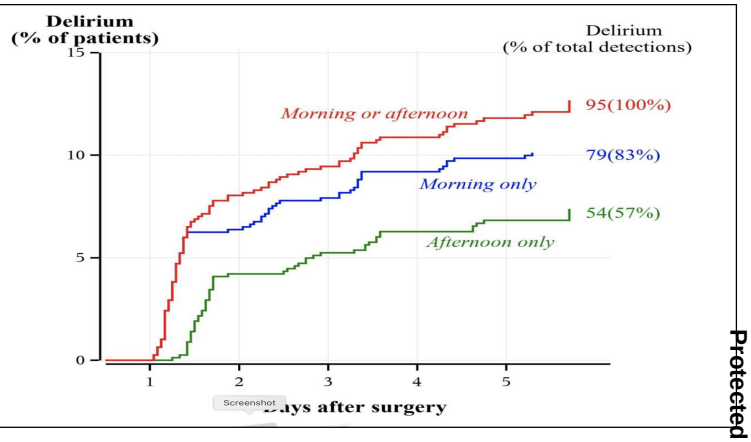


Fig. 4. Detection of delirium with CAM-ICU as a function of assessment times over postoperative days 1-5. Nearly all delirium was detected with twice daily assessments for the initial four postoperative days. From Hamadnalla, et al, in review.

Acute kidney injury. Postoperative Acute Kidney Injury will be defined by Kidney Disease Improving Global Guidelines (KDIGO) Clinical Practice Guidelines.110 By convention in perioperative studies, urine output will not be considered since it is rarely available.111 Specifically, patients will be considered to have Stage 1 acute kidney injury (risk) if the postoperative serum creatinine increases at 1.5-1.9-fold or by more than 0.3 mg/dl (≥26.5 μmol/L) within a 48-hour period. Stage 2 will be defined by a 2.0-2.9-fold increase in creatinine, and Stage 3 will be defined by a 3-fold increase in creatinine or an increase from baseline by ≥4 mg/dl (≥353.6 μmol/L) or initiation of renal replacement therapy.We will compare the preoperative creatinine concentration closest to surgery to the highest postoperative concentration measured within 7 days. Only Stages 2 and 3 will be considered for the primary perioperative composite.

Outcomes and clinically meaningful differences

The first co-primary feasibility outcomes are the fraction of time when intraoperative MAP >85 mmHg, intraoperative area of MAP >85 mmHg, and intraoperative area of MAP <65 mmHg. The area of MAP below (above) a threshold refers to the cumulative sum of areas for the MAP-time curve below (above) the specified threshold.

The second co-primary feasibility outcome is postoperative blood pressure management, characterized by the time routine antihypertensive medications restarted after surgery.

The secondary feasibility outcome measures are time-weighted average (TWA) intraoperative MAP, cumulative minimum MAP for 10 minutes, average postoperative systolic blood pressure (SBP), and mean of the lowest 3 postoperative SBPs.

The exploratory efficacy outcome measures are: 1) perfusion-related complications within 30 days of surgery; and 2) postoperative delirium within the first 4 postoperative days.

Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose: is life-threatening; or requires inpatient hospitalization or prolongation of existing hospitalization; or results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect; or is a medically important event.

Suspected unexpected serious adverse reactions (SUSARs) are events that meet the following criteria: 1) suspected to be causally associated with blood pressure management, anesthetic induction agent, or vasopressor; 2) unexpected if the nature, severity, or outcome of the reaction(s) is

not consistent with the reference information (i.e., product monograph for trial drugs); 3) serious (as defined above for an SAE); and 4) not a defined efficacy.

Efficacy and safety outcomes will be recorded separately and not as SAEs, except if, because of the course or severity or any other feature of such events, the investigator, according to his/her best medical judgment, considers these events as exceptional in this medical condition.

Hospitalizations, which were planned before inclusion in the study (e.g., elective or scheduled surgery or other interventions), will not be regarded as SAEs. This pertains also to hospitalizations which are part of the normal treatment or monitoring of the studied disease or another disease present before inclusion in the study (e.g., patient returning to the hospital for chemotherapy), and which did not result in a worsening of the disease.

All SAEs need to be reported within 48 hours of knowledge of the event to the Project Office. For such events, research personnel will complete an SAE CRF in the database. The Project Office will then inform regulatory authorities in a timely manner, as necessary, according to the applicable regulations.

The DMC will provide oversight of patients' safety throughout the trial by reviewing aggregate data (including all reported study outcome events and SAEs) by treatment group at regular intervals throughout the duration of the trial and as defined in the DMC Charter.

Data Analysis

Primary, secondary, and exploratory outcomes will be analyzed on a modified intent-to-treat basis by randomized group assignments. Specifically, we will include all randomized patients who have surgery, even if the operation is changed to one that would not otherwise qualify for Pilot GUARDIAN.

Balance on baseline characteristics will be assessed using absolute standardized difference (ASD), which is defined as the absolute difference in means, ranks, or proportions divided by the pooled standard deviation. Groups are considered to be imbalanced with respect to a baseline characteristic when ASD exceeded 0.44 [$1.96*\text{sqrt}(1/n_1 + 1/n_2)$].

We primarily evaluate the effect of tight blood pressure control on the fraction of time when intraoperative MAP exceeded 85 mmHg using a t-test. Wilcoxon rank-sum tests will be used to evaluate the effect of tight perioperative BP control on intraoperative area of MAP >85 mmHg, intraoperative area of MAP <65 mmHg, and time to restart routine antihypertensive medications after surgery.

Sample Size Considerations

The study will enroll 40 patients in each treatment group. Design analysis for the study will be done after data collection but before we conducted the analysis.

The fraction of time spent above 85 mmHg is assumed to be distributed as Beta (5, 5) and with the above sample size, the confidence interval half-width for estimating the mean would be 0.05 which is deemed to be sufficiently precise. The beta distribution is appropriate as the outcome is restricted to the closed interval between 0 and 1. The observed confidence interval widths are 0.01.

Schedule of Procedures

	BP	anti-HP medicine	Creatinine	Troponin I+ECG(Positive)	3D-CAM/ICU-CAM	Perfusion-related complications	Mortality
Baseline(<30d)	Y	Y	Y	Y			
DOS	IBP+MAP≥85/IBP	Y/N	Y	Y			
POD1	Y	Y/N	Y	Y	Twice		
POD2	Y	Y/N	Y	Y	Twice		
POD3	Y	Y			Twice		
POD4		Y			Twice		
Ward request	Y	Y	Y	Y			
Discharged						Y	Y
POD30-35						Y	Y

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吉林大学中日联谊医院科研伦理委员会
涉及人的生物医学研究伦理审批件

（2020 年）临审（20201120）

项目名称	严格围术期血压管理减少心血管意外、肾衰、认知障碍-GUARDIAN 研究的预实验 Pilot of "tight perioperative blood pressure management to reduce serious cardiovascular, renal, and cognitive complications"		
申请科室	麻醉科	项目负责人	李凯
工作证号	603972	身份证号	410205198210062011
联系方式	13596195176	类别	干预性研究
研究目的	为我院与美国克利夫兰诊所临床预后中心共同发起的国际多中心研究，提供参照，验证研究方案的可行性，组间区分性；初步探讨严格围术期血压管理对减少心血管意外、肾衰、认知障碍的作用		

主要审查文件（含版本号）如下：

1 研究者发起的临床研究申请表受理申请表
2 临床研究方案（版本号：V1.0，版本日期：2020 年 11 月 01 日）
3 知情同意书及其他书面资料（版本号：1.0，版本日期：2020 年 11 月 01 日）
4 研究者简历、临床试验项目组成人员清单
5 研究者资质认证

研究者声明：(Inspection contents)	1、真实性：本表格内所写内容真实有效，若非真实，责任由申请人本人自负。 2、利益冲突：在此研究中不存在经济上、物质上、以及社会关系方面的利益冲突。倘若在研究开展过程中发现目前尚未知晓的利益冲突，我将及时向伦理委员会报告。 1. Authenticity: The content written in this form is true and valid. If it is not true, the responsibility is my own responsibility. 2. Conflict of interest: there is no conflict of interest in economic, material, or social relations in this research. If there is a conflict of interest that is not yet known during the research, I will report to the ethics committee in time.

申请人签名(Signature of applicant)	李凯	日期(date)：2020 年(year)11 月(month)30 日(day)

同意	作必要的修正后同意	作必要的修正后重审	不同意	终止或暂停该试验	弃权	回避
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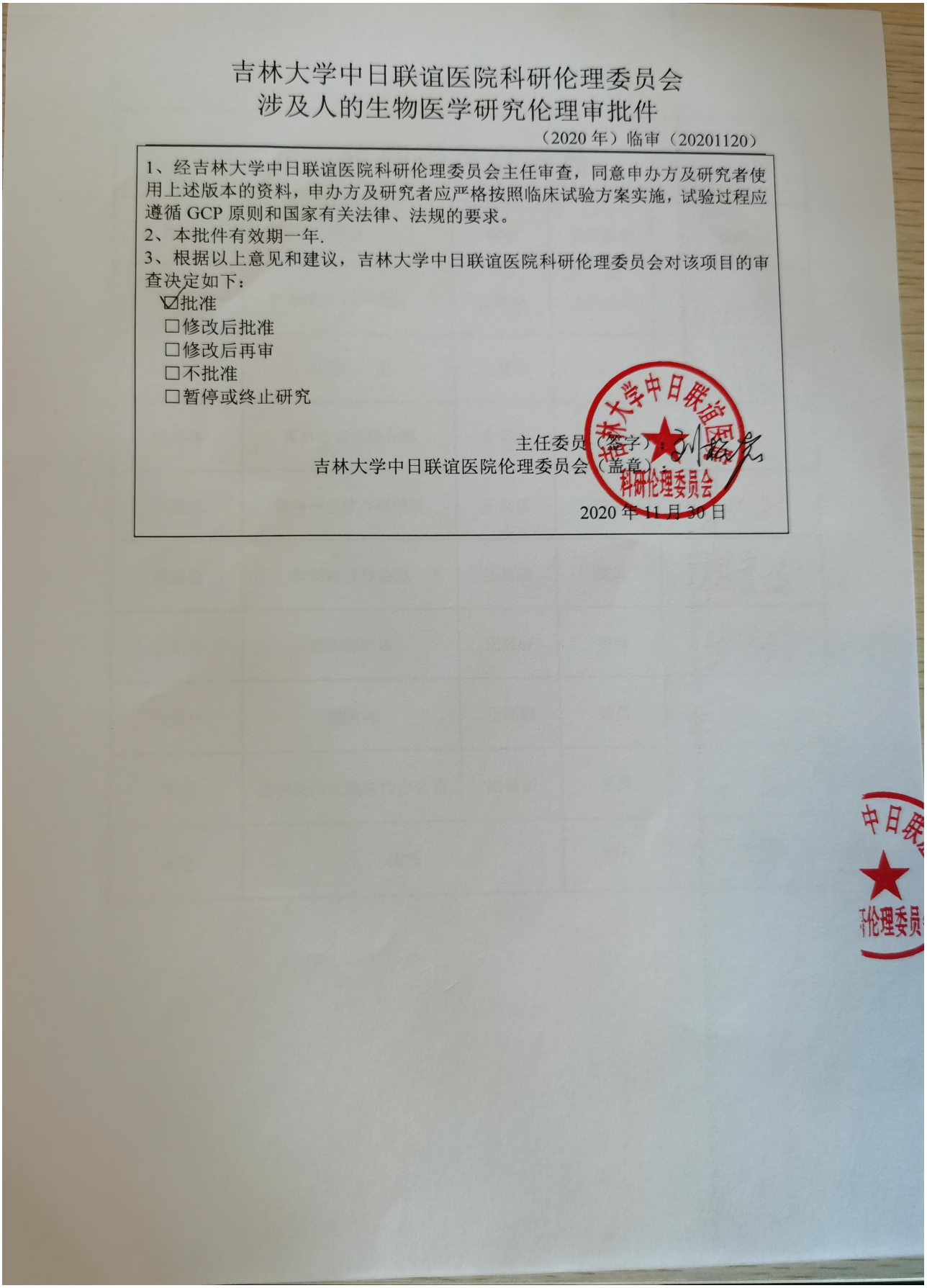

吉林大学中日联谊医院科研伦理委员会
涉及人的生物医学研究伦理审批件

（2020 年）临审（20201120）

1、经吉林大学中日联谊医院科研伦理委员会主任审查，同意申办方及研究者使用上述版本的资料，申办方及研究者应严格按照临床试验方案实施，试验过程应遵循 GCP 原则和国家有关法律、法规的要求。

2、本批件有效期一年.

3、根据以上意见和建议，吉林大学中日联谊医院科研伦理委员会对该项目的审查决定如下：

☑批准

☐修改后批准

☐修改后再审

☐不批准

☐暂停或终止研究

主任委员（签字）：

吉林大学中日联谊医院伦理委员会（盖章）：

2020 年 11 月 30 日

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	2
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance, see CONSORT for abstracts)	2-3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	3-4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	4
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4-5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	-
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	4
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	4
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	4
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	5

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	5
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6-7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	6-7
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	7
	13b	For each group, losses and exclusions after randomisation, together with reasons	7
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7
	14b	Why the trial ended or was stopped	-
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	7-8
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	8-10
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	9-10
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	9-10
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	-
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	11
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	10-11
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	10-11
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	4
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	13

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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Tight perioperative blood pressure management to reduce complications: a randomized feasibility trial

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ABSTRACT

- **Objective:** Evaluate feasibility of a trial of perioperative hypotension and serious complications.
- **Design:** A patient and assessor blinded randomized feasibility trial.
- **Setting:** We included patients in tertiary university hospital.
- **Participants:** We enrolled 80 adults scheduled for major non-cardiac surgery.
- **Interventions:** In patients randomized to tight blood pressure control, intraoperative mean arterial pressure (MAP) was targeted to ≥85 mmHg maintained with norepinephrine infusion, and restarting chronic antihypertensive medications was delayed until the third postoperative day. In the reference group, intraoperative blood pressure was managed per routine and antihypertensive medications were restarted immediately after surgery.
- **Primary and secondary outcome measures:** Our first co-primary outcome was the fraction of time when intraoperative MAP was >85 mmHg, intraoperative area (time integral)of MAP >85 mmHg, and MAP <65 mmHg. The second co-primary outcome was time until antihypertensive medications were restarted after surgery. Secondary outcomes were time-weighted average (TWA) intraoperative MAP, cumulative minimum MAP for 10 minutes, average postoperative systolic blood pressure (SBP), and mean of the lowest 3 postoperative SBPs.
- **Results:** Forty patients in each group were analyzed. The median for intraoperative area of MAP >85 mmHg was 1303 [772-2419] mmHg*min in routine BP cases and 2425 [1926- 3545] mmHg*min in tight BP control. The area for intraoperative MAP <65 mmHg was 7 [0-40] mmHg*min with routine BP management, and 0 [0-0] mmHg*min with tight BP control. The fraction of time with MAP>85 mmHg was 0.52 (0.25) and 0.87 (0.15). Antihypertensive medications were restarted 2 [1 to 3] days later in tight BP control cases. However, postoperative systolic pressures were similar.
- **Conclusions:** Tight BP management markedly increased intraoperative MAP and reduced the amount of hypotension. In contrast, delaying chronic antihypertensive medications had little effect on postoperative systolic pressure. The full trial appears feasible and remains necessary but should not include postoperative antihypertensive

management.

- **Trial registration:** www.clinicaltrials.gov (NCT04789733).
- **Keywords:** Anesthesia, blood pressure, perioperative management, myocardial injury after non-cardiac surgery, myocardial infarction, acute kidney injury, delirium.

Strengths and limitations of this study

• The protocol was practical, and intraoperative pressure management resulted in excellent separation..

• However, we failed to manipulate postoperative blood pressure by changing when antihypertensive medications were restarted.

• Feasibility in one site does not mean that it will prove practical at all trial sites.

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INTRODUCTION

Mortality in the 30 days after surgery is more than 100 times higher than intraoperative mortality.[1] Myocardial injury and associated vascular complications are among the leading causes of postoperative mortality.[2]Intraoperative hypotension is associated with myocardial injury after non-cardiac surgery (MINS) and myocardial infarction (MI), with the apparent harm threshold being a mean arterial pressure (MAP) ≈ 65 mmHg.[3, 4]Furthermore, postoperative hypotension is associated with myocardial infarction even after adjustment for intraoperative hypotension.[5]

The harm threshold for perioperative acute kidney injury (AKI) also appears to be a mean arterial pressure (MAP) near 65 mmHg.[6]Perioperative hypotension is also associated with delirium and cognitive decline,[7, 8]although inconsistently.[9] Furthermore, cumulative duration of MAP less than 50, 55, 60, 70, and 80 mmHg appear associated with increased odds of 30-day mortality after noncardiac surgery is reported in a retrospective cohort.[4] Hypotension prevention may therefore be a modifiable factor that reduces postoperative cardiovascular and perfusion related complications.

There is currently sparse evidence that the associations observed between hypotension and myocardial and renal injury are casual. A small randomized trial (n=292) reports that preventing intraoperative hypotension reduces the risk of major complications by 25%.[10] In contrast, a 458-patient randomized trial demonstrated no improvement with tight intraoperative blood pressure control.[11] Limited randomized data (n=199) also suggests that hypotension causes delirium.[12]

A robust trial remains necessary to characterize the potential benefits of reducing perioperative hypotension in high-risk patients. We therefore plan a multi-national randomized trial to test the primary hypothesis that perioperative hypotension prevention in high-risk patients reduces a composite of perfusion-related complications in the 30 days after major non-cardiac surgery. In anticipation of the full trial, we conducted a pre-planned feasibility trial — reported here — designed to evaluate feasibility, especially the ability to target blood pressure per protocol.

METHODS AND ANALYSIS: PARTICIPANTS, INTERVENTION, AND OUTCOMES

Study design

This single-center trial was performed in China-Japan Union Hospital of Jilin University (Jilin, China). The study was approved by the Institutional Review Board (IRB #20201120) on November 30, 2020 and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at clinicaltrials.gov (NCT04789733, named as The GUARDIAN Pilot Trial, Principal investigator: K.L.).

Inclusion criteria

Major inclusion criteria were age ≥45 years; noncardiac surgery expected to last at least 2 hours; overnight hospitalization; ASA physical status 2-4; chronically taking at least one anti-hypertensive medication; and expected to have an arterial catheter before anaesthesia induction. Participants were also required to have at least one of following risk factors: 1) history of peripheral arterial surgery; 2) history of coronary artery disease; 3) history of stroke or transient ischemic attack; 4) serum creatinine >175 μmol/L (>2.0 mg/dl); 5) diabetes requiring medication; 6) current smoking or 15 pack-year history of smoking tobacco; 7) scheduled for major vascular surgery; 8) body mass index ≥ 35 kg/m^2; 9) preoperative high-sensitivity troponin T >14 ng/L or troponin I equivalent; or 10) B-type natriuretic protein (BNP) >80 ng/L or N-terminal B-type natriuretic protein (NT-proBNP) >100 ng/L.

Exclusion criteria

Patients were excluded when they were scheduled for carotid artery surgery, intracranial surgery, partial or complete nephrectomy, pheochromocytoma surgery or liver transplantation. Patients were similarly excluded if they had a condition that precluded routine or tight blood pressure management or had end-stage renal disease. And finally, we also excluded patients with dementia or impairments that might compromise cognitive assessments.

Randomization and masking

Participants were randomly allocated using computer-generated assignments to tight or routine pressure management in a 1:1 ratio without stratification in a block size of four by an independent statistician (D.S.Y) using SAS 9.2 software (SAS Institute, USA). Allocation was concealed within sealed opaque envelopes until shortly before anesthesia induction.

Intervention

The original protocol is detailed in Supplemental Text Document. No changes were made before trial data were accessed. This manuscript adheres to the applicable CONSORT guidelines.

Our feasibility trial was designed to inform a future pivotal trial by considering two co-primary feasibility hypotheses. First that there is suitable statistically significant and clinically meaningful separation of intraoperative and postoperative blood pressure across two blood pressure management strategies (intraoperative MAP maintained ≥ 85 mmHg and postoperative tight pressure control versus routine care with some hypotension expected). And second, that restarting routine antihypertensive medications per protocol is feasible (restart delayed until the third postoperative day versus immediate restart). We also consider the exploratory efficacy hypothesis that perfusion-related complications and delirium are reduced by tight perioperative blood pressure control.

In patients assigned to tight pressure management, angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) were not given the morning of surgery. A norepinephrine peripherally intravenous infusion was adjusted to maintain intraoperative MAP ≥85 mmHg. Either intermittent bolus 4-8 ug noradrenaline at 2 mg/500 ml or a continuous

infusion noradrenaline 3-10 ml/h of a 2 mg/50 ml solution was used per clinical routine in our institution. General anesthesia was induced and maintained per routine as intraoperative bispectral index value of 40-60. Fluid administration and blood transfusion were also per clinical judgement. Resumption of chronic anti-hypertensive medications was delayed until the third postoperative day unless deemed necessary to treat hypertension or for another clinical indication.

In patients assigned to routine pressure management, routinely used ACEIs and ARBs were given the morning of surgery if deemed appropriate by the attending anesthesiologist. Vasopressors, as above, were used per the attending clinician's discretion. General anesthesia was induced and maintained per routine as intraoperative bispectral index of 40-60. Fluid administration and blood transfusion were also per clinical judgement. Intraoperative pressure management was per routine. As usual, chronic anti-hypertensive medication was restarted shortly after surgery unless contraindicated by hypotension.

Blinding

Randomization and group assignment were performed by an investigator (K.L) who did not participate in perioperative care or data collection. Anesthesiologists who were responsible for anesthetic management were not involved in trial follow up. Investigators(Z.T.H, W.Y.L)who performed postoperative follow-up and patients were masked to study group assignment. The trial was thus assessor and patients blinded.

Data collection

The required data was collected by trained research staff, recorded in paper based case report forms (CRFs) and then stored into Excel digital forms. Assessors will conduct the follow-up procedures in person.

Measurements

Intraoperative pressures from the required arterial catheter were automatically recorded in our electronic anesthesia records at 1-minute intervals before anesthesia induction. Typically, postoperative pressures were measured oscillometrically at 8-hour intervals in surgical ward.
For perfusion-related complications, we considered a collapsed (one or more) composite of myocardial injury, stroke, non-fatal cardiac arrest, Stage 2-3 acute kidney injury defined by the creatinine component of the Kidney Disease: Improving Global Outcomes (KIDGO) definition, deep or organ-space infection, sepsis, and all-cause mortality within 30 days of surgery. We required high-sensitivity troponin I and creatinine preoperatively and daily for the initial three postoperative days.

Myocardial injury after non-cardiac surgery was defined as troponin I exceeding the local 99th percentile (0.04 ng/mL).[13] Strokes were detected based on clinical symptoms and required radiographic evidence consistent with new-onset cerebral ischemic or hemorrhagic injury. Delirium was assessed between 7-10 AM and again between 5-8 PM by 3D-CAM for the initial four postoperative days while patients remain hospitalized,[14] with any positive assessment being considered evidence of delirium.

Primary outcomes

The first co-primary outcome was the fraction of time when intraoperative MAP was >85 mmHg, intraoperative area (time integral) of MAP >85 mmHg, and intraoperative area (time integral) of MAP <65 mmHg.

The second co-primary outcome was postoperative blood pressure management, characterized by the time routine antihypertensive medications were restarted after surgery.

Secondary outcomes

The secondary feasibility outcome measures were time-weighted average (TWA) intraoperative MAP, cumulative minimum MAP for 10 minutes, average postoperative systolic blood pressure (SBP), and mean of the lowest 3 postoperative SBPs. Cumulative minimum MAP for 10 minutes was calculated as the lowest MAP, at or below which a patient's MAP was sustained for at least 10 minutes during the surgery. Post-hoc, we also defined the measures intraoperative area over MAP >80 mmHg and area of MAP <60 mmHg as additional secondary outcomes.

The exploratory efficacy outcome measures were: 1) perfusion-related complications within 30 days of surgery; and 2) postoperative delirium within the first 4 postoperative days.

Data and sample storage

All relevant clinical trial materials will be saved for at least 3 years after termination of the trial. The investigators and statistician have access to the entire data set.

Data monitoring

The trial was coordinated by an Executive Committee, but there was not an external Data and Safety Monitoring Board.

Protocol changes

No protocol changes were made during the trial or before trial data were accessed.

Power calculation

The study enrolled 40 patients in each treatment group. The statistical analysis plan was finalized after patients were enrolled, but before data were accessed. As this was a feasibility trial, our primary goal was to assess implementation of the protocol. We nonetheless estimate how many patients were required to give us a reasonable sense of dispersion that would be the basis for a subsequent full trial.

The fraction of time spent above 85 mmHg was not expected to be normally distributed and instead, assumed to have a Beta(5,5) distribution. Using the above sample size, the confidence interval half-width for estimating the mean would be 0.05, which was deemed to be sufficiently precise. The observed confidence interval widths were 0.01.

Area of MAP <65 mmHg is typically heavily skewed and not normally distributed. Using the same sample size as above, we assumed that area of MAP <65 mmHg would be distributed as

Gamma (0.25, 0.1) which would give us a confidence interval half-width of 0.73. This was deemed to be sufficiently precise for estimation of the mean area of MAP <65 mmHg. The observed CI half-widths were 8.6 [reference group] and 0 [treatment group].

Statistical analysis

Balance on baseline characteristics was assessed using absolute standardized difference (ASD), which is defined as the absolute difference in means, ranks, or proportions divided by the pooled standard deviation. Groups were considered to be imbalanced with respect to a baseline characteristic when ASD exceeded 0.44 [1.96*sqrt(1/n1 + 1/n2)].[15]

We primarily evaluated the effect of tight blood pressure control on the fraction of time when intraoperative MAP exceeded 85 mmHg using a t-test. Wilcoxon rank-sum tests were used to evaluate the effect of tight perioperative BP control on intraoperative area of MAP >85 mmHg, intraoperative area of MAP <65 mmHg, and time to restart routine antihypertensive medications after surgery.

We also evaluated the effect of tight blood pressure control on intraoperative area of MAP >80 mmHg, and intraoperative area of MAP <60 mmHg using Wilcoxon rank-sum tests. We used two-sided, two-sample t-tests to evaluate the effect of blood pressure control on time-weighted average intraoperative mean arterial pressure, cumulative minimum MAP for 10 minutes, time weighted average SBP, and mean of the lowest 3 postoperative SBPs. On an exploratory bases, we used log-binomial models to evaluate a collapsed composite of perfusion-related complications, and postoperative delirium.

All analyses were conducted using R 4.0.2.

Patient and public involvement

There was no public or patient involvement.

Ethics and dissemination:

The protocol was approved by The Ethics Committee of the China-Japan Union Hospital of Jilin University, Changchun, China, (Chairperson Prof. Songyan Liu) on November 30, 2020 (Approval number: 20201120).and written informed consent was obtained from all subjects participating in the trial.

Results

Between May 23, 2021, and September 29, 2021, 9618 cases were screened, and 393 were deemed eligible. Two-hundred and ninety cases were preferentially enrolled by another trial. A total of 103 patients were approached, and 80 consented. Forty patients were randomized to tight pressure management and 40 were randomized to routine pressure management. No patients withdrew before hospital discharge. Our CONSORT flow diagram is presented in Figure 1. Three patients assigned to tight pressure management were lost between discharge and the 1-month follow-up assessment. There were thus 80 patients included in the primary analysis, and 77 in the 1-month analysis. The last patient follow-up was completed on November 1, 2021.

Patient demographic and baseline characteristics are presented in Table 1. Only diastolic blood pressure (DBP) and surgery type were imbalanced, with ASD >0.44. The median [Q1, Q3] blood loss was 175 [100, 300] ml in the tight perioperative BP control group and 50 [50, 200] ml in the routine BP management group.

Table 1.Patient baseline and demographic characteristics

Characteristic	Routine perioperative BP control	Tight perioperative BP management	ASD
	N=40	*N=40*	
Age	68 (10)	67 (10)	0.12
Height - cm	166 (8)	165 (8)	0.06
Weight - kg	66 (12)	71 (16)	0.28
SBP	142 (18)	148 (21)	0.31
DBP	80 (10)	86 (10)	0.67*
Surgery length (hours)	2.56 [2, 4]	2.25 [1.7, 2.8]	0.26
Surgery Type			0.66*
Abdominal	23 (58%)	18 (45%)	
Gynecologic	0 (0)	1 (2%)	
Neurosurgical	2 (5%)	6 (15%)	
Orthopedic	6 (15%)	3 (8%)	
Thoracic	7 (18%)	12 (30%)	
Thoracic and abdominal	1 (2%)	0 (0)	
Urology	1 (2%)	0 (0)	
Smokers	8 (20%)	6 (15%)	0.13

Data are presented as mean (SD), median [Q1, Q3] or n (%) as appropriate.
*ASD – Absolute Standardized Difference; *ASD > 0.44 indicates imbalance.*

The mean (SD) fraction of time with intraoperative MAP exceeding 85 mmHg (i.e., time when MAP >85 mmHg divided by total surgery duration) was 0.52(0.25) in patients assigned to routine blood pressure management and 0.87(0.15) in those assigned to tight control. The estimated absolute difference in the mean fraction of time between tight and routine blood pressure management was 0.35 [95% CI: 0.26, 0.44].

The median [Q1-Q3] intraoperative area of MAP >85 mmHg was 1303 [772-2419] mmHg*min in patients assigned to routine perioperative BP control and 2425 [1926- 3545] mmHg*min in those assigned to tight perioperative BP management (Figure 2). Tight blood pressure control

increased area of MAP >85 mmHg by 1102 [95% CI: 596, 1608] mmHg*min. Similarly, for intraoperative area of MAP <65 mmHg, the median [Q1-Q3] was 7 [0-40] mmHg*min with routine pressure management, and 0 [0-0] mmHg*min with tight control (Figure 3). Tight pressure control thus reduced exposure to MAP <65 mmHg by 6 [95% CI: 2, 15] mmHg*min. In the routine pressure management group, 40% (n = 16) of the patients experienced hypotension (any time below 65 mmHg) with a median [Q1-Q3] duration of 6 [2-9] minutes compared to 10% (n = 4) in the tight blood pressure control group, with a median duration of 5 [4-6] minutes (Supplemental Figure 1).

The median [Q1, Q3] intraoperative area of MAP >80 mmHg was 1917 [1249-3169] mmHg*min in patients assigned to routine BP control and 3355 [2549-4417] mmHg*min in the patients assigned to tight BP control. The area of MAP >80 mmHg was thus 1335 [95% CI: 667, 1928] mmHg*min greater in patients assigned to tight pressure control. For intraoperative area of MAP <60 mmHg, the median was 0 [0-6] mmHg*min with routine pressure management and 0 [0-0] mmHg*min with tight pressure control, for an estimated treatment effect of 0 [95% CI: 0, 0] (Table 2).

Table 2. Summary of analysis results.

Outcome	**Routine BP Management*** ***N = 40***	**Tight Perioperative BP Control*** ***N = 40***	**Estimated treatment effect [95% CI]**
Primary Outcomes			
Fraction of intraoperative period with MAP >85 mmHg	0.52 (0.25)	0.87 (0.15)	0.35 [0.26 to 0.44]**
Area of intraoperative MAP >85 mmHg (mmHg*min)	1303 [772-2419]	2425 [1926- 3545]	1102 [596 to 1608]***
Area of intraoperative MAP ≤65 mmHg (mmHg*min)	7 [0-40]	0 [0-0]	-6 [-15 to -2]***
Time to restart antihypertensive medications (days)	1 [1-1]	4 [3-4]	2 [1 to 3]***
Secondary Outcomes			
Area of intraoperative MAP >80 mmHg (mmHg*min)	1917 [1249- 3169]	3355 [2549-4417]	1335 [667 to 1928]**

Area of intraoperative MAP ≤60 mmHg (mmHg*min)	0 [0-6]	0 [0-0]	0 [0 to 0]**
Time-weighted average intraoperative MAP (mmHg)	89(9)	101(8)	12 [8 to 16]***
Minimum intraoperative MAP sustained for 10 cumulative minutes (mmHg)	71(9)	85(9)	14 [11 to 18]***
Mean postoperative systolic pressure (mmHg)	133(15)	138(13)	5 [-1 to 11]***
Mean of 3 lowest postoperative systolic pressures [mmHg]	122(14)	127(14)	5 [-1 to11]***

*Data presented as means (SD) or medians [IQR]
** Difference in means and 95% CI
*** Hodges Lehmann shift estimator

The mean difference in the intraoperative TWA MAP between tight and routine pressure management was 12 [95% CI: 8 to 16] mmHg, and the difference in cumulative intraoperative minimum MAP sustained for 10 minutes was 14 [95% CI: 11 to 18] mmHg. (Supplemental Figure 2; Table 2).

Antihypertensive medications were restarted 2 [95% CI: 1 to 3] days later in patients assigned to tight blood pressure control. The difference [95% CI] in postoperative mean SBP between tight and routine pressure management was 5 [-1 to 11] mmHg, and the difference in mean of the lowest 3 postoperative SBP measurements was also 5 [-1 to 11] mmHg (Supplemental Figure 3; Table 2).

The incidence of perfusion related complications was 12% in both groups and the relative risk was estimated to be 1.0 [0.3 to 3.3]. No delirium was detected in either group. No severe adverse events were attributed to the study.

DISCUSSION

Intraoperative blood pressure management was well maintained in patients assigned to tight control titrated with norepinephrine intravenous infusion, and MAP exceeded the target of 85 mmHg in 87% of the time. Furthermore, the average of the lowest mean arterial pressures sustained for ten minutes in the tight group was 85 mmHg, indicating that mean arterial pressures in these patients was only rarely and transiently less than 85 mmHg. Intraoperative pressures also exceeded 85 mmHg about half the time in patients assigned to routine management which is unsurprising since hypertension was an inclusion criterion for the trial.

Because patients cannot be randomized to hypotension, the more important question is the

extent to which pressures were <65 mmHg, which is thought to be the intraoperative harm threshold, with routine management. There was almost no hypotension in patients assigned to tight control whereas the median area <65 mmHg was 7 mmHg*min in those with routine management. Furthermore, the lowest mean arterial pressures sustained for ten minutes in patients assigned to routine management was 71 (9) mmHg, and about 40% of patients had lowest sustained pressures ≤65 mmHg. There were thus distinct differences in mean arterial pressures in the two management groups, with one having virtually no hypotension and the other often experiencing mean pressures ≤65 mmHg.

Antihypertensive management was successful with the mean restart day being 1 with routine management and 4 with tight management, corresponding to a difference of 2 [95% CI: 1 to 3] days which is a clinically meaningful difference. However, antihypertensive management had little effect on postoperative systolic pressures, with the lowest three measurements differing by only 5 mmHg. Furthermore, the average lowest measurements exceeded 120 mmHg which is well above proposed postoperative harm threshold defined either by a mean arterial pressure of 75 mmHg[16] or a systolic pressure of 90 mmHg.[5]These results suggest that antihypertensive management should not be included in the full trial.

Previous studies report considerably more postoperative hypotension than we observed. For example, Liem reported that 2 cumulative hours below threshold of 60 mmHg occurred in 8% patients and 4 continuous hours less than 75 mmHg occurred in 48% patients.[16] Khanna and colleagues similarly reported that 63% of patients experienced a MAP ≤75 mmHg within 48 hours after surgery, and that 22% experienced MAP ≤65 mmHg.[17]However, there were two important differences between our trial and previous observational reports. The first is that both previous reports were based on continuous noninvasive blood pressure monitoring rather than oscillometric assessments at 8-hour intervals. Continuous monitoring will obviously detect more hypotension than intermittent monitoring. Furthermore, continuous non-invasive monitors are not well validated and may at times generate false low values. More frequent postoperative measurements would be helpful in a full trial. The second important difference between current and previous results is that enrollment in our feasibility trial was restricted to patients taking anti-hypertensive medications, and thus having a diagnosis of hypertension. It is understandable that hypertensive patients would have less hypotension than a general surgical population.

Only 10 of 80 patients experienced our composite outcome of major perfusion-related complications, evenly split between the treatment groups. With so few events, the (lack of) difference between the groups is noninformative. Curiously, no delirium was observed in our 80 patients. The incidence of delirium after noncardiac surgery varies widely, but is probably now lower than previously reported.[18, 19] Delirium incidence also clearly depends strongly on age, with the incidence increasing markedly in patients older than 65 years.[9]The average age in our patients was 67 years which is relatively young which may have contributed to lack of observed delirium.

The major limitation of our trial is that it was conducted in a single center whereas our planned

full trial will involve dozens of centers around the world. Our results demonstrating that intraoperative pressure and postoperative antihypertensive management is feasible does not mean that it will prove practical at all trial sites. Because the trial was only powered for feasibility and pressure management, the incidence of hard outcomes (based on only ten events) is essentially non-informative. Patients assigned to routine care had slightly lower diastolic blood pressures, 80 versus 86 mmHg. However, this small difference seems unlikely to have much influenced our conclusions.

Conclusion

We achieved substantial separation of intraoperative mean arterial pressures. Similarly, we were able to control restarting antihypertensive medications per protocol — although doing so had relatively little effect on postoperative systolic pressures. Furthermore, the requirement that all patients have chronic hypertension resulted in relatively high intraoperative and postoperative pressures. Consequently, we amended the protocol for the full trial to include patients without chronic hypertension and no longer specify posotoperative antihypertensive management. The full trial appears feasible and remains well warranted.

Contributorship statement

Kai Li was principal investigator and helped design the protocol, applied for ethics approval, registered the trial, assigned groups, and drafted the manuscript. Zhouting Hu and Wangyu Li helped collect data. Karan Shah was responsible for data analysis. Daniel I. Sessler designed the protocol and provided overall trial guidance. All authors reviewed and revised the manuscript.

Competing interests

Dr. Sessler is a consultant for Edwards Lifesciences (Irvine, California). He serves on advisory boards and has equity interests in Calorint (Philadelphia, Philadelphia), TransQtronics (Philadelphia, Philadelphia), the Health Data Analytics Institute (Boston, Massachusetts), Medasense (Tel Aviv, Israel), Serenno (Tel Aviv, Israel), and Perceptive Medical (Newport Beach, California). The other authors declare no competing interests.

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Data sharing statement

The investigators and statistician have access to the whole data set. Data will be shared collaboratively with external parties with approval of the Executive Committee and appropriate data-use agreements.

Ethics approval

The protocol was approved by The Ethics Committee of the China-Japan Union Hospital of Jilin University, Changchun, China, (Chairperson Prof. Songyan Liu) on November 30, 2020 .. (Approval number: 20201120).

Patient consent for publication.

Consent obtained directly from patient(s).

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Figure Legends

Figure 1. CONSORT flow diagram. Patient flow through stages of the trial.

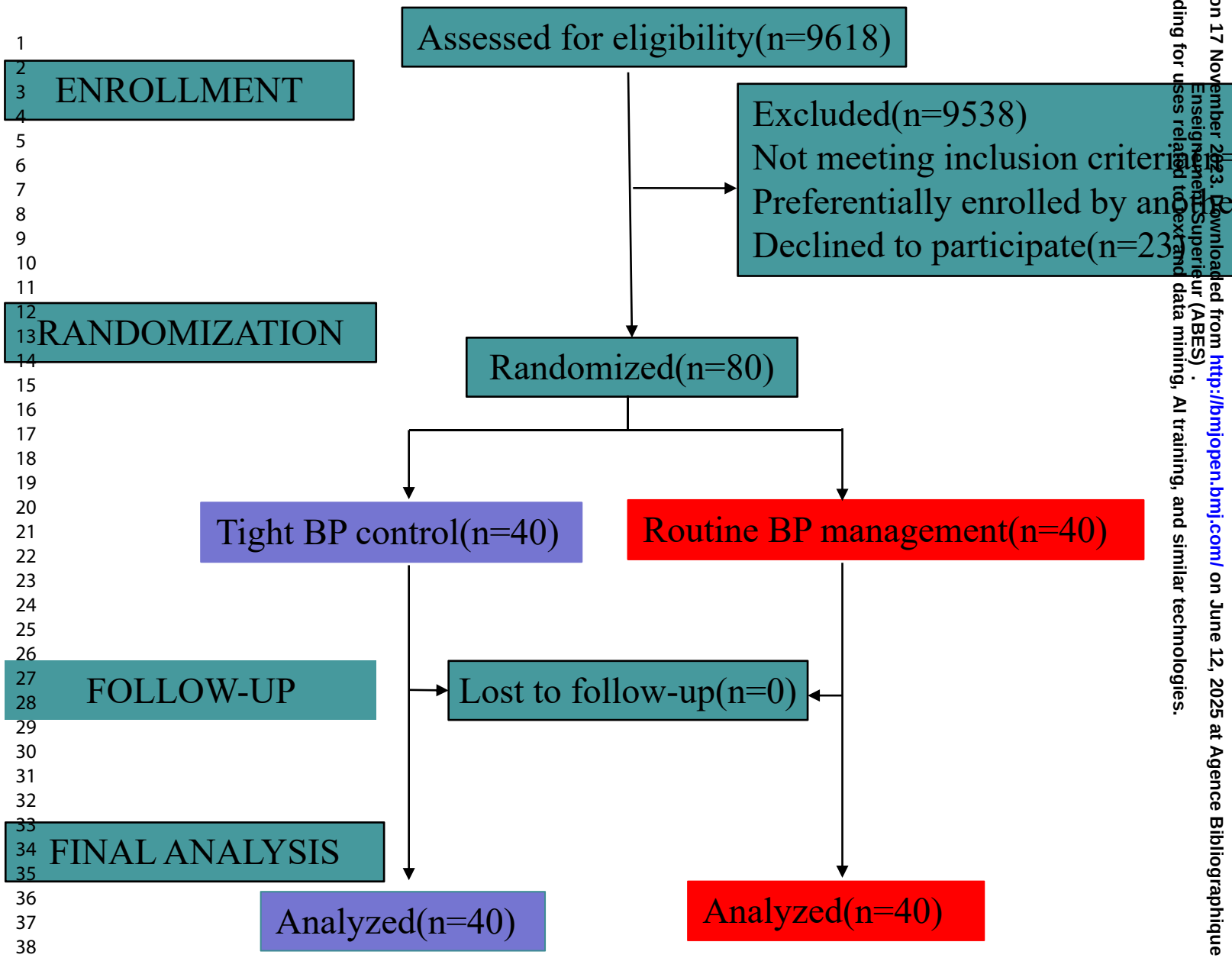
Figure 2. Area of intraoperative MAP >85 mmHg by blood pressure management group. The lower and upper edges of the box correspond to 25th and 75th percentile respectively, with the central line representing the median; whiskers extend to 1.5 times the interquartile range from the edges of the box; data beyond the whiskers are outliers and plotted individually.

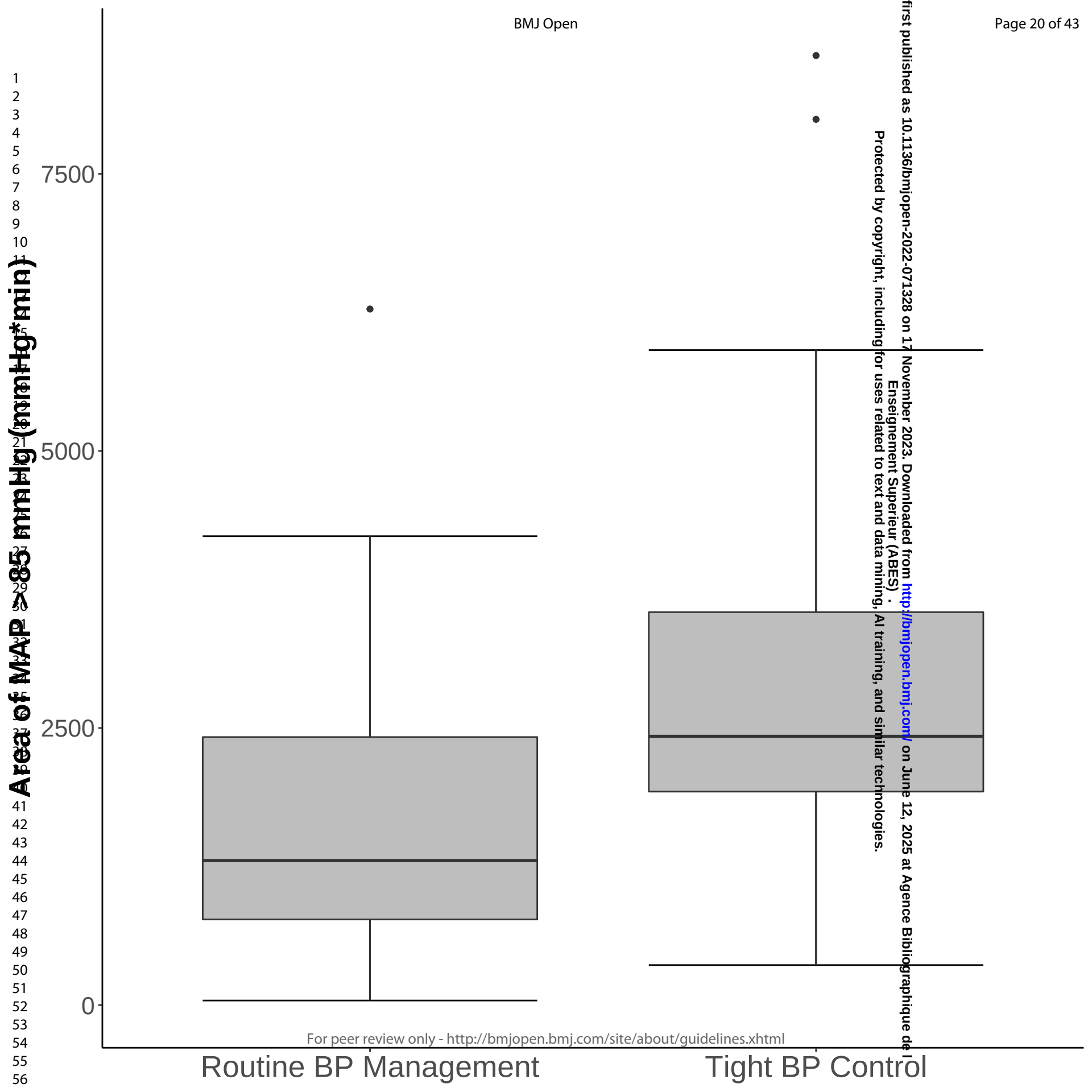
Figure 3. Area of intraoperative MAP <65 mmHg by blood pressure management group. The lower and upper edges of the box correspond to 25th and 75th percentile respectively, with the central line representing the median; whiskers extend to 1.5 times the interquartile range from the edges of the box; data beyond the whiskers are outliers and plotted individually.

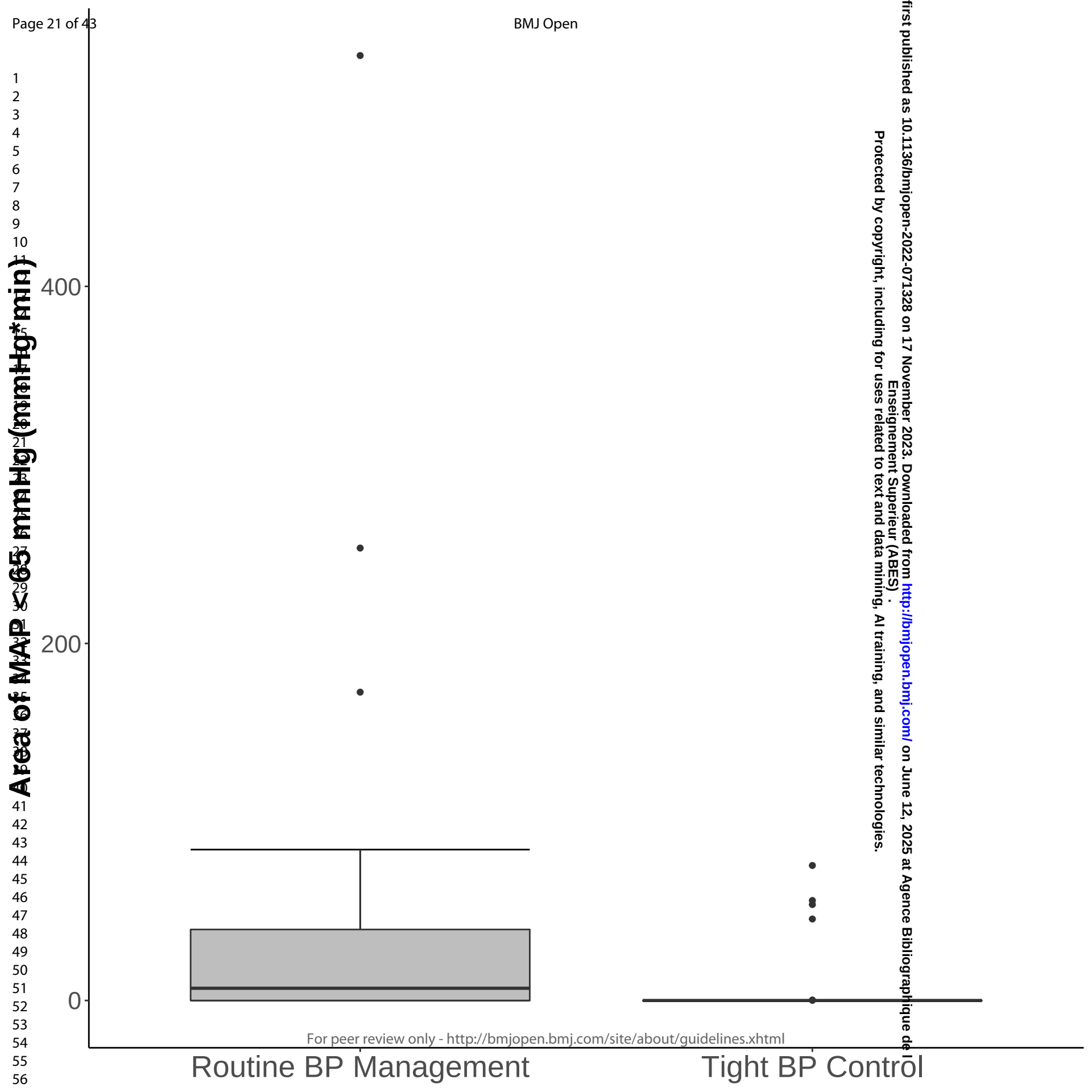
Supplemental Figure 1. Time spent below 65 mmHg by blood pressure management group. Patients who never went below 65mmHg not shown.

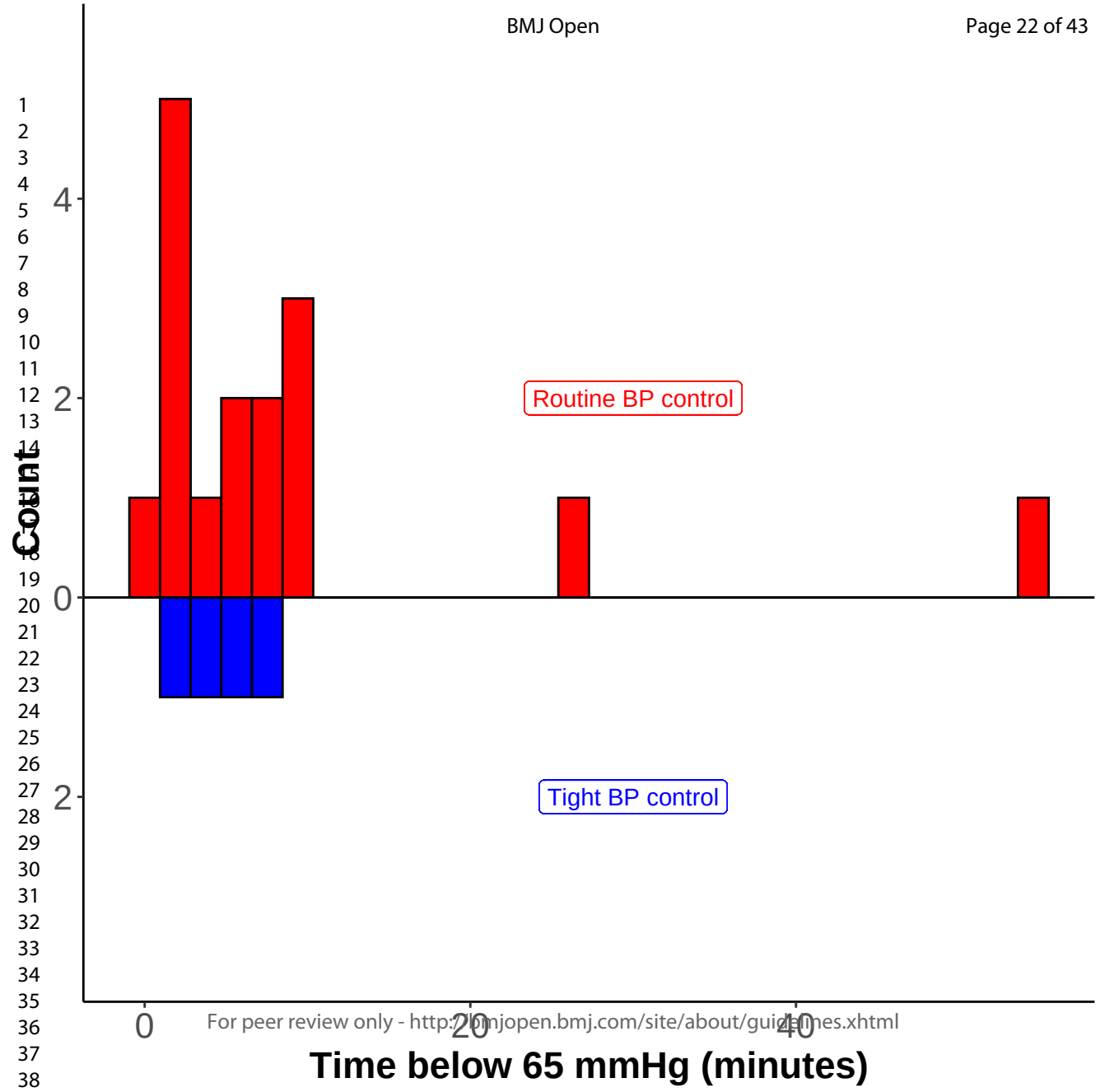
Supplemental Figure 2. Cumulative lowest intraoperative MAP sustained for 10 minutes by treatment group. The lower and upper edges of the box correspond to 25th and 75th percentile respectively, with the central line representing the median; whiskers extend to 1.5 times the interquartile range from the edges of the box; all data points are plotted individually and superimposed on the boxplot.

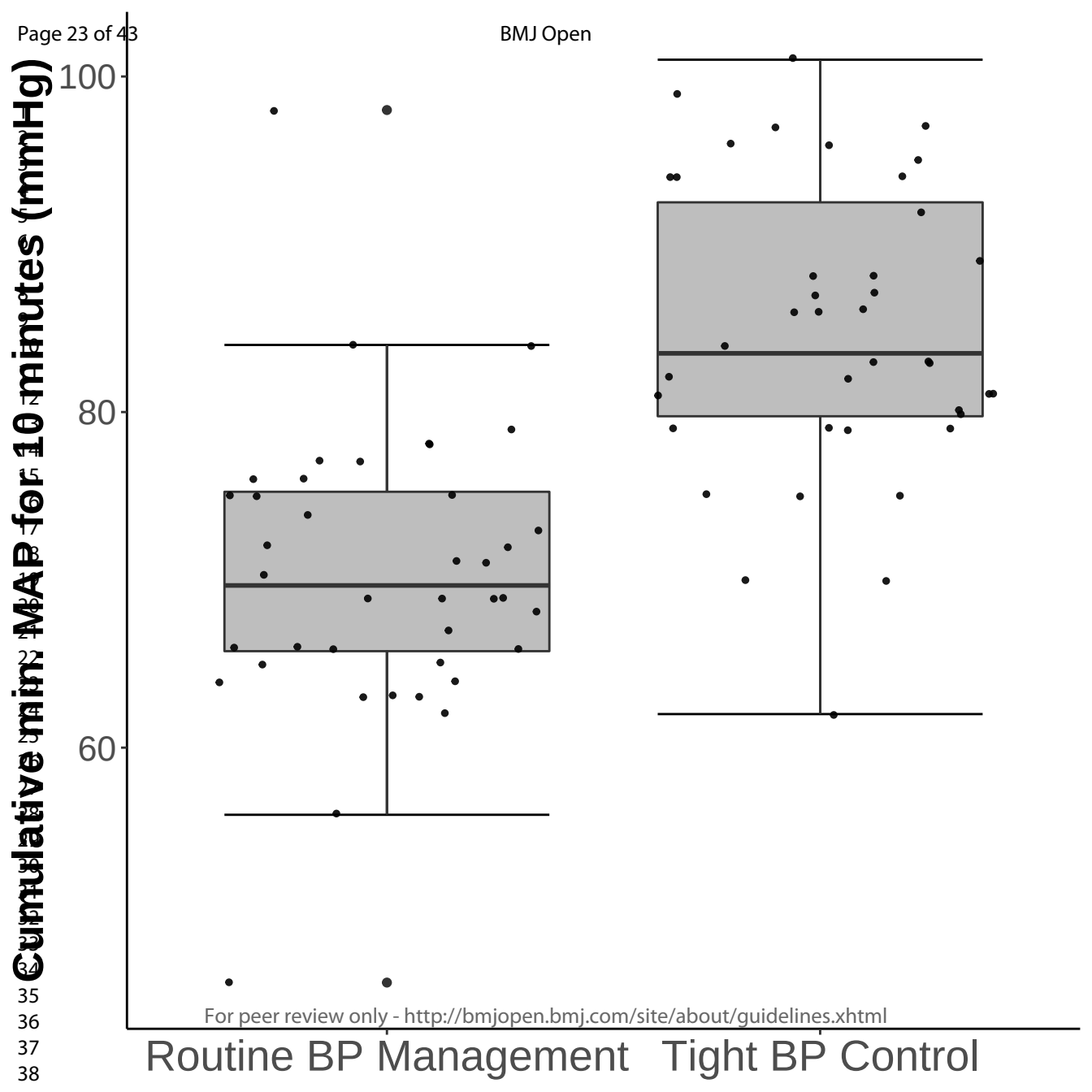
Supplemental Figure 3. Mean of lowest 3 postoperative systolic blood pressure measurements by treatment group. The lower and upper edges of the box correspond to 25th and 75th percentile respectively, with the central line representing the median; whiskers extend to 1.5 times the interquartile range from the edges of the box; all data points are plotted individually and superimposed on the boxplot.

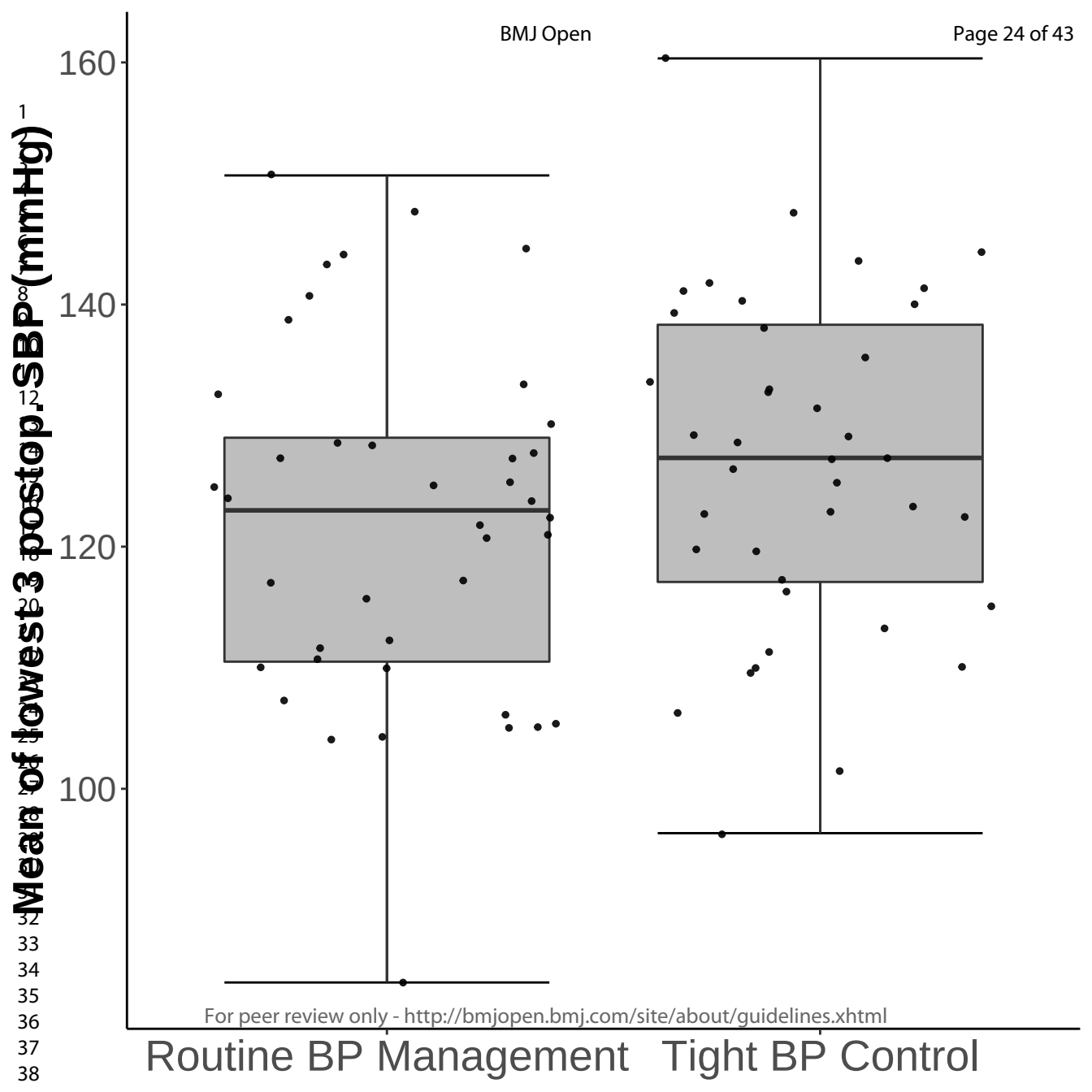












Pilot of "tight perioperative blood pressure management to reduce serious cardiovascular, renal, and cognitive complications"

The GUARDIAN Pilot Trial

Single-center prospective randomized pilot trial

Principal Investigator

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Summary

We are planing to propose a robust international randomized trial in 6,254 patients to test the primary hypothesis that perioperative tight blood pressure management reduces a composite of major perfusion-related complications (myocardial injury, stroke, non-fatal cardiac arrest, Stage 2-3 acute kidney injury, deep or organ-space infection, sepsis, and death) in the 30 days after major non-cardiac surgery.

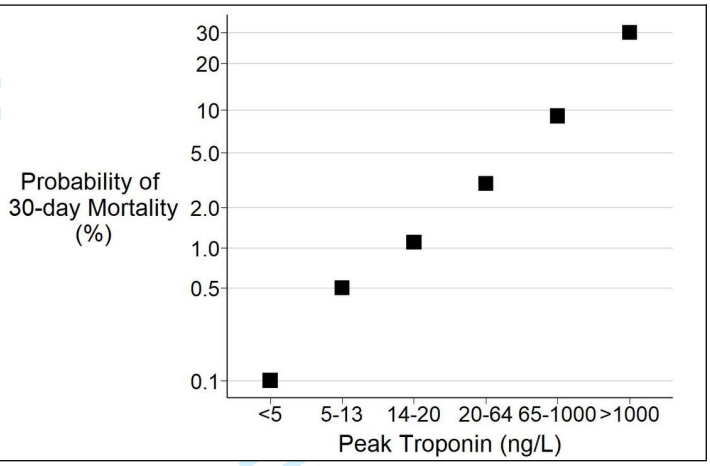
In anticipation of the full trial, we will conduct the pre-planned pilot trial designed to evaluate feasibility, especially the ability to target blood pressure per protocol. The pilot trial of 80 cases will be designed to inform a future pivotal trial by considering two co-primary feasibility hypotheses. First that there is suitable separation of intraoperative and postoperative blood pressure across two blood pressure management strategies (intraoperative MAP maintained ≥85 mmHg and postoperative tight pressure control *versus* routine care with some hypotension expected). And second, that restarting routine antihypertensive medications per protocol is feasible (restart delayed until the third postoperative day *versus* immediate restart). We also consider the exploratory efficacy hypothesis that perfusion-related complications and delirium are reduced by tight perioperative blood pressure control.

Introduction

When patients having major surgery reach the post-anaesthesia care unit, families naturally assume that they have survived the most dangerous part of the perioperative experience. Their assumption is wrong. Mortality in the 30 days after surgery is 1,000 times higher than intraoperative mortality.[1,2] In fact, if the month after surgery were considered a disease, it would be the third leading cause of death in the United States.[3] Most postoperative mortality occurs during the initial hospitalization, that is, under direct medical care in our highest-level facilities. The two most common and comparable causes of 30-day mortality after non-cardiac surgery are major bleeding which cannot easily be prevented, and myocardial injury which possibly can be; sepsis is a distant third.[4]

Myocardial injury after non-cardiac surgery (MINS) is defined by troponin elevation of presumably ischemic origin, and is highly associated with 30-day[5] (Fig. 1) and one-year[6] mortality. Myocardial infarction (MI), per 4th Universal Definition, is defined by troponin elevation *and* either symptoms or signs of myocardial ischemia.[7] More than 90% of MINS and MI occur within the initial two postoperative days.[8] Both are strongly associated with many *unmodifiable* baseline characteristics including age, diabetes, and cardiovascular history. In large randomized trials (n=7,000-10,000), we have shown that MI cannot be safely prevented by beta blockers,[9] avoiding nitrous oxide,[10] clonidine,[11] or aspirin.[12] In a recent large trial, one patient in seven who had MINS suffered re-infarction within 17 postoperative months.[13]

Fig. 1. 30-day mortality as a function of postoperative peak high-sensitivity troponin T. Mortality increases markedly from 0.1% at a troponin T concentration <5 ng/L to 30% mortality when troponin T exceeds 1,000 ng/L. Data from The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators: Association between complications and death within 30 days after noncardiac surgery. Can Med Assoc J 2019; 191: E830-E7



Intraoperative hypotension is associated with MINS and MI, with the harm threshold being a mean arterial pressure (MAP) ≈65 mmHg (Fig. 2).[14,15] The harm threshold for acute kidney injury (AKI) is similar,[14,16,17] and 40% of Stage 2 AKI persists or is worse 1-2 years after surgery (Turan, Anesthesiology, in press). We and others have also shown that postoperative hypotension is associated with myocardial infarction, *independent of intraoperative hypotension* (Fig. 3).[18,19]

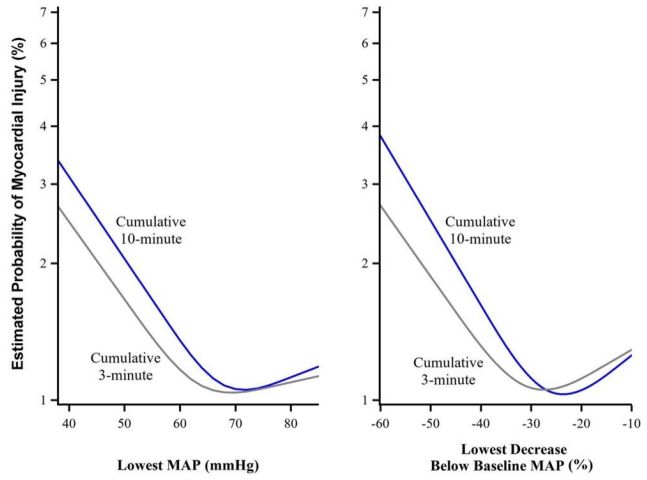


Fig. 2. Lowest mean arterial pressure (MAP) thresholds for myocardial injury after non-cardiac surgery. The left graph shows the relationship between the lowest cumulative absolute mean arterial pressure maintained for 3 and 10 minutes and myocardial injury. The right graph shows the relationship between the lowest cumulative relative mean arterial pressure maintained for 3 and 10 minutes and myocardial injury. Both graphs are multivariable logistic regressions adjusted for baseline characteristics and smoothed by restricted cubic spline with three degrees and knots at 10th, 50th, and 90th percentiles of given exposure variable. From Salmasi, et al: Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after non-cardiac surgery: A retrospective cohort analysis. Anesthesiology 2017; 126: 47-65.

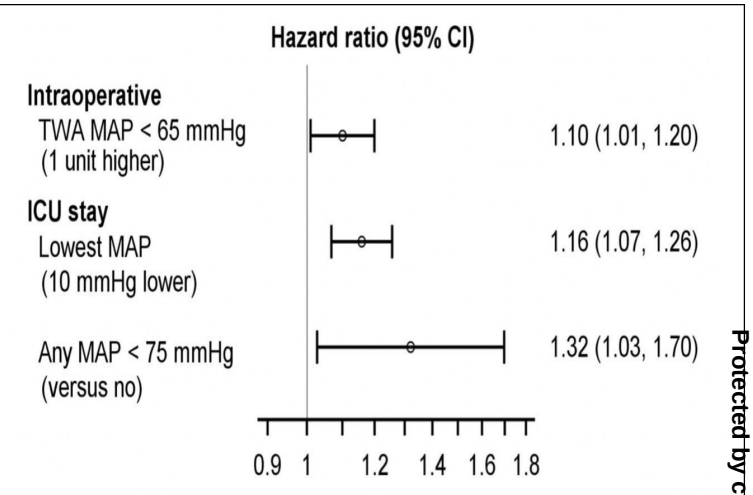


Fig. 3. Odds ratios of average relative effect on the primary composite of 30-day myocardial infarction and mortality for three perioperative periods: intraoperative, remaining day of surgery, and the initial four PODs of hospitalization. CIs for multiple comparisons were adjusted by Bonferroni correction. Correspondingly, P < 0.017 (0.05/3) was considered to be significant for the average relative effect. The circles present the odds ratios, and the bars present the CIs. POD = postoperative day. From Sessler 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: 317-27

There is currently sparse evidence that the associations are casual. But a small fragile randomized trial (n=292) shows that preventing intraoperative hypotension reduces the risk of major complications by 25%.[20] Perioperative hypotension is also associated with stroke,[9,21-24] although inconsistently.[25] Blood pressure — specifically hypotension prevention — is therefore a modifiable factor that may reduce cardiovascular complications.

Delirium is a common complication of cardiac surgery and is associated with morbidity and mortality.[26-32] The reported incidence of delirium after major non-cardiac surgery is typically about 10%, and increases markedly as age increases beyond 65 years. The pathophysiology of delirium is multifactorial but surely includes inadequate brain perfusion that results when mean arterial pressure is less than the lower limit of autoregulation.[33-35] Consistent with this theory, hypotension is associated with delirium and cognitive decline,[28,36,37] although inconsistently.[27,38,39] Limited randomized data (n=199) indicate that hypotension causes delirium.[40] Patients who have delirium after surgery are far more likely than others to develop long-term cognitive impairment,[41] although it remains unknown whether the association is causal. Hypotension may also provoke overt or (far more commonly) covert strokes which is strongly linked to delirium.[42]

No robust randomized trial has been published.

Specific Aims

Mortality in the 30 days after surgery is surprisingly common, and usually occurs during the initial hospitalization. Major bleeding and cardiovascular complications are the most common causes of 30-day postoperative mortality. Cardiovascular complications are independently associated with intraoperative and postoperative hypotension. Cognitive impairment, both acute delirium and long-term, are common after major surgery. There is increasing evidence that perioperative hypotension may contribute to brain injury. However, there is currently only sparse and fragile randomized evidence indicating that intraoperative hypotension prevention reduces cardiovascular risk and/or cognitive impairment in non-cardiac surgical patients. We are planing to propose a robust international randomized trial in 6,254 patients to test the primary hypothesis that perioperative tight blood pressure management reduces a composite of major perfusion-related complications (myocardial injury, stroke, non-fatal cardiac arrest, Stage 2-3 acute kidney injury, deep or organ-space infection, sepsis, and death) in the 30 days after major non-cardiac surgery.

In anticipation of the full trial, we will conduct the pre-planned pilot trial designed to evaluate feasibility, especially the ability to target blood pressure per protocol.

Aims

First, we will test whether there is suitable separation of intraoperative and postoperative blood pressure across two blood pressure management strategies (intraoperative MAP maintained ≥85 mmHg and postoperative tight pressure control versus routine care with some hypotension expected).

Second, that restarting routine antihypertensive medications per protocol should be feasible (restart delayed until the third postoperative day versus immediate restart).

We also consider the exploratory efficacy hypothesis that perfusion-related complications and delirium are reduced by tight perioperative blood pressure control.

Methods

The trial will be conducted with IRB approval and written patient consent will be obtained. There will be no restriction on sex, or ethnicity. All qualifying patients will be asked to consider the trial. The trial is restricted to patients ≥45 years old because cardiovascular outcomes are rare in younger patients, but there is no upper age restriction. The trial will be registered on ClinicalTrial.gov before enrollment.Pilot patients will be enrolled before normal enrollment.A full statistical analysis plan will be developed before any data are evaluated. Reporting will be consistent with the CONSORT guidelines.

Subject selection

Consenting patients will be **eligible** if they are:

1. Scheduled for major noncardiac surgery expected to last at least 2 hours;
2. Having general endotracheal anesthesia;
3. Expected to require at least overnight hospitalization;
4. Are designated ASA physical status 2-4;
5. Chronically taking at least one anti-hypertensive medication;
6. Expected to have direct blood pressure monitoring with an arterial catheter;
7. At least 45 years old;
8. Cared for by clinicians willing to follow the protocol;
9. Subject to at least one of the following risk factors:
    a. History of peripheral arterial surgery;
    b. History of coronary artery disease;
    c. History of stroke or transient ischemic attack;
    d. Serum creatinine >175 µmal/L (>2.0 mg/dl);
    e. Diabetes requiring medication;
    f. Current smoking or 15 pack-year history of smoking tobacco
    g. Scheduled for major vascular surgery
    h. Body mass index ≥35 kg/m^2;
    i. Preoperative high-sensitivity troponin T >14 ng/L or troponin I equivalent
    j. B-type natriuretic protein (BNP) >80 ng/ml or N-terminal B-type natriuretic protein (NT-ProBNP) >200 ng/ml.

Patients will be **ineligible** if they:

1. Are scheduled for carotid artery surgery;
2. Are scheduled for intracranial surgery;
3. Are scheduled for partial or complete nephrectomy
4. Are scheduled for pheochromocytoma surgery;
5. Are scheduled for liver transplantation;
6. Have a condition that precludes routine or tight blood pressure management such as surgeon request for relative hypotension or relatively high pressure required for carotid artery surgery;
7. Have end-stage renal disease requiring dialysis or estimated glomerular filtration rate (eGFR) <30 ml/min;
8. Have a documented history of dementia;
9. Have language, vision, or hearing impairments that may compromise cognitive assessments;

Protocol

Consenting patients who take either ACEIs or ARBs will be asked not to take the medications on the morning of surgery, and instead bring them with them to the hospital. Qualifying patients will be randomly allocated using computer-generated assignments 1:1 ratio without stratification in a block of four. Allocation will be concealed within sealed opaque envelopes until shortly before anesthesia induction. Allocation will thus remain concealed until the last practical moment. Randomization will be implemented by clinicians in collaboration with research personnel. Arterial catheter transducers will be positioned at the level of the right atrium, and adjusted as necessary if

patient position is changed. A fast-flush square-wave test will be performed shortly after catheter insertion to confirm that dynamic characteristics of the pressure monitoring system are appropriate.[10]

The treatments will be:1) norepinephrine infusion to maintain intraoperative MAP ≥85 mmHg, delayed resumption of chronic antihypertensive medications, and a target ward systolic pressure of at least 120 mmHg (tight pressure management); or, 2) routine intraoperative blood pressure management and prompt resumption of chronic antihypertensive medications (routine pressure management)

Tight pressure management: In patients assigned to tight pressure management, angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) will not be given the morning of surgery. Clinicians will be encouraged to insert the required arterial catheter before anesthetic induction because much hypotension occurs shortly after anesthetic induction.[46] A norepinephrine infusion (in the preferred local concentration) will be prepared, connected to an intravenous catheter, and activated at a low rate. Norepinephrine can be safely given through a central catheter or peripherally. In a recent study of 14,328 patients, there were only 5 extravasation events and not a single patient experienced local tissue injury.[47] It can be substituted if norepinephrine is contraindicated or impractical.

General anesthesia will be induced with propofol which will be given in repeated small boluses in an effort to keep intraoperative MAP ≥85 mmHg. Simultaneously, the vasopressor infusion will be adjusted with the same goal. Anesthetic dose, fluid administration, and vasopressor administration will be adjusted with the goal of maintaining intraoperative MAP ≥85 mmHg.

Resumption of chronic anti-hypertensive medications will be delayed until the third postoperative day unless deemed necessary to treat hypertension or for some other clear indication (e.g., preventing atrial fibrillation in a chronic beta-blocker user) because >90% of MINS occurs within 48 hours after surgery. When necessary to treat hypertension, chronic antihypertensive or new medications can be used per clinician preference. Clinicians will make what efforts they can to maintain postoperative systolic pressure of at least 120 mmHg during the initial three postoperative days by maintaining adequate hydration, using inotropic and chronotropic drugs, and vasopressor as necessary. This protocol specifies the blood pressure target, but leaves implementation to clinical judgement.

Routine pressure management: In patients assigned to routine pressure management, ACEIs and ARBs can be given the morning of surgery if deemed appropriate by the attending anesthesiologist. The arterial catheter will be inserted before or after induction of anesthesia per clinician preference. General anesthesia will be induced and maintained per routine. Intraoperative pressure management will be per routine. As usual, chronic anti-hypertensive medications will be restarted shortly after surgery unless contraindicated by hypotension.

In both groups, other aspects of anesthetic management will be at the discretion of the responsible anesthesiologist, including the types and volumes of various fluids. Volatile or intravenous anesthesia is permitted. There is increasing evidence that deep anesthesia promotes delirium and long-term cognitive dysfunction (Evered, in review).[49] Therefore, processed EEG monitoring, such as the Bispectral Index (BIS) or Patient State Index (PSI), should be used. If BIS is

the method, a value of 50 should be targeted from soon after induction until shortly before emergence. If another EEG system is used, a comparable hypnotic depth should be targeted.

There will be no limitation on ancillary vasoactive, chronotropic, and inotropic drugs. Clinicians will be free to use advanced hemodynamic monitoring (e.g., FlowTrac, esophageal Doppler, etc.). Blood products will be given per routine. Similarly, postoperative analgesic management will be per routine and clinician preference. Neuraxial and peripheral nerve blocks are permitted, but epidural catheters should not be activated until surgery is nearly finished.

Because patients must be fairly sick to qualify for Pilot GUARDIAN, some will go to directly from surgery to critical care units, or much less often, become unstable and require transfer from a routine ward to an ICU. In either case, every effort will be to maintain randomized treatments and blood pressure targets.

In all cases, good judgement will predominate. Clinicians should always act in their patients best interests, irrespective of the GUARDIAN protocol.

Measurements

Baseline

Baseline demographic and morphometric characteristics will be recorded, including height, weight, and sex. Routine anesthetic variables will be recorded including volatile anesthetic partial pressure, Fluid type and volume, estimated blood loss, and transfusions. Cardiovascular risks will be recorded, including hypertension requiring treatment, diabetes requiring oral medications or insulin, history of previous myocardial infarction, congestive heart failure, chronic obstructive pulmonary disease, current smoking status, and pack-years of smoking history. Cardiovascular medications will be similarly recorded by category, including beta blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and statins. Types of surgery will be characterized as orthopedic, laparoscopic, open abdominal, neurosurgical (including spine), thoracic, urologic, gynecologic, vascular, and other. Timing will be characterized as elective, urgent, or emergent.

Baseline laboratory values (within 30 days before surgery) will be recorded on an as-available basis, including albumin, BNP, and NT-ProBNP. Baseline electrocardiogram and echocardiogram interpretations will also be recorded as available, as will hemoglobin and creatinine other than specified below.

Perioperative

Blood pressure is our primary exposure and will therefore be carefully recorded. The most recent pressure from a clinic assessment will be used. Our institution have electronic anesthesia records that will automatically record systolic, mean, and diastolic pressures from the required arterial catheter at no less than 1-minute intervals. When possible, we will obtain electronic data which are efficient, denser, and more reliable than manual recording. But where necessary, intraoperative blood pressures will be recorded manually at 5-minute intervals. Ward blood pressure will normally be recorded by nurses at 8-hour-intervals. Any pressures obtained for clinical purposes will be recorded for use in the trial.Additional ward pressures might also be obtained. However, all blood pressures during the initial three postoperative days will be retrieved and included in the trial database. We will restrict recording to this period because >90% of postoperative myocardial injury occurs within the

initial two postoperative days. High-risk patients may require ICU admission. Blood pressure is measured frequently in critical care units, and all available pressures will be recorded.

We will require **creatinine** preoperatively (within 30 days), and on the initial three postoperative days while patients remain hospitalized. Additional values obtained for clinical reasons will be recorded during the initial 30 postoperative days. Hemoglobin will be recorded on an as-available basis for the initial three postoperative days.

Blood for generations 4 or 5 **troponin** T, or troponin I will be recorded preoperatively up to 30 days before surgery, and on the first three postoperative days so long as patients remain hospitalized.[8] Additional troponin samples will also be obtained if patients have shortness of breath or experience chest, neck, or arm pain. Blood troponin concentrations exceeding thresholds (depending on individual types of troponin tests) should prompt cardiology consultation, an electrocardiogram, and when practical an echocardiogram.

Myocardial injury will be diagnosed by objective screening based on preoperative and first three postoperative day troponin I values crossing specific thresholds for MINS so long as patients remain hospitalized. Abnormal troponin concentrations will be evaluated as clinically indicated with ECG, echocardiography, and clinical symptoms; the resulting values will be recorded, as will other cardiovascular interventions such as angioplasty. MINS will be diagnosed by troponin exceeding thresholds apparently of ischemic origin (e.g., no other obvious cause for artifactual elevation). Myocardial infarction will also be centrally adjudicated and require *both* MINS and at least one symptom (e.g., chest pain or shortness of breath) or sign (e.g. ECG or echocardiogram abnormality).

We will consider all patients who had an elevated serum troponin concentration anytime during the first 30 days after surgery and determine the presence of any ischemic features (*i.e.*, whether patients fulfilled the universal definition of myocardial infarction),[50] whether there was a non-ischemic etiology that could explain the elevated troponin measurement, and whether the myocardial injury appears to have occurred during or after surgery (*i.e.*, no evidence to support it was due to a preoperative event).

Myocardial injury after non-cardiac surgery will be defined as having values exceeding local 99th percentile for troponin I. Patients meeting diagnostic criteria for MINS will be evaluated for myocardial infarction with an electrocardiogram, echocardiogram (when possible), and a cardiac consultation. Non-fatal cardiac arrest and mortality will be determined from case-reports and medical records. Strokes will be detected based on clinical symptoms, and require radiographic evidence, consistent with new-onset cerebral ischemic or hemorrhagic injury.

Delirium will be assessed 7-10 AM and 5-8 PM for the initial four postoperative days while patients remain hospitalized because this approach will detect nearly all postoperative delirium (Fig. 4). Delirium will not be evaluated the evening after surgery because confusion might result from residual anesthetic effects. We will use the 3D-CAM which is based on a three-minute questionnaire, and has a sensitivity of 95% (95% CI, 84, 99), and specificity of 94% (CI: 90, 97) compared with formal psychometric evaluation.[51] The test works well in patients with dementia.[51] CAM-ICU, which is also well validated, will be substituted when patients are intubated.[52] Delirium will be assessed by investigators trained in the methods. Any positive CAM test will be considered evidence of delirium which will analyzed dichotomously.

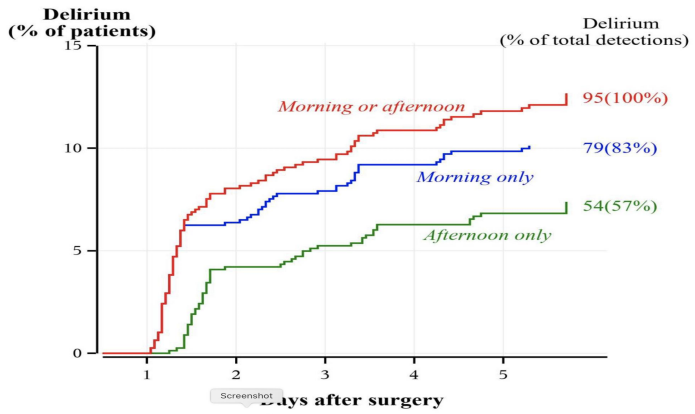


Fig. 4. Detection of delirium with CAM-ICU as a function of assessment times over postoperative days 1-5. Nearly all delirium was detected with twice daily assessments for the initial four postoperative days. From Hamadnalla, et al, in review.

Acute kidney injury. Postoperative Acute Kidney Injury will be defined by Kidney Disease Improving Global Guidelines (KDIGO) Clinical Practice Guidelines.110 By convention in perioperative studies, urine output will not be considered since it is rarely available.111 Specifically, patients will be considered to have Stage 1 acute kidney injury (risk) if the postoperative serum creatinine increases at 1.5-1.9-fold or by more than 0.3 mg/dl (≥26.5 μmol/L) within a 48-hour period. Stage 2 will be defined by a 2.0-2.9-fold increase in creatinine, and Stage 3 will be defined by a 3-fold increase in creatinine or an increase from baseline by ≥4 mg/dl (≥353.6 μmol/L) or initiation of renal replacement therapy.We will compare the preoperative creatinine concentration closest to surgery to the highest postoperative concentration measured within 7 days. Only Stages 2 and 3 will be considered for the primary perioperative composite.

Outcomes and clinically meaningful differences

The first co-primary feasibility outcomes are the fraction of time when intraoperative MAP >85 mmHg, intraoperative area of MAP >85 mmHg, and intraoperative area of MAP <65 mmHg. The area of MAP below (above) a threshold refers to the cumulative sum of areas for the MAP-time curve below (above) the specified threshold.

The second co-primary feasibility outcome is postoperative blood pressure management, characterized by the time routine antihypertensive medications restarted after surgery.

The secondary feasibility outcome measures are time-weighted average (TWA) intraoperative MAP, cumulative minimum MAP for 10 minutes, average postoperative systolic blood pressure (SBP), and mean of the lowest 3 postoperative SBPs.

The exploratory efficacy outcome measures are: 1) perfusion-related complications within 30 days of surgery; and 2) postoperative delirium within the first 4 postoperative days.

Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose: is life-threatening; or requires inpatient hospitalization or prolongation of existing hospitalization; or results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect; or is a medically important event.

Suspected unexpected serious adverse reactions (SUSARs) are events that meet the following criteria: 1) suspected to be causally associated with blood pressure management, anesthetic induction agent, or vasopressor; 2) unexpected if the nature, severity, or outcome of the reaction(s) is

not consistent with the reference information (i.e., product monograph for trial drugs); 3) serious (as defined above for an SAE); and 4) not a defined efficacy.

Efficacy and safety outcomes will be recorded separately and not as SAEs, except if, because of the course or severity or any other feature of such events, the investigator, according to his/her best medical judgment, considers these events as exceptional in this medical condition.

Hospitalizations, which were planned before inclusion in the study (e.g., elective or scheduled surgery or other interventions), will not be regarded as SAEs. This pertains also to hospitalizations which are part of the normal treatment or monitoring of the studied disease or another disease present before inclusion in the study (e.g., patient returning to the hospital for chemotherapy), and which did not result in a worsening of the disease.

All SAEs need to be reported within 48 hours of knowledge of the event to the Project Office. For such events, research personnel will complete an SAE CRF in the database. The Project Office will then inform regulatory authorities in a timely manner, as necessary, according to the applicable regulations.

The DMC will provide oversight of patients' safety throughout the trial by reviewing aggregate data (including all reported study outcome events and SAEs) by treatment group at regular intervals throughout the duration of the trial and as defined in the DMC Charter.

Data Analysis

Primary, secondary, and exploratory outcomes will be analyzed on a modified intent-to-treat basis by randomized group assignments. Specifically, we will include all randomized patients who have surgery, even if the operation is changed to one that would not otherwise qualify for Pilot GUARDIAN.

Balance on baseline characteristics will be assessed using absolute standardized difference (ASD), which is defined as the absolute difference in means, ranks, or proportions divided by the pooled standard deviation. Groups are considered to be imbalanced with respect to a baseline characteristic when ASD exceeded 0.44 [$1.96*\text{sqrt}(1/n_1 + 1/n_2)$].

We primarily evaluate the effect of tight blood pressure control on the fraction of time when intraoperative MAP exceeded 85 mmHg using a t-test. Wilcoxon rank-sum tests will be used to evaluate the effect of tight perioperative BP control on intraoperative area of MAP >85 mmHg, intraoperative area of MAP <65 mmHg, and time to restart routine antihypertensive medications after surgery.

Sample Size Considerations

The study will enroll 40 patients in each treatment group. Design analysis for the study will be done after data collection but before we conducted the analysis.

The fraction of time spent above 85 mmHg is assumed to be distributed as Beta (5, 5) and with the above sample size, the confidence interval half-width for estimating the mean would be 0.05 which is deemed to be sufficiently precise. The beta distribution is appropriate as the outcome is restricted to the closed interval between 0 and 1. The observed confidence interval widths are 0.01.

Schedule of Procedures

	BP	anti-HP medicine	Creatinine	Troponin I+ECG(Positive)	3D-CAM/ICU-CAM	Perfusion-related complications	Mortality
Baseline(<30d)	Y	Y	Y	Y			
DOS	IBP+MAP≥85/IBP	Y/N	Y	Y			
POD1	Y	Y/N	Y	Y	Twice		
POD2	Y	Y/N	Y	Y	Twice		
POD3	Y	Y			Twice		
POD4		Y			Twice		
Ward request	Y	Y	Y	Y			
Discharged						Y	Y
POD30-35						Y	Y

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吉林大学中日联谊医院科研伦理委员会
涉及人的生物医学研究伦理审批件

（2020 年）临审（20201120）

项目名称	严格围术期血压管理减少心血管意外、肾衰、认知障碍-GUARDIAN 研究的预实验 Pilot of "tight perioperative blood pressure management to reduce serious cardiovascular, renal, and cognitive complications"		
申请科室	麻醉科	项目负责人	李凯
工作证号	603972	身份证号	410205198210062011
联系方式	13596195176	类别	干预性研究
研究目的	为我院与美国克利夫兰诊所临床预后中心共同发起的国际多中心研究，提供参照，验证研究方案的可行性，组间区分性；初步探讨严格围术期血压管理对减少心血管意外、肾衰、认知障碍的作用		

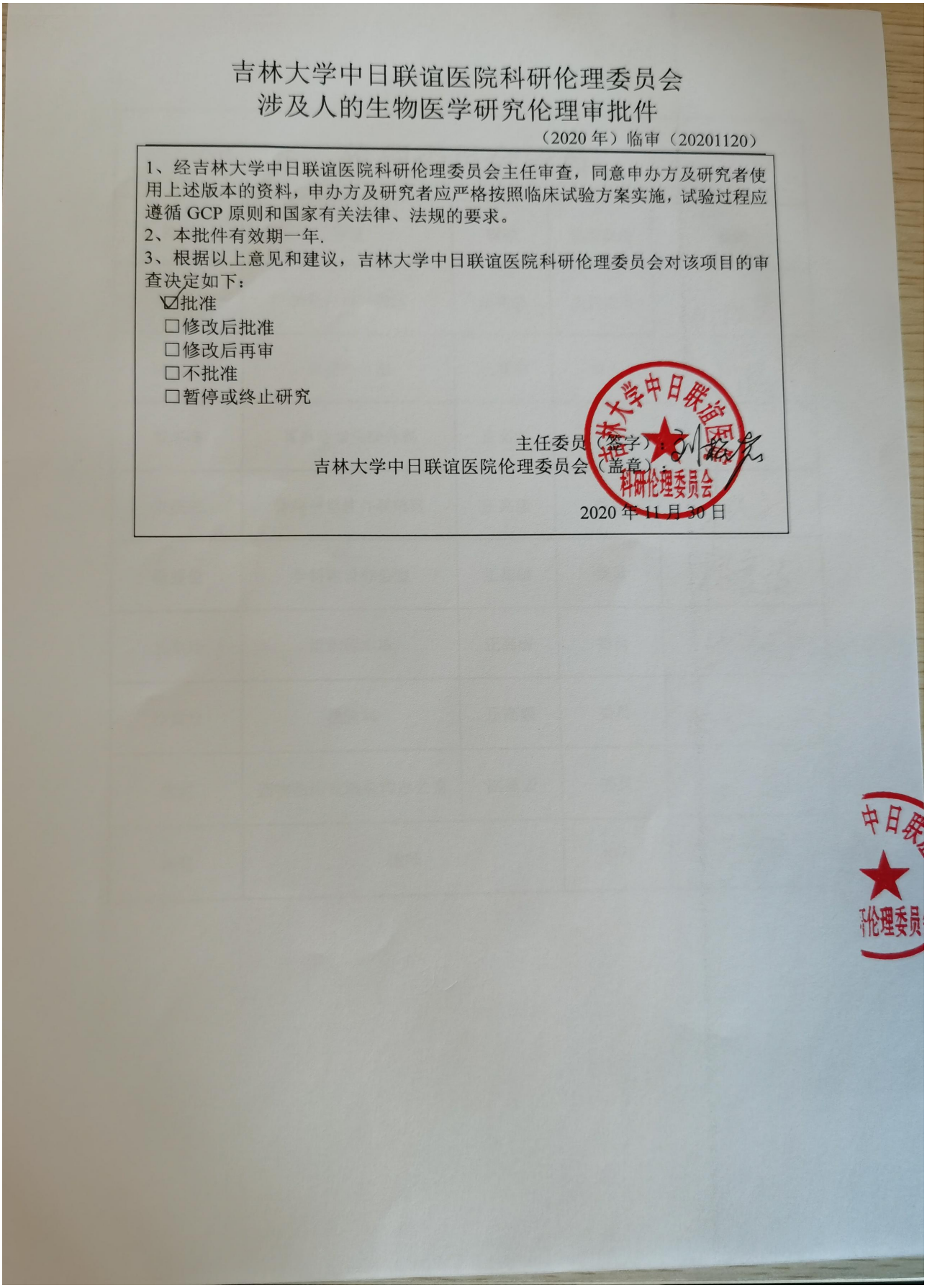
主要审查文件（含版本号）如下：

1 研究者发起的临床研究申请表受理申请表
2 临床研究方案（版本号：V1.0，版本日期：2020 年 11 月 01 日）
3 知情同意书及其他书面资料（版本号：1.0，版本日期：2020 年 11 月 01 日）
4 研究者简历、临床试验项目组成人员清单
5 研究者资质认证

研究者声明：(Inspection contents)	1、真实性：本表格内所写内容真实有效，若非真实，责任由申请人本人自负。 2、利益冲突：在此研究中不存在经济上、物质上、以及社会关系方面的利益冲突。倘若在研究开展过程中发现目前尚未知晓的利益冲突，我将及时向伦理委员会报告。 1. Authenticity: The content written in this form is true and valid. If it is not true, the responsibility is my own responsibility. 2. Conflict of interest: there is no conflict of interest in economic, material, or social relations in this research. If there is a conflict of interest that is not yet known during the research, I will report to the ethics committee in time.

申请人签名(Signature of applicant)	李凯	日期(date): 2020 年(year)11 月(month)30 日(day)

同意	作必要的修正后同意	作必要的修正后重审	不同意	终止或暂停该试验	弃权	回避
7 票	票	票	票	票	票	票



吉林大学中日联谊医院科研伦理委员会
涉及人的生物医学研究伦理审批件

（2020 年）临审（20201120）

1、经吉林大学中日联谊医院科研伦理委员会主任审查，同意申办方及研究者使用上述版本的资料，申办方及研究者应严格按照临床试验方案实施，试验过程应遵循 GCP 原则和国家有关法律、法规的要求。

2、本批件有效期一年.

3、根据以上意见和建议，吉林大学中日联谊医院科研伦理委员会对该项目的审查决定如下：

☑批准

☐修改后批准

☐修改后再审

☐不批准

☐暂停或终止研究

主任委员（签字）：

吉林大学中日联谊医院伦理委员会（盖章）：

2020 年 11 月 30 日

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance, see CONSORT for abstracts)	2-3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4-5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5-6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7-8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	7
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	5

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	NA
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	8, Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	8
Recruitment	14a	Dates defining the periods of recruitment and follow-up	8
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	8-11,Table 2, Figure 2-S2
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	11
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	11
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	12-13
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	12-13
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11-13
Other information			
Registration	23	Registration number and name of trial registry	3,4
Protocol	24	Where the full trial protocol can be accessed, if available	Supplemental text document
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	NA

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.