HYPOTENSION AFTER NONCARDIAC SURGERY

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ABSTRACT

Background

Early postoperative cardiovascular complication rates are high and are associated with hemodynamic compromise. A large proportion of hypotensive episodes are missed with routine ward monitoring strategies due to low measurement frequency and nursing limitations.

Objectives

The aim of this study was to determine the incidence of postoperative hypotension using a frequent monitoring strategy. Second, we looked at the relationship between postoperative hypotension and composite of mortality, non-fatal myocardial infarction, non-fatal stroke and new dialysis requirements. Finally, we sought to uncover significant predictors of postoperative hypotension.

Methods

Patients >45-years of age enrolled in the VISION Study were included in this sub-study. The COVIDIEN vital sign monitor was used to collect blinded hourly blood pressure measurements in patients post non-cardiac surgery until post-operative day three.

Results

1248 patients were included in this analysis. The three-day incidence of hypotension in the compliant intensively monitored group was almost twice higher (31.4% - 81/258 patients) than in the routine monitoring group, and the average delay in identifying a drop in BP under 90mmHg was almost 1.5 hours (87.5min) (IQR 21.3-153.3min). Severe hypotension (SBP <80mmHg) in the first three postoperative days, had the strongest association amongst all perioperative factors with the composite outcome of death, MI, stroke and new requirement for dialysis after non-cardiac surgery at 30 days [adjusted OR of 2.83 (95%CI, 1.25-6.44)]. Significant predictors of postoperative hypotension include a history of dialysis [adjusted OR 3.1 (95%CI, 1.14-12.96)], open surgery [adjusted OR 2.39 (95%CI, 1.57-3.62)], abdominal surgery [adjusted OR 1.79 (95%CI, 1.25-2.57)], and orthopedic surgery [adjusted OR 1.72 (95%CI, 1.112.74)].

Conclusion

Early postoperative cardiovascular complication rates are high and are associated with hemodynamic compromise. A large proportion of hypotensive episodes are missed with routine ward monitoring strategies.

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DECLARATION OF ACADEMIC ACHIEVMENT

I am the primary writer of all the chapters of this thesis. I am primarily responsible for the statistical analysis, interpretation and reporting of the data. Patient data reported in this thesis were collected by the VISION Study team led by Dr. P.J. Devereaux.

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LIST OF ABBREVIATIONS

ACS – Acute Coronary Syndrome
AF – Atrial Fibrillation
BP – Blood Pressure
BMI – Body Mass Index
CAD – Coronary Artery Disease
CCB – Calcium Channel Blocker
CHF – Congestive Heart Failure
CI – Confidence Interval
COX-2 – Cyclo-oxygenase inhibitor sub-type 2
DM- Diabetes Mellitus
DVT – Deep Venous Thrombosis
HR – Heart Rate
HTN – Hypertension
ICU – Intensive Care Unit
IQR – interquartile range
PE – Pulmonary Embolus
PHRI – Population Health Research Institute
PVD – Peripheral Vascular Disease
RCT – Randomized controlled trial
SBP – Systolic Blood Pressure
SD – Standard Deviation
VIF – Variance inflation factor
VISION – Vascular events in noncardiac surgery patients cohort evaluation

Background and Study Design

It is estimated that more than 200 million major surgical procedures are done every year.[1,2] Perioperative cardiovascular complications represent a major burden in this population. The 30-day mortality rate in these patients is estimated at more than 1% and approximately 7% of them are at risk of suffering a cardiovascular event (myocardial events and stroke).[2] Data from recent large trials suggests that operative and perioperative hypotension may be associated with clinical outcomes.[2,6] Although intraoperative hemodynamic monitoring is generally performed continuously and disturbances are corrected quickly, postoperative ward monitoring is much less frequent and it is a potential area for improvement.

Anesthesia-related mortality has decreased dramatically over the last century.[3] This is largely due to intensification of intraoperative hemodynamic monitoring, allowing for timely recognition and prevention of patient deterioration. In the VISION Study[4], a prospective cohort of 40,000 noncardiac surgical patients (23 centres, 17 countries) examining risk factors independently associated with postoperative mortality, only 0.6% of the 30-day mortality occurred in the operating room at the time of surgery. The majority of deaths (71% of 30-day mortality) happened postoperatively during the index hospitalization, while 29% occurred post hospital discharge. It is counterintuitive that the lowest risk of mortality is at the time when the patient is most vulnerable, on the operating table, with blunted sensory and motor function, under anesthetic medications and other physiologic perturbations caused by the surgical procedure. However, real time continuous monitoring and management by the anesthesiologist and operative team allow for a highly controlled environment where patient deterioration is rapidly

detected and corrected. This level of monitoring and specialist management is unfortunately not feasible outside of the OR, due to current health care and technological limitations. Once the patient leaves the operative setting, vital sign monitoring [blood pressure (BP), heart rate (HR), respiratory rate (RR), temperature (T), Oxygen saturation (O2sat)] is dramatically decreased, commonly shifting to every 4-6 hours on the surgical wards. Furthermore, monitoring and primary care is deescalated from medical/surgical subspecialists to nursing staff, and patient to health care provider ratio is increased from 1:1 to 4:1 or more in most cases.

Intraoperative hypotension

Several observational studies demonstrated an association between intraoperative hypotension and postoperative complications in noncardiac surgery. [2,5,6,7] A 1,064-patient prospective cohort of noncardiac surgical patients, led by Monk et al., showed an independent association between intraoperative hypotension, described as SBP<80mmHg, and 1-year mortality (RR 1.42, 95%CI 1.06-1.89 per 10 minutes of hypotension duration). [5]

Furthermore, in a recent analysis of a cohort of the VISION study by Roshanov et al. (n=14,687), a strong association was described between the duration of clinically significant hypotension and incidence of major cardiovascular complications. An intraoperative hypotensive episode lasting more than 30 minutes represented an adjusted relative risk of the composite outcome (30-day mortality, MINS, and stroke) of 1.19 (95%CI, 0.95-1.15). When intraoperative hypotension lasted more than 120 minutes, the adjusted relative risk increased to 1.66 (95%CI, 1.03-2.69).[7]

Postoperative Hypotension

Perioperative hypotension has been strongly associated with postoperative adverse outcomes, including death and stroke.[2,5] Data from POISE-1 Trial[2], a 8,351-patient RCT that recruited noncardiac surgical patients >45 years of age or at risk of cardiovascular events, reported a 6.9% postoperative incidence of cardiovascular complications (cardiovascular mortality, non-fatal myocardial infarction [MI], non-fatal cardiac arrest) and a 0.5% stroke incidence at 30 days post-surgery. In a post-hoc analysis of POISE-1, the adjusted hazard ratio (HR) of hypotension, defined as SBP < 90 mm Hg requiring treatment, for death within 30 days was 4.97 (95% CI 3.62-6.81) and for stroke within 30 days was 2.13 (95% CI 1.15-3.96). Furthermore, in POISE-1, clinically significant hypotension had the largest population attributable risks (PAR) (37.3%) for death and the largest perioperative PAR (14.7%) for stroke.

Clinically important hypotension also remained a concern beyond the intraoperative period in a sub-study (n= 14,687) of the VISION study. In this cohort, those who were hypotensive postoperatively (postoperative days 0-3) were at significant increased risk for death or vascular events (adjusted risk ratio, 1.68; 95% CI, 1.53-1.85).[7]

In POISE-2[8], a blinded factorial RCT of 10,010 patients (135 centers, 23 countries) allocated to aspirin or clonidine vs placebo (primary outcome: composite of death, nonfatal MI at 30 days), the median duration of clinically important hypotension in the operating room was 15 minutes (Q1-Q3, 5-30 minutes). However, on postoperative day 1, the median duration was 150 minutes (Q1-Q3, 60-374 minutes). Multivariable analyses showed that clinically important hypotension was an independent predictor of subsequent risk of perioperative MI (adjusted HR,

1.37; 95% CI, 1.16-1.62).[8,11]

Ward Monitoring and Hypoxemia

Further evidence of ward monitoring limitations was presented in an analysis of postoperative ward hypoxemia by Sun, Z et al.[9] In a subgroup (n= 1 250) of VISION, continuous oximetry was performed blindly on postoperative wards and compared to routine nursing data. In the blinded data, 37% of patients had desaturations below 90% for at least one hour, compared to a 5% incidence of hypoxemia with routine care. Overall, the vast majority (90%) of desaturations were missed with periodic (4-6 hour) checks. Similar trends would be expected with hypotension given the current limitations of hemodynamic monitoring in a ward setting.

HYVISION Study Objectives

Current evidence suggests an association between hypotension and clinical outcomes post-surgery. Routine patient ward monitoring is limited and infrequent (every 4-6-hour nursing assessment). The goal of this sub-study was to evaluate the incidence of hypotension using increased frequency of hemodynamic monitoring and review the relationship between postoperative hypotension and clinical outcomes.

The primary objective was to determine the incidence of postoperative hypotension in noncardiac surgical patients with routine vital signs measurements compared with intensive/frequent measurements, and to analyze device compliance. The second objective was to evaluate the relationship between postoperative hypotension and a composite of all-cause mortality, nonfatal MI, nonfatal stroke, and new dialysis requirements. The third objective was to

determine the preoperative predictors of postoperative hypotension based on patient baseline characteristics, comorbidities and surgical/anesthetic considerations.

HYVISION Study Design

Patient Population

HYVISION is an independent sub-study of VISION[4], a prospective multicentered cohort study evaluating cardiovascular outcomes in patients undergoing noncardiac surgery (ClinicalTrials.gov: NCT00512109). This study was performed at the Cleveland Clinic and McMaster University. All patients were 45 years or older, were planned to undergo non-cardiac surgery under general or regional anesthesia with a predicted hospital admission of 48 hours.

Screening and Patient Enrolment

Patients undergoing elective and emergency procedures were screened by the VISION study personnel. A separate consent was obtained for participants who agreed to participate in VISION.

Data Collection

Baseline patient data collection included: demographics, coronary artery disease, recent high-risk coronary artery disease, coronary artery revascularization, cerebrovascular disease, peripheral vascular disease, critical aortic valvular stenosis, congestive heart failure, atrial fibrillation, diabetes, hypertension, hypercholesterolemia treated with drug therapy tobacco history, chronic obstructive lung disease, obstructive sleep apnea, renal insufficiency, and preoperative

medications. Operative data included type of anesthesia, type of surgery, perioperative hemodynamic, respiratory and anesthesia related information as well as postoperative medications. Postoperative data included complications (See appendix 1 for definitions), and blood pressure measurement by routine nurse monitoring and blinded frequent device monitoring.

Study Device

The study device (COVIDIEN Nellcor N-600x, hemodynamic monitor) consisted of an IV pole-mounted monitor connected to an oscillometric pressure cuff and a finger oximeter, both attached to the patient for the duration of the trial (up to 72 hours or until discharge). The device total weight was near 33 kg. The blood pressure monitor was set to hourly daytime measurements (7am to 10pm), and every 2 hours nighttime measurements (10pm to 7am). Decreased nighttime monitoring was done to reduce potential sleep interruptions and improve patient comfort. This device recorded hemodynamic values but did not display it for healthcare providers and did not interfere with routine clinical care in any way.

Follow-up

Clinical outcomes and patient data were collected at hospital discharge and at 30-days by phone follow up. Appropriate documentation was obtained from patients who had experienced an event.

Sample Size

The original proposed sample size was 1500 patients. This was based on an evaluation of confidential preliminary data on 17,655 patients in the VISION Study, which had revealed an incidence of the primary composite outcome of 5.7%. This would provide 80% power to detect an odds ratio of >2.0 comparing patients with any hypotension to patients with no hypotension, with a Type I error rate of 0.025, 20% of variability in a binary indicator variable for hypotension. The estimated predicted incidence of hypotension (SBP<90mmHg) was 42%.

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Objective 1: HYVISION – Frequent Hemodynamic Monitoring and Patient Compliance

Background

Currently reported rates of postoperative hypotension are primarily based on routine nursing monitoring data, measured at an interval of 4-6 hours.[2,3] The aim of this study was to explore the risk of hemodynamic compromise using a more frequent monitoring technique. The primary objective was to assess patient compliance to the blinded frequent monitoring system and describe the incidence of hypotension as determined by routine and intensive monitoring strategies. Compliance was assessed using various thresholds (100%, 80%, 60%, 30%). The incidence of hypotension is reported based on at least one measurement of SBP under 90mmHg per patient during the monitoring period. This was further differentiated by monitoring group and by postoperative day. This analysis was then repeated for increasing severity of hypotension, with a SBP threshold of 80mmHg. Finally, we reported the delay in identifying significant hypotension between the intensive monitoring group and routine care.

Methods

Monitoring Frequency and Compliance Determination

Given the preset diurnal BP monitoring frequency, a total of 20 measurements (15 hourly daytime measurements and 5 nighttime measurements) were expected in a 24-hour period in a fully compliant patient. A 60% monitoring compliance rate (12/20 blinded measurements in 24 hours), which represents a 50% increase in routine nursing vital sign measurement frequency (every 4 hours) was determined as the minimum compliance rate in this analysis. This

compliance threshold was decided retrospectively after review of available data (see Table 2 for the compliance analysis).

Statistical Analysis

Patient baseline characteristics and pre-specified plausible risk factors for hypotension including preoperative comorbidities, medications, operative and anesthetic factors were examined and compared between patients who were at least 60% compliant with the intervention and those who were not. The chi-square and student's t-test were used where appropriate. Specific risk factors included: age, gender, BMI, clinical comorbidities: history of hypertension (HTN), coronary artery disease (CAD), congestive heart failure (CHF), stroke (CVA), peripheral vascular disease (PVD), atrial fibrillation (AF), pulmonary embolus/deep vein thrombosis (PE/DVT), diabetes (DM), dialysis. We also reviewed preoperative antihypertensive use: B-blocker, ACE inhibitor/angiotensin receptor blocker (ACEi/ARB), calcium channel blocker (CCB), and anesthetic factors (use of general anesthesia/ spinal anesthetic) and general surgical categories (See appendix B for definitions).

Analyses were performed using SPSS (Version 25).

Results

Compliance Analysis

Please see Table 2 demonstrating patient compliance on post-operative day one (POD1) as a function of different compliance thresholds. POD1 was chosen for the primary compliance

analysis since it had the largest number of patients with usable data from the blinded devices and was not subject to variability in monitoring times (POD-0/surgery date, monitoring differed based on surgery end time and transition between recovery locations / PACU-Ward).

Blinded monitoring data was available for 743 patients on the day of surgery (POD0), 815 patients on POD1, 587 patients on POD2, and 60 patients on POD3. On POD1, 60% compliance was achieved in 31% of patients (252/815 patients). Only 118 (15% of patient) achieved 80% compliance, and 44 patients (5%) were fully compliant with the intervention. On POD2, 13% (74/587) of patients were 60% compliant. On POD3, 10% (6/60) of patients were 60% compliant. (Table 2)

Patient Characteristics – Compliant VS Non-Compliant Group

Overall, patients who were 60% compliant with the intensive monitoring strategy did not differ significantly from patients who were not, based on preoperative baseline characteristics, medical comorbidities, preoperative medication use and surgical subtypes. Prevalence of peripheral vascular disease (PVD) differed significantly between the two groups and was higher in the non-compliant group (12.1% vs 4.4%, $p<0.001$). Furthermore, thoracic surgery and vascular surgery patients were less likely to be compliant with the intensive monitoring strategy [0.8% vs 6.7% ($p<0.001$), and 2.8% vs 8.4% ($p<0.002$) respectively] (Table 1).

Overall, mean age was 65 (SD 10) years (See appendix D for age distribution). Mean BMI was 28.2 (SD 7.6) kg. More than half had a history of cigarette smoking (57.6%; 708 patients). Preoperative hypertension was a diagnosis of 67.6% of patients. Surgery was performed with an

open approach in 76.8% of patients and under general anesthesia in 90.1% of cases. Mean length of hospital stay was stay 4.9 (SD 4.56) days.

Table 1: Population Parameters

	Overall		Monitor Compliant		Monitor Non-Compliant		p-value
	N=1248	%	N=252	%	N=996	%	
Age (yr) (mean, SD)	65 (10)	--	65.0(10.6)	--	64.7(10.1)	--	0.367
Sex (M)	670	53.7	138	54.8	532	53.4	0.701
BMI (kg/m2)(mean, SD)	28.9(7.6)	--	29.9(8.6)	--	30.3(7.3)	--	0.368
Smoker	708	56.7	132	52.4	576	57.8	0.119
Medical History							
Hypertension	844	67.6	159	63.1	685	68.8	0.085
Diabetes	276	22.1	50	19.8	226	22.7	0.330
CAD	292	23.4	51	20.2	241	24.2	0.185
PVD	132	10.6	11	4.4	121	12.1	≤0.001
CHF	89	7.1	21	8.3	68	6.8	0.407
Stroke	79	6.3	11	4.4	68	6.8	0.152
Dialysis	13	1.0	2	0.8	11	1.1	0.664
COPD	148	11.9	25	9.9	123	12.3	0.287
Preoperative							
SBP (mmHg)	141 (23)	--	141(22)	--	141(24)	--	0.304
HR (bpm)	74 (13)	--	74(12)	--	75((13)	--	0.083
Preoperative Medications							
ACEi or ARB	313	25.1	61	24.2	252	25.3	0.720
CCB	173	13.9	27	10.7	146	14.7	0.105
B-Blocker	394	31.6	67	26.6	327	32.9	0.057
Surgery							
Open	959	76.8	191	75.8	768	77.1	0.658
Endoscopic	334	26.8	72	28.6	262	26.3	0.468
Anaesthetic							
General	1125	90.1	227	90.0	898	90.1	0.969
Spinal	115	9.2	22	8.7	93	9.3	0.766
Surgery Type							
Thoracic	69	5.5	2	0.8	67	6.7	≤0.001
General/Abdominal	464	37.2	109	43.3	355	35.6	0.070
Orthopedic	235	18.8	52	20.6	183	18.4	0.412
Spinal	227	18.2	46	18.3	181	18.2	0.976
Vascular	91	7.3	7	2.8	84	8.4	0.002

Table 1Continuous variables are presented as means ± SD; categorical variables were presented as number (percent).
ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BMI = body mass index; CAD = coronary artery disease; CCB = calcium channel blocker; CHF = congestive heart failure; HR = heart rate; MI = myocardial infarction; POD = postoperative day; PVD = peripheral vascular disease; SBP = systolic blood pressure. Compliance rate: 60%

Table 2: Monitor compliance by post-operative day (POD)

Monitor Compliance	POD 1 N=815	POD 2 N=587	POD3 N=60
30%	68% (558)	56% (328)	50% (30)
60%	31% (252)	13% (74)	10% (6)
80%	15% (118)	4% (26)	3% (2)
100%	5% (44)	1% (8)	0% (0)

Incidence of Hypotension

Overall, 1,248 patients had available outcome and routine monitoring data for the first 72 post-operative hours, or until hospital discharge. This is based on the combined analysis of routinely and intensively monitored patients. In this population, with routine nursing monitoring, 17.9% (223/1248) of patients were identified having at least one recording of SBP under 90mmHg. In the frequent monitoring group, with no adjustment for device compliance, the incidence of hypotension was 11.9% (149/1248 patients). The lower incidence of detected hypotension in the unadjusted frequent monitoring group is expected given the overall low compliance rate (Table 2). However, adjusting for compliance (set at 60%), the 3-day incidence of hypotension in the intensively monitored group was threefold higher, 31.4% (81/258 patients). In these 258 patients who were 60% compliant with the intervention, routine monitoring revealed a 19.8% incidence of hypotension (51/258 patients). Overall, this represents a 11.6% (absolute) or a 58.6% (relative) increase in detected hypotension between the two monitoring strategies with 60% compliance analysis. Furthermore, 71 of the 149 patients identified as hypotensive with the blinded device, irrespective of compliance analysis, were not identified as such by routine

monitoring within the study duration. This number represents a 32% relative rate of missed hypotension by routine nursing monitoring, which is most likely an underestimate given the low compliance rates. Therefore, our most sensitive estimate of incidence of hypotension in the initial 72-hour postoperative period, combining both monitoring strategies, is 23.6% (294/1248 patients).

Delay in identifying hypotension

Amongst patients who were compliant with the intensive monitoring strategy and identified as hypotensive (SBP<90mmHg) first by the intensive monitoring then by routine monitoring, the median delay in recognizing hypotension was 88 minutes (IQR 21-153 min). The longest delay was 381 minutes. See Appendix C.

Discussion

The co-primary objectives of this analysis were to determine the device compliance and incidence of postoperative hypotension using an increased frequency of hemodynamic monitoring. The Covidien Monitor is a health Canada approved and patient validated hemodynamic monitor and therefore did not require accuracy and reliability testing.

Device Compliance

Due to the bulky nature and multiple wired attachment points of the Covidien monitor, careful evaluation of monitoring compliance was necessary to ensure data reliability. Compliance issues were anticipated prior to study completion although the magnitude was unpredictable. Therefore, the compliance threshold was determined retrospectively and set at 60% (12/20) of expected measurements, which also represents a 50% increase in routine nursing monitoring frequency (6 measurements / 24 hours), and still offers a reasonable number of compliant participants (252 patients – 20.2%) in our study.

Population Parameters

Specific patient baseline parameters, medical comorbidities, surgical and anesthetic factors reviewed in this analysis were preselected in consultation with specialists in the perioperative field and based on their potential to be associated with cardiovascular complications from medical literature. Running the risk of missing potential predictors, we had to be relatively selective due to the population size limitations. Parameters were preselected from the VISION Study databank.[1]

Incidence of hypotension

With only routine monitoring, 18% of patients were identified as hypotensive (SBP<90mmHg).

This is consistent with earlier data in the postoperative period.[2,3] However, in the compliant portion of the intensive monitoring group, hypotension was identified in 31% of patients. This represent a 58% relative increase in hypotension detection by simply automating and doubling the frequency of routine patient monitoring. Since the compliance threshold was set at 60% of expected measurements, true incidence of hypotension as detected by hourly monitoring would be expected to be significantly higher than 31%. Therefore, despite compliance limitations, this data uncovered an important fact, that true incidence of postoperative hypotension is much higher than seen by routine ward monitoring.

Comparison between monitor compliant (60% compliance threshold) and non-compliant patients revealed a statistical difference within the vascular and thoracic surgery groups. Although it appears that these two groups are less compliant with the monitoring strategy, the absolute patient numbers are very low (2 vs 67 patients for thoracic surgery and 7 vs 84 patients for vascular surgery) and this likely represents a spurious effect.

Delay in Identification of Hypotension

A significant limitation of routine hemodynamic monitoring is the delay in identifying clinical compromise and early signs of vital sign deterioration. Since routine monitoring is usually set at 4-6 hour intervals, undetected vital sign deterioration can go on for hours before being identified. This was shown to be true when looking at the compliant/hypotensive subset of our population. The average delay in identifying a drop in BP under 90mmHg was almost 1.5 hours (87.5min) (IQR 21.3-153.3min). This is only based on a very small subset of patients (n=40) and is once again likely an underestimate of true duration of delay in identifying hypotension.

Duration of Hypotension

Due to frequent prolonged gaps in monitoring data both in the routine monitoring but especially in the experimental group, calculation of the duration of hypotension for individual patients was not attempted as this would be prone to significant error and overestimation.

Strengths and Limitations

A major strength of this analysis is the increased frequency of hemodynamic monitoring compared to routine care. Although the compliance threshold for analysis was set at 60% (12/20) of expected measurements, this was still twice as often as routine care. This represents measurements every 2 hours. Secondarily, data completeness and follow up was excellent.

Limitations include primarily the low compliance rate with intensive monitoring. Although there was no formal evaluation of reasons for monitor discontinuation, the monitor size, power cord tethering and oscillometric BP cuff are likely important contributors of this. Finally, due to gaps in BP monitoring even in the compliant group, delays in hypotension measurements have to be interpreted with caution, and measures of the duration of hypotensive episodes was not completed.

Conclusion

In summary, current routine hemodynamic monitoring on postoperative wards has significant limitations and only captures a fraction of important hypotensive events. Since healthcare resources are increasingly limited in a growing and aging population, technological advances are being relied upon more and more heavily. Although our current monitoring device has significant compliance issues, it still uncovered many patients with hypotensive episodes that would have otherwise been missed. Future research should focus on remote, automated hemodynamic monitors that are portable, comfortable and non-invasive.

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Objective 2: Hypotension and Clinical Outcomes

The secondary objective of this analysis was to evaluate the relationship between postoperative hypotension and clinical outcomes at 30 days after noncardiac surgery. The primary outcome was a composite binary endpoint of all-cause mortality, non-fatal MI, stroke and new renal failure requiring dialysis. In the secondary analysis, we evaluated the relationship between hypotension and individual components of the primary outcome (all-cause mortality, non-fatal MI, stroke and new renal failure requiring dialysis), as well as other clinical outcomes such as non-fatal cardiac arrest, new renal failure requiring dialysis, new clinically important atrial fibrillation, and new congestive heart failure. Clinical outcomes are defined in Appendix A.

Statistical analysis

Binary logistic regression was used to characterize the odds of postoperative clinical outcomes for hypotensive versus normotensive patients. Deepening severity of hypotension (SBP>90mmHg, SBP>80mmHg) was used to further describe the relationship between hypotension and clinical outcomes. All patients who were identified as hypotensive by either routine monitoring or intensive monitoring during the first 72 hours post-surgery were included in this analysis. This is the most accurate representation of true incidence of postoperative hypotension in this study population.

The composite and individual clinical outcomes were classified as binary variables. Hypotension was classified as a categorical variable (normotensive reference, hypotensive SBP 80mmHg to

89mmHg, and hypotensive SBP below 80mmHg). Other baseline characteristics such as medical comorbidities, preoperative medication use, procedure type and anesthesia type, were classified as binary categorical variables. Age and BMI were classified as continuous variables.

Collinearity was assessed using a threshold variance inflation factor (VIF) of 2. A semi-parsimonious approach was used to address collinearity. Highly correlated variables (VIF>2) were evaluated based on clinical value and coefficient value.[1,2,3] The concordance statistic (c-statistic) was used to assess goodness of fit of our primary model with a x1000 bootstrap, using standardized criteria (0.5 indicating a poor predictive model, 0.7 indicating a good model, 0.8 indicating a strong model, and 1 indicating a perfect model).[5] All tests were two-sided with a significance p-value <0.05.

Results

A total of 1,248 patients (out of 1,300 patients) from the Cleveland Clinic had available BP data and discharge/30 day follow-up completed and were included in this analysis. The mean age was 65 (SD 10) years, and 46.3% were females. Most common preoperative comorbidities were: hypertension (844 pts., 67.6%), CAD (292 pts., 23.4%), diabetes (276 pts., 22.1%) and COPD (148 pts., 11.9%). More than half the patients had a history of tobacco use (708 pts., 56.7%). Other patient baseline parameters are reviewed in Table 1 (Objective 1).

The most common type of surgical procedure was general/abdominal (464 pts., 37.2%), followed by orthopedic (235 pts., 18.8%), spinal (227pts, 18.2%) and thoracic (69 pts., 5.5%). See

appendix 2 for sub-classification of surgical categories. Open surgery was performed in the majority of patients (959 pts., 76.8%), whereas endoscopic procedures were done in 334 patients (26.8%). General anesthesia was administered in 1125 patients (90.1%). Spinal anesthesia was performed in 115 patients (9.2%). (See table 1, Objective 1)

More than one in four patients undergoing surgery had taken a blood pressure lowering medication within a day from surgery. B-blockers were taken by 394 patients (31.6%) and ACE inhibitors or ARBs were taken by 313 patients (25.1%).

The primary composite outcome of 30-day mortality, stroke, MI or new dialysis requirement occurred in 48 patients (3.8%). The breakdown of the composite outcome was as follows: death (11 pts., 0.9%), MI (38 pts. 3.0%), Stroke (3 pts., 0.2%), new dialysis requirements (3 pts., 0.2%). The incidence of moderate hypotension (SBP 80-89mmHg) was 15.1% (189 pts.), and the incidence of severe hypotension (SBP under 80mmHg) was 8.3% (104 pts.). See table 2 for individual outcome rates and unadjusted analysis of hypotension.

Table 1 shows the analysis of the primary outcome of the second objective, the relationship between the composite outcome (death, MI, stroke, new dialysis) and postoperative hypotension, preoperative variables and surgical variables. Multivariable logistic regression demonstrated that severe hypotension (SBP<80mmHg) was associated with an adjusted OR of 2.83 (95%CI, 1.25-6.44) for the primary composite outcome, whereas moderate hypotension (SBP 80-89mmHg) had an adjusted OR of 0.75 (95%CI, 0.27-2.08). The corresponding 30-day composite outcome rate was 10.6% in patients who suffered severe hypotension and 2.6% for moderate hypotension.

Other significant associations with the primary composite outcome included history of chronic obstructive pulmonary disease (COPD) (OR 2.48, 95%CI, 1.17-5.24). Male gender was associated with a decrease in the primary outcome (OR 0.41, 95%CI, 0.21-0.80). See table 1 for the analysis of other perioperative clinical factors.

Table 1 Predictors of Composite (Death, MI, CVA, New Dialysis) – Logistic Regression

Parameters	Odds Ratio (OR)	95% Confidence Intervals (CI)	P-Value
Hypotension Reference (SBP≥ 90mmHg)	1.0	-	-
Hypotension Day 0-3 (SBP80-89mmHg)	0.75	0.27-2.08	0.574
Hypotension Day 0-3 (SBP <80mHg))	2.83	1.25-6.44	0.013
Age (y)	1.03	0.99-1.06	0.125
Gender (Male)	0.41	0.21-0.80	0.008
BMI (kg/m2)	0.96	0.92-1.01	0.110
Hx AF	2.36	0.73-7.62	0.151
Hx CAD	2.02	0.95-4.32	0.069
Hx DVT/PE	0.87	0.31-2.45	0.791
Hx CVE	1.54	0.61-3.93	0.363
Hx PVD	0.92	0.37-2.27	0.853
Hx HTN	1.18	0.42-3.29	0.751
Hx COPD	2.48	1.17-5.24	0.018
Hx Diabetes	1.79	0.85-3.76	0.125
Hx Dialysis	4.13	0.83-20.55	0.083
Hx CHF	1.16	0.46-2.91	0.748
Vascular Surgery Combined	1.30	0.42-4.01	0.650
Thoracic Surgery Combined	0.72	0.14-3.76	0.692
Abdominal Surgery Combined	1.12	0.47-2.71	0.794
Orthopedic Surgery Combined	0.79	0.22-2.81	0.712
Endoscopic	0.35	0.03-4.26	0.407
Open	0.22	0.02-2.82	0.246
General Anesthesia	4.13	0.43-36.13	0.200
ACEi/ARB <1d	0.91	0.44-1.90	0.801
Beta-blocker <1d	1.60	0.74-3.46	0.236
Rate Control CCB <1d	0.40	0.05-3.37	0.398

Collinearity (VIF >2) was demonstrated with general/abdominal surgery (VIF 2.5), orthopedic surgery (VIF 2.8), spine surgery (VIF 2.01), general anesthesia (VIF 7.8), spinal anesthesia (VIF 8.5), endoscopic approach (VIF 6.2), and open approach (VIF 6.0) (Appendix E). The least significant variable (lower coefficient) was dropped from the model. The resulting c-statistic is 0.85, and the corrected c-statistic with 1000x bootstrap is 0.76 (Appendix F).

Table 2 reports the unadjusted effect of postoperative hypotension (moderate and severe) on individual clinical outcomes at 30-days. The incidence of death was 0.9% (11 pts.), MI (3%, 38 pts.), stroke (0.2%, 3 pts), new dialysis requirement (0.2%, 3 pts.). There were no patients in the moderate hypotension group who died at 30 days, 2.9% (3 patients) in the severe hypotension group died (OR 3.52, 95%CI 0.92-13.46). Myocardial infarction was diagnosed in 3 patients (1.6%) in the moderate hypotension group (OR 0.60, 95%CI, 0.18-2.01), and in 10 patients (9.6%) in the severe hypotension group (OR 3.96, 95% CI, 1.84-8.49). Stroke incidence was 0.5% (1 patient) in the moderate hypotension group (OR 2.54, 95%CI, 0.23-28.09), and 0% in the severe hypotension group. The incidence of new dialysis was 0.5% (1 patient) in the moderate hypotension group (OR 2.07, 95%CI 0.32-81.49), and 0.9% (1 patient) in the severe hypotension group (OR 9.26, 95%CI 0.58-149.19).

Table 2: 30-Day Individual Outcomes – Exposure: Hypotension

Outcome	Overall n=1248	Patients who did not have Hypotension n=955	Patients who had Hypotension SBP 80-89mmHg n=189		Patients who had Severe Hypotension SBP under 80mmHg n=104	
	n (%)	n (%)	n (%)	Unadjusted Odds Ratio (95% CI)	n (%)	Unadjusted Odds Ratio (95% CI)
Composite (Death, MI, CVA, New Dialysis)	48 (3.8)	32 (3.4)	5 (2.6)	0.78 (0.30-2.04)	11 (10.6)	3.41 (1.67-6.99)
Death	11 (0.9)	8 (0.8)	0 (0)	--	3 (2.9)	3.52 (0.92-13.46)
MI	38 (3.0)	25 (2.6)	3 (1.6)	0.60 (0.18-2.01)	10 (9.6)	3.96 (1.84-8.49)
Stroke	3 (0.2)	2 (0.2)	1 (0.5)	2.54 (0.23-28.09)	0 (0)	--
New Dialysis	3 (0.2)	1 (0.1)	1 (0.5)	2.07 (0.32-81.49)	1 (0.9)	9.26 (0.58-149.19)
Non-Fatal Cardiac Arrest	2 (0.2)	1 (0.1)	0 (0)	--	1 (0.9)	9.26 (0.56-149.19)
New AFib	24 (1.9)	17 (1.8)	4 (2.1)	1.19 (0.40-3.59)	3 (2.9)	1.64 (0.47-5.69)
CHF	14 (1.1)	8 (0.8)	3 (1.6)	1.91 (0.50-7.26)	3 (2.9)	3.52 (0.92-13.46

+Comparator group was patients who did not have hypotension.

Discussion:

The main goal of this sub-study was to explore potential predictors of postoperative complications. Given the relatively low number of clinical events and the high number of predictors, increasing the risk of model overfitting, this analysis was primarily done for exploratory purposes. A significant asset of our data was the improved detection rate of true incidence of hypotension, using frequent blinded BP measurements. This was particularly

promising given that hypotension was identified as a predictor of postoperative complications in other large trials where postoperative hemodynamic data was solely based on routine nursing monitoring.[6,7]

The primary adjusted analysis of the second objective showed that severe hypotension (SBP <80mmHg) in the first 3 postoperative days, had the strongest association amongst all perioperative factors with the composite outcome of death, MI, stroke and new requirement for dialysis after non-cardiac surgery at 30 days [adjusted OR of 2.83 (95%CI, 1.25-6.44)]. Furthermore, the unadjusted analysis of individual clinical outcomes demonstrated an association between severe hypotension and myocardial infarction.

This data is consistent with other trials, notably POISE-1[6], where clinically significant hypotension had the largest population attributable risks (PAR) (37.3%) for death and the largest perioperative PAR (14.7%) for stroke.

Male gender was associated with a decreased risk of the composite outcome in our adjusted analysis [OR of 0.41 (95%CI, 0.21-0.80)]. This is surprising given that current epidemiological evidence suggests that males are generally at an increased risk of cardiovascular disease and hypertension in age matched cohorts.[9] However, it is possible that this association we found was spurious given the overall low event numbers and the risk of multicollinearity given our VIF threshold. If we decreased the VIF threshold to 1, gender would be considered as highly correlated to other variables in the model.

Duration of hypotension has been previously shown to have significant effects on postoperative complications. In a sub-study of the POISE-2 Trial[8], a 10,010-patient factorial-randomized trial of aspirin and clonidine for prevention of myocardial infarction, every 10-minute increased duration of postoperative hypotension on the day of surgery was associated an increased risk of postoperative death or MI with an odds ratio of 1.03 (98.2% CI, 1.01-1.05). Unfortunately, our data did now allow for an accurate description of the duration of hypotensive events due to frequent prolonged gaps in BP measurements, especially in the blinded arm.

Our model for the composite outcome had a corrected c-statistic of 0.76. Although not ideal, this model appears to have a good predictive power as per standardized criteria.[5]

Strengths and Limitations

A major strength of this sub-study is the increased frequency of blood pressure determinations, combining routine monitoring and blinded frequent measurements, resulting in a more accurate incidence of hypotension over a critical postoperative period. Furthermore, 96% of patients had complete follow-up at 30-days and events were independently adjudicated by the VISION study adjudicators.

This study has several limitations. The small total population and resulting low number of outcomes (48 patients, 3.8% event rate for the composite primary outcome) created significant restrictions in the number of explanatory variables and the risk of model overfitting. This also resulted in wide 95% confidence intervals for many individual outcomes, limiting clinical

significance. Additionally, low compliance rate of the intensive blinded monitoring system resulted in under-capture of true incidence of postoperative hypotension, which likely led to underestimating of the true impact of hypotension on clinical outcomes.

Conclusion

Patients undergoing non-cardiac surgery are at an increased risk of major cardiovascular complications including death, myocardial infarction, stroke, and new dialysis requirements. Hypotension within 3 days from surgery was strongly associated with the 30-day incidence of major complications. Postoperative hypotension was much more common than what is seen on routine ward monitoring.

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Objective 3: Predictors of Postoperative Hypotension

Postoperative hypotension had the strongest association with the primary composite outcome amongst all other perioperative factors reviewed in objective 2, with an adjusted OR of 2.83 (95%CI, 1.25-6.44). The focus of the third objective of this study was to evaluate the relationship between preoperative factors and postoperative hypotension. The predetermined outcome of interest was hypotension, defined as SBP <90mmHg in the first three days post noncardiac surgery.

Plausible predictors of interest included age, gender, BMI, clinical comorbidities: coronary artery disease (CAD), congestive heart failure (CHF), stroke (CVA), peripheral vascular disease (PVD), atrial fibrillation (AF), pulmonary embolus/deep vein thrombosis (PE/DVT), diabetes (DM), and dialysis. We also looked at preoperative antihypertensive use: B-blocker, ACE inhibitor/angiotensin receptor blocker (ACEi/ARB), calcium channel blocker (CCB), and anesthetic considerations (use of general anesthesia/ spinal anesthetic) and surgical procedure type.

Surgical procedure types were divided as follows: Intra-abdominal surgery (general surgery / visceral surgery), Thoracic Surgery (combined lobectomy, pneumonectomy and other thoracic surgery), Orthopedic surgery (combined major hip/pelvis, hip/knee arthroplasty), Spine surgery, and Vascular surgery (Thoracic aorta, Aorto-Iliac, Peripheral vascular and EVAR). Additionally, surgical approach was subdivided into open versus endovascular/interventional.

Statistical Analysis

Binary logistic regression was used to characterize the odds of postoperative hypotension based on selected preoperative and operative predictors. All patients who had available preoperative/operative and 30day/discharge data available were included in this analysis. Patients who were identified as reaching the hypotensive threshold (SBP <90 mmHg) by either routine or intensive monitoring strategies during the first postoperative 72 hours were classified as such. Severe hypotension (SBP <80 mmHg) was characterized separately using the same analysis and variables.

Hypotension was classified as a binary variable, with a threshold SBP of 90 mmHg, and a normotensive reference point. Other baseline characteristics such as medical comorbidities, preoperative medication use, procedure type and anesthesia type, were classified as binary categorical variables. Age and BMI were classified as continuous variables.

Collinearity was assessed with a threshold VIF (Variance Inflation Factor) of 2. A semi-parsimonious approach was used to address collinearity. Highly correlated variables (VIF>2) were evaluated based on clinical value and coefficient value[1,2] All tests were two-sided with a significance p-value <0.05. All statistical analyses were performed using SPSS v25 software.

Results

A total of 1,248 patients who had available pre/postoperative data and 30-day follow-up, were included in this analysis. Patient baseline characteristics, preoperative medications, comorbidities and surgical details are available in Table 1 (Objective 1).

Hypotension (SBP <90mmHg) occurred in 23.4% (292 patients) of the study population. The incidence of severe hypotension (SBP<80mmHg) was 8.3% (104 patients).

The variables with the strongest association with postoperative hypotension (SBP<90mmHg) were: history of dialysis [adjusted OR 3.1 (95%CI, 1.14-12.96)], open surgery [adjusted OR 2.39 (95%CI, 1.57-3.62)], abdominal surgery [adjusted OR 1.79 (95%CI, 1.25-2.57)], orthopedic surgery [adjusted OR 1.72 (95%CI, 1.112.74)]. Male gender was associated with a decreased risk of hypotension [adjusted OR 0.36 (95%CI, 0.27-0.48)]. (Table 1)

Table 1: Complete Case Analysis – Logistic Regression for Hypotension (SBP<90mmHg)

Parameters	Odds Ratio (OR)	95% Confidence Intervals (CI)	P-Value
Age (y)	0.99	0.97—0.99	0.154
Gender (Male)	**0.36**	**0.27-0.48**	**<0.001**
BMI (kg/m^2)	1.00	0.98-1.02	0.820
Hx CHF	0.85	0.47-1.54	0.593
Hx Tobacco use	1.34	0.99-1.81	0.054
Hx AFib	1.45	0.65-3.26	0.368
Hx CAD	1.14	0.77-1.69	0.517
Hx DVT/PE	1.10	0.71-1.72	0.669
Hx CVA	1.12	0.63-1.99	0.703
Hx PVD	1.45	0.87-2.41	0.158
Hx HTN	1.15	0.79-1.67	0.458

Hx COPD	1.01	0.64-1.58	0.981
Hx Diabetes	0.77	0.53-1.12	0.169
Hx Dialysis	**3.84**	**1.14-12.96**	**0.031**
ACEi/ARB	1.00	0.70-1.43	0.992
Beta-Blocker	1.23	0.87-1.75	0.250
CCB	1.18	0.57-2.43	0.66
Open Surgery	**2.39**	**1.57-3.61**	**<0.001**
General Anesthesia	0.95	0.56-1.63	0.863
Thoracic Surgery	1.35	0.68-2.68	0.397
Abdominal Surgery	**1.79**	**1.25-2.57**	**0.001**
Orthopedic Surgery	**1.74**	**1.11-2.74**	**0.016**
Vascular Surgery	0.88	0.45-1.73	0.71

Similarly, when looking at severe hypotension (SBP<80mmHg), significant predictors were orthopedic surgery [OR 3.01 (95% CI, 1.24-7.29)], abdominal surgery [OR 2.46 (90% CI, 1.08-5.59)], epidural anesthetic use [OR 3.16 (95%CI 1.77-5.63)], history of CVA [OR 2.26 (95%CI 1.07-4.75)]. Decreased incidence of severe hypotension was associated with male gender [OR 0.39 (95% CI 0.25-0.61)] and history of diabetes [OR 0.54 (95% CI 0.30-0.99)]. (Appendix H)

Collinearity (VIF>2) was seen with the following parameters: endoscopic procedure (VIF 6.2), open surgery VIF (5.9), general anesthesia (VIF 7.8), spinal anesthesia (8.5), abdominal surgery (VIF 4.5), orthopedic surgery (VIF 2.8), and spine surgery (VIF 2.0). The least significant variable (lower coefficient) was dropped from the model. See Appendix G for pre and post adjustment VIFs.

Discussion

In the second objective of this study, we determined that hypotension within 3 days of surgery was strongly associated with an increased risk of major postoperative cardiovascular complications (death, myocardial infarction, stroke and new requirement for dialysis) at 30 days from non-cardiac surgery. Furthermore, our blinded data suggests that the incidence of significant hypotension is much higher than previously reported. Given the strength of association between clinical outcomes and hypotension, and how prevalent this potentially preventable exposure is, it was important to further investigate potential predictors of hypotension. The primary goal of the third objective was to further characterize factors related to postoperative hypotension looking at patient characteristics and perioperative aspects.

In a recently published sub-study of the VISION Study[3], looking at 14,687 patients undergoing non-cardiac surgery, the incidence of postoperative hypotension was 19.5%, of which 95.4% occurred within the first 3 postoperative days. This is consistent with our 3-day incidence of hypotension as observed by routine nursing care, set at 17.9%. Furthermore, our blinded BP monitoring data suggests that the true incidence of postoperative hypotension is much higher, likely more than 31.4% (objective 1). This data suggests that one in three patients will be at risk of suffering from postoperative hypotension.

In our analysis, severe hypotension was associated with adjusted odds ratio (OR) of 2.83 (95% CI, 1.25-6.44) for our primary composite outcome (death, MI, stroke, new dialysis). In another sub-study of VISION[3] (n=14,687), looking at the effect of ACEi/ARBs on perioperative clinical outcomes, patients who had experienced postoperative hypotension were more likely to die or

suffer from vascular complications than those who did not (adjusted Risk Ratio 1.68; 95%CI, 1.53-1.85). In the POISE trial[5] (n=8,351), the adjusted hazard ratio (HR) of hypotension for death within 30 days was 4.97 (95% CI 3.62-6.81) and for stroke within 30 days it was 2.13 (95% CI 1.15-3.96).

Our results suggest a significant relationship between dialysis use and postoperative hypotension [adjusted OR 3.1 (95%CI, 1.14-12.96)]. Historically, dialysis has been associated with up to 50% incidence of hypotension, largely due to a state of relative hypovolemia resulting from solute and water removal, a decrease in blood oncotic pressure causing a further third space shift.[7] This is further exacerbated with general anesthesia and the use of certain myocardial depressant drugs, and its systemic vasodilatory and inflammatory properties. Unfortunately, specific drugs used during anesthesia were not available in the collected data. In a study of 238 chronic hemodialysis patients with surgery under general anesthesia, incidence of postoperative hypotension within 48 hours from surgery significantly increased the closer it was done to the index surgery. Those who were dialyzed within 7 hours of surgery had an incidence of 63.6% of postoperative hypotension.[7]

The impact and increased incidence of hypotension after major abdominal and orthopedic surgery has been studied extensively and shown to be multifactorial.[8,9] In our data, these types of surgeries were linked to increased postoperative hypotension. Due to patient number limitations, our surgical groups are very broad, and we did not attempt to further investigate specific procedure subtypes.

Male gender was associated with a decreased risk of hypotension [adjusted OR 0.36 (95%CI, 0.27-0.48)], which is consistent with epidemiological literature suggesting that males are generally at an increased risk of hypertension compared to females in age-matched cohorts.[11] This should however be interpreted carefully due to the overall low population numbers and risk of multicollinearity.

In the unadjusted analysis of potential predictors of severe hypotension (SBP<80mmHg), use of epidural anesthesia had the strongest association with a odds ratio of 3.16 (95%CI, 1.77-5.63). This is also seen in the literature and explained by the primary effect of epidural anesthetics on sympathetic nervous system blockade, resulting in arterial and venous vasodilation and a state of "functional" hypovolemia. [4]

Strengths and Limitations

The major strengths of this analysis are first of all the improved accuracy of the incidence of true postoperative hypotension due to the inclusion of available blinded hemodynamic data. Furthermore, data completion at 30-day follow-up was very high. Finally, event adjudication was performed, increasing the quality and reliability of our data.

There are several important limitations in this report. The available data granularity unfortunately did not allow for specific timing of occurrence of complications in relation to the hypotensive event, as time of specific complications was not recorded. It is plausible that in some cases hypotension could have occurred prior to a recorded complication or afterwards. Furthermore, duration of hypotension was not calculated due to frequent gaps in measurements,

especially in the intensive monitoring group. Finally, we did not have adequate statistical power due to the overall low population number, event rates, and compliance issues.

Conclusion:

In conclusion, our data suggests that postoperative hypotension is strongly associated with major cardiovascular complications after non-cardiac surgery. Predictors of postoperative hypotension included history of dialysis, major open, abdominal and orthopedic surgery, use of epidural anesthesia, and female gender.

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Conclusion and Future Directions

HYVISION was a sub-study of a large prospective multinational cohort study, the VISION Study[1] (n= 40 000), looking at perioperative care and predictors of myocardial injury and other clinically important complications. A significant advantage of HY-VISION was the increased frequency of blinded hemodynamic monitoring on postoperative wards in the first 72 hours post-surgery. It was shown that a large proportion of postoperative complications occur during this period and that current monitoring strategies are inadequate.

Our data showed that the incidence of postoperative hypotension was twice as common as previously seen with routine monitoring, by simply doubling the frequency of blood pressure measurement on postoperative wards. One in three patients (31% incidence) suffered from hypotension within 3 days of index surgery. Furthermore, on average, there was an almost 1.5-hour delay in detecting hypotension with current routine care.

Severe hypotension had the strongest independent association with our composite outcome of death, myocardial infarction, stroke and new dialysis requirements. The overall incidence of the composite outcome was 3.8% at 30-days post-surgery. Furthermore, hypotension was associated with increased rates of myocardial infarction, sepsis, and major bleeding. This data suggests that major cardiovascular complications are common in postoperative patients and have a strong association with postoperative hypotension.

Finally, our data suggests that predictors of postoperative hypotension include history of dialysis, major open, abdominal and orthopedic surgery, use of epidural anesthesia, and female gender.

There were several limitations in this study. Patient compliance with the intensive hemodynamic monitoring strategy was very low. Overall population size was limited, and study power was inadequate for outcomes like mortality and stroke.

On the other hand, data completion and follow-up were exceptionally high. Procedural variety was high, making this data broadly applicable. Finally, major patient outcomes were adjudicated by trained study personnel.

Future Directions

Early postoperative cardiovascular complication rates are high and are associated with hemodynamic compromise. A large proportion of hypotensive episodes are missed with routine ward monitoring strategies due to low measurement frequency and nursing limitations. Currently used ward monitoring devices are poorly mobile, bulky and rely on external energy sources for function. This leads to poor patient and health care provider compliance. Future directions in patient monitoring should include improved device portability, reliability and comfort, and should allow for continuous data acquisition and wireless real time alerting of deteriorations.

Appendix

Appendix A: Perioperative Outcomes Definitions (borrowed from the VISION Study Protocol)

Ref: Devereaux, P. J., et al. "Association of postoperative high-sensitivity troponin levels with myocardial injury and 30-day mortality among patients undergoing noncardiac surgery." Jama 317.16 (2017): 1642-1651.

1. Mortality – All cause mortality.

2. Myocardial Infarction - One of the following criterion:

1. A typical rise of troponin or a typical fall of an elevated troponin detected at its peak post surgery in a patient without a documented alternative explanation for an elevated troponin. This criterion also requires that 1 of the following must also exist:

A. ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema)

B. development of pathologic Q waves present in any two contiguous leads that are > 30 milliseconds

C. ECG changes indicative of ischemia (i.e., ST segment elevation [≥ 2 mm in leads V1, V2, or V3 OR > 1 mm in the other leads], ST segment depression [≥ 1 mm], or symmetric inversion of T waves > 1 mm) in at least two contiguous leads

D. coronary artery intervention (i.e., PCI or CABG surgery)

E. new or presumed new cardiac wall motion abnormality on echocardiography or new or presumed new fixed defect on radionuclide imaging

- Pathologic findings of an acute or healing myocardial infarction
- Development of new pathological Q waves on an ECG if troponin levels were not obtained or were obtained at times that could have missed the clinical event

2. **Nonfatal cardiac arrest** – Successful resuscitation from either documented or presumed ventricular fibrillation, sustained ventricular tachycardia, asystole, or pulseless electrical activity requiring cardiopulmonary resuscitation, pharmacological therapy, or cardiac defibrillation.

3. **Congestive heart failure** – At least one of the following clinical signs (i.e., an elevated jugular venous pressure, respiratory rales/crackles, crepitations, or presence of S3) and at least one of the following radiographic findings (i.e., vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema).

4. **New clinically important atrial fibrillation** –New atrial fibrillation that resulted in angina, congestive heart failure, symptomatic hypotension, or that required treatment with a rate controlling drug, antiarrhythmic drug, or electrical cardioversion.

6**. Stroke** – Stroke was defined as a new focal neurological deficit thought to be vascular in origin with signs and symptoms lasting >24 hours.

7. **Pulmonary embolus** One of the following:

- high probability ventilation/perfusion lung scan;
- an intraluminal filling defect of segmental or larger artery on a helical computed tomography (CT) scan;
- an intraluminal filling defect on pulmonary angiography; or
- a positive diagnostic test for deep venous thrombosis, and one of the following: non-diagnostic, ventilation/perfusion lung scan, or a non-diagnostic helical CT scan.

8. **Leg or arm deep venous thrombosis** –Any one of the following:

- persistent intraluminal filling defect on contrast venography;
- non-compressibility of one or more venous segments on B mode compression ultrasonography;
- a clearly defined intraluminal filling defect on contrast enhanced CT.

9. **Major bleeding** – Bleeding that resulted in a drop in hemoglobin to <70 g/L, transfusion of ≥1 unit of packed red blood cells, or death.

10. **Pneumonia** – The diagnosis of pneumonia required any one of the following:

- rales or dullness to percussion on physical examination of the chest AND any of the following:

A. new onset of purulent sputum or change in character of sputum,

B. isolation of organism from blood culture, or

C. isolation of pathogen from specimen obtained by tracheal aspirate, bronchial brushing, or biopsy; OR

- chest radiography showing new or progressive infiltrate, consolidation, cavitation, or pleural effusion AND any of the following:

A. new onset of purulent sputum or change in character of sputum,

B. isolation of organism from blood culture,

C. isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy,

D. isolation of virus or detection of viral antigen in respiratory secretions,

E. diagnostic single antibody titer (IgM) or fourfold increase in paired serum samples (IgG) for pathogen, or

F. histopathologic evidence of pneumonia.

11. **Sepsis** – Clinical syndrome defined by the presence of both infection and a systemic inflammatory response. Systemic inflammatory response required 2 or more of the following factors: core temperature >38º C or <36º C; heart rate >90 beats per minute; respiratory rate >20 breaths per minute; white blood cell count >12 x 109/L or <4 x 109/L.

Appendix B

Surgical definitions (borrowed from VISION Study 2017[14])

Ref: Devereaux, P. J., et al. "Association of postoperative high-sensitivity troponin levels with myocardial injury and 30-day mortality among patients undergoing noncardiac surgery." Jama 317.16 (2017): 1642-1651.

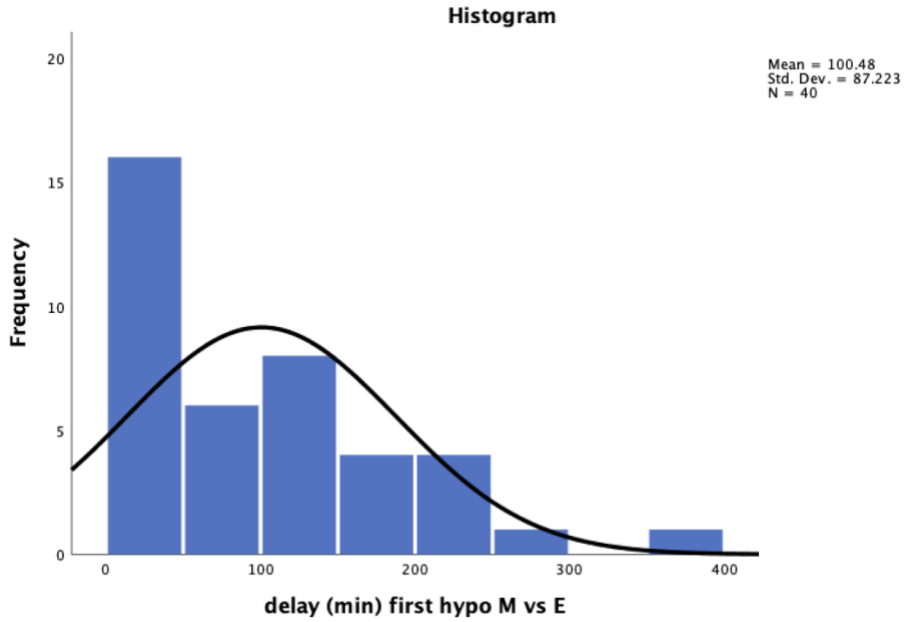
1**. Major orthopedic surgery** – A patient undergoing one or more of the following orthopedic surgeries: major hip or pelvis surgery, internal fixation of femur, knee arthroplasty, above knee amputations, or lower leg amputation (amputation below knee but above foot).

2. **Major general surgery** – A patient undergoing one or more of the following general surgeries: complex visceral resection, partial or total colectomy or stomach surgery, other intra-abdominal surgery, or major head and neck resection for non-thyroid tumor.

5. **Major vascular surgery** – A patient undergoing one or more of the following vascular surgeries: thoracic aorta reconstructive vascular surgery, aorto-iliac reconstructive vascular surgery, peripheral vascular reconstruction without aortic cross-clamping, extracranial cerebrovascular surgery, or endovascular abdominal aortic aneurysm repair.

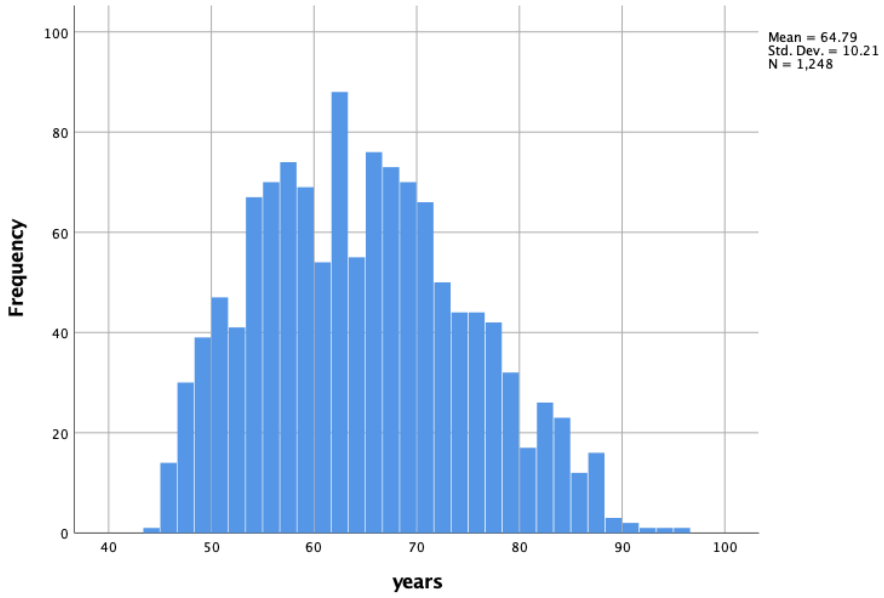
6. **Major thoracic surgery** – A patient undergoing one or more of the following thoracic surgeries: pneumonectomy, lobectomy, wedge resection of lung, resection of mediastinal tumor, or major chest wall resection.

Appendix C- Delay in detecting hypotension (SBP<90mmHg) with routine vs intensive monitoring



Histogram displays distribution of hypotension detection delay. Distribution is skewed and potential outlier. Median (IQR) reports of central tendency. Median 87.5 min, IQR [Q1Q3 21.3-153.3min]

Appendix D
Age distribution – all patients



Appendix E – Objective 2 - VIF Unadjusted – Composite Outcome – Logistic Regression

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients			Collinearity Statistics	
		B	Std. Error	Beta	t	Sig.	Tolerance	VIF
1	(Constant)	-.207	.137		-1.512	.131		
	hxCHFrecoded	.013	.023	.018	.589	.556	.817	1.223
	hx of tobacco use	-.004	.012	-.009	-.304	.761	.860	1.163
	hx AF	.063	.033	.055	1.907	.057	.899	1.112
	hx CAD recoded	.031	.015	.069	2.037	.042	.663	1.509
	hx dvt pe recoded	-.006	.018	-.010	-.347	.729	.939	1.065
	hx cve recoded	.019	.023	.023	.812	.417	.913	1.096
	hx pvd recoded	-.018	.021	-.028	-.852	.394	.690	1.450
	hx HTN recoded	.004	.014	.010	.278	.781	.614	1.629
	hx COPD recoded	.051	.018	.086	2.881	.004	.844	1.184
	hxdiab Recoded	.017	.014	.036	1.200	.231	.842	1.188
	hx dialysis recoded	.170	.056	.090	3.055	.002	.881	1.135
	Any BP<90day0-3	.020	.009	.065	2.238	.025	.900	1.111
	Thoracic Combined	-.034	.028	-.041	-1.210	.226	.675	1.482
	Abdominal surgery combined	-.015	.017	-.037	-.852	.395	.401	2.497
	orthopedic surgery combined	-.026	.023	-.052	-1.137	.256	.358	2.793
	spine surgery combined	-.037	.019	-.075	-1.908	.057	.497	2.012
	vascular surgery combined	.018	.027	.024	.651	.515	.559	1.788
	kg/m2	-.001	.001	-.049	-1.599	.110	.826	1.211
	years	.001	.001	.059	1.845	.065	.755	1.325
	8. General anaesth.	.026	.050	.041	.533	.594	.128	7.795
	8. spinal anaesth.	.010	.053	.015	.185	.853	.118	8.491
	8. nerve block anaesth.	-.033	.025	-.045	-1.345	.179	.688	1.454
	8. epidural anaesth.	-.012	.019	-.020	-.636	.525	.763	1.311
	2. Endoscopic	-.013	.030	-.030	-.429	.668	.160	6.252
	2. Open	-.022	.031	-.049	-.732	.464	.168	5.966
	15. Dihydrop. CCB <1d	-.004	.016	-.006	-.218	.828	.884	1.131
	14. Rate Control CCB <1d	.022	.030	.021	.720	.471	.938	1.067
	13. Alpha2 agonist <1d	.078	.042	.053	1.849	.065	.912	1.096
	7. Beta-blocker <1d	-.017	.014	-.041	-1.224	.221	.681	1.469
	6. ACEI/ARB <1d	-.001	.014	-.001	-.042	.967	.811	1.233
	2. Male or Female	.028	.011	.071	2.455	.014	.898	1.113

Dependent Variable: Composite(Death, MI, Stroke, Dialysis)

Appendix E– Objective 2 VIF Adjusted – Composite Outcome – Logistic Regression

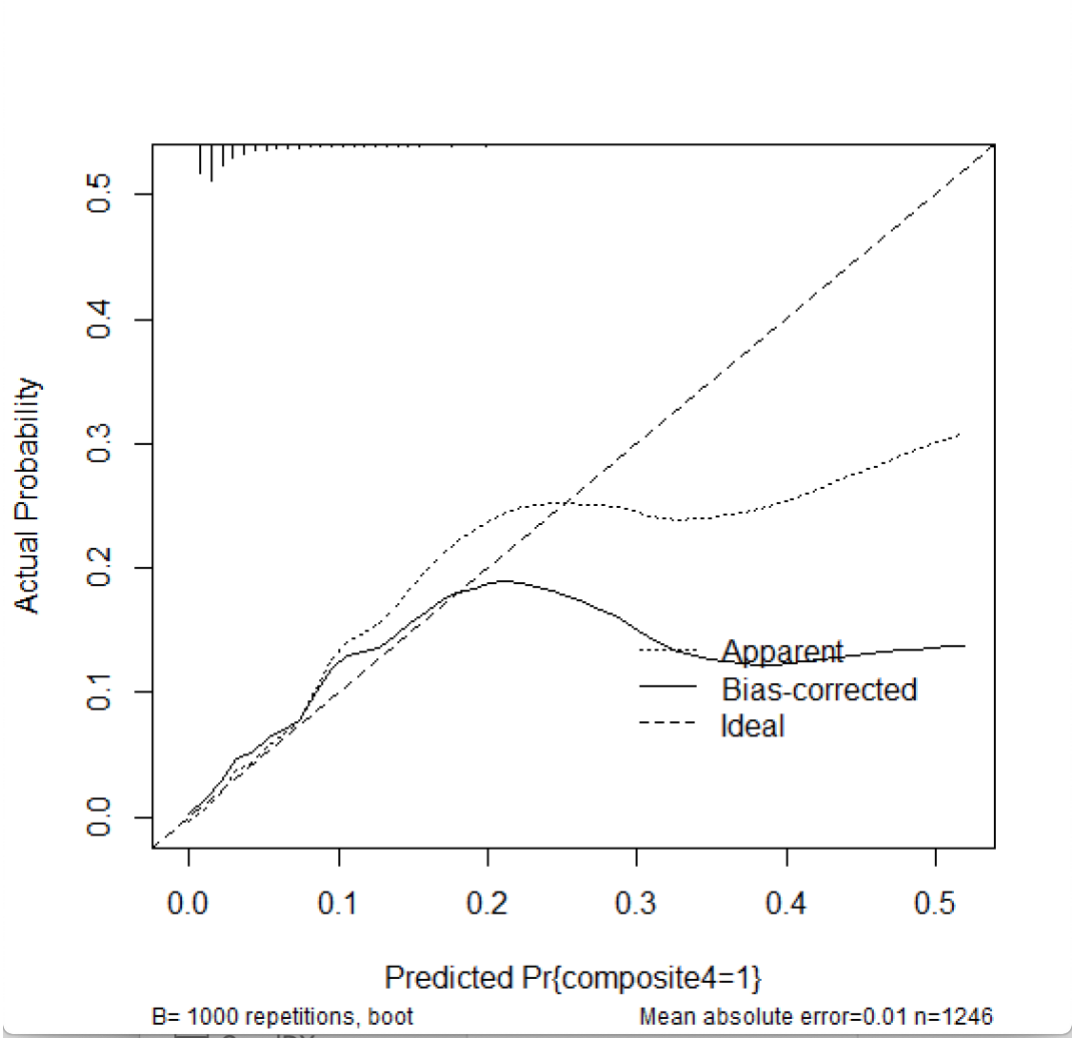
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B		Collinearity Statistics	
		B	Std. Error	Beta			Lower Bound	Upper Bound	Tolerance	VIF
1	(Constant)	-.236	.137		-1.717	.086	-.505	.034		
	Any BP<90day0-3	.020	.009	.064	2.218	.027	.002	.038	.900	1.111
	hxCHFrecoded	.014	.023	.018	.605	.545	-.031	.058	.818	1.222
	hx of tobacco use	-.003	.012	-.009	-.291	.771	-.026	.019	.862	1.160
	hx AF	.063	.033	.056	1.919	.055	-.001	.128	.899	1.112
	hx CAD recoded	.030	.015	.066	1.960	.050	.000	.060	.668	1.498
	hx dvt pe recoded	-.006	.018	-.009	-.323	.747	-.041	.029	.939	1.065
	hx cve recoded	.020	.023	.025	.858	.391	-.025	.064	.914	1.095
	hx pvd recoded	-.014	.021	-.022	-.668	.504	-.054	.027	.697	1.435
	hx HTN recoded	.003	.014	.008	.238	.812	-.025	.032	.615	1.625
	hx COPD recoded	.052	.018	.087	2.886	.004	.016	.087	.845	1.184
	hxdiab Recoded	.017	.014	.036	1.187	.236	-.011	.044	.843	1.186
	hx dialysis recoded	.168	.056	.089	3.025	.003	.059	.278	.881	1.135
	Thoracic Combined	-.019	.027	-.023	-.718	.473	-.072	.033	.746	1.341
	Abdominal surgery combined	.003	.014	.006	.185	.854	-.025	.030	.619	1.614
	orthopedic surgery combined	-.005	.019	-.009	-.238	.812	-.042	.033	.505	1.981
	vascular surgery combined	.036	.025	.049	1.429	.153	-.014	.086	.646	1.548
	kg/m2	-.001	.001	-.051	-1.692	.091	-.003	.000	.828	1.208
	years	.001	.001	.054	1.694	.091	.000	.002	.760	1.316
	2. Open	-.018	.015	-.040	-1.195	.232	-.048	.012	.690	1.450
	3. Surgery min. invasive	.012	.032	.011	.376	.707	-.051	.076	.929	1.076
	8. General anaesth.	.016	.023	.025	.707	.480	-.029	.061	.602	1.661
	8. nerve block anaesth.	-.031	.025	-.041	-1.248	.212	-.079	.018	.691	1.447
	8. epidural anaesth.	-.012	.018	-.021	-.677	.499	-.048	.023	.798	1.253
	15. Dihydrop. CCB <1d	-.005	.016	-.008	-.276	.782	-.037	.028	.884	1.131
	14. Rate Control CCB <1d	.023	.030	.022	.757	.449	-.036	.082	.939	1.065
	13. Alpha2 agonist <1d	.078	.042	.053	1.838	.066	-.005	.160	.911	1.098
	7. Beta-blocker <1d	-.019	.014	-.045	-1.354	.176	-.046	.008	.682	1.466
	6. ACEI/ARB <1d	-.001	.014	-.002	-.051	.959	-.027	.026	.811	1.233
	2. Male or Female	.028	.011	.072	2.475	.013	.006	.050	.899	1.113

a. Dependent Variable: Composite(Death, MI, Stroke, Dialysis)

Appendix F Objective 2 - Composite Outcome Model

C-statistics original: 0.8455

C-statistics optimism corrected using bootstrap x 1000: 0.7644



Appendix G

Objective 3: Collinearity Statistics (Hypotension <90mmHg) - unadjusted

Model		Tolerance	VIF
1	Age (y)	.757	1.322
	Gender Male	.931	1.074
	BMI (kg/m2)	.826	1.210
	hx CHF	.818	1.223
	hx of Tobacco use	.864	1.158
	hx AF	.900	1.111
	hx CAD	.670	1.493
	hx DVT/PE	.940	1.064
	hx CVE	.917	1.091
	hx PVD	.690	1.449
	hx HTN	.615	1.625
	hx COPD	.844	1.184
	hx Diabetes	.844	1.184
	hx Dialysis	.929	1.076
	ACEI/ARB <1d	.811	1.232
	Beta-blocker <1d	.685	1.460
	Rate Control CCB <1d	.940	1.064
	Dihydrop. CCB <1d	.888	1.125
	Endoscopic	.160	6.245
	Open	.168	5.965
	General anaesth.	.128	7.788
	spinal anaesth.	.118	8.486
	Enerve block anaesth.	.689	1.452
	epidural anaesth.	.779	1.283
	Thoracic Combined	.677	1.478
	Abdominal surgery combined	.403	2.480
	Orthopedic surgery combined	.360	2.777
	Spine surgery combined	.497	2.012
	Vascular surgery combined	.559	1.788

Objective 3: Collinearity Statistic – Adjusted – (Endoscopic, Spinal, Spine s, epidural/n. block)

Model		Collinearity Statistics	
		Tolerance	VIF
1	Age (y)	.767	1.304
	Gender Male	.936	1.069
	BMI (kg/m2)	.832	1.202
	hx CHF	.824	1.213
	hx of Tobacco use	.869	1.151
	hx AF	.901	1.110
	hx CAD	.675	1.481
	hx DVT/PE	.942	1.062
	hx CVE	.921	1.085
	hx PVD	.700	1.429
	hx HTN	.617	1.620
	hx COPD	.847	1.181
	hx Diabetes	.852	1.174
	hx Dialysis	.931	1.075
	ACEI/ARB <1d	.812	1.231
	Beta-blocker <1d	.688	1.453
	Rate Control CCB <1d	.944	1.059
	Dihydrop. CCB <1d	.890	1.124
	Open	.770	1.298
	General anaesth.	.652	1.533
	Thoracic Combined	.840	1.191
	Abdominal surgery combined	.655	1.527
	Orthopedic surgery combined	.557	1.794
	Vascular surgery combined	.647	1.546

a. Dependent Variable: Any BP<90day0-3

Appendix H

Unadjusted logistic regression (SBP<80mmHg)

Variable	Sign.	OR	95% CI	
hx CHF	.647	1.218	.524	2.835
hx of Tobacco use	.172	1.376	.870	2.176
hx AF	.825	1.135	.372	3.465
hx CAD	.214	1.440	.810	2.559
hx DVT/PE	.114	1.635	.888	3.009
hx CVE	.032	2.257	1.072	4.752
hx PVD	.595	.808	.368	1.774
hx HTN	.755	.912	.513	1.624
hx COPD	.993	1.003	.522	1.929
hx Diabetes	.046	.544	.299	.990
hx Dialysis	.243	2.752	.502	15.067
Thoracic Combined	.201	.351	.071	1.744
Abdominal surgery combined	.031	2.461	1.084	5.587
Orthopedic surgery combined	.015	3.005	1.239	7.292
Spine surgery combined	.895	1.067	.412	2.764
Vascular surgery combined	.703	1.246	.403	3.851
BMI (kg/m2)	.957	.999	.970	1.029
Age (y)	.715	.996	.972	1.020
epidural anaesth.	.000	3.156	1.771	5.626
General anaesth.	.683	1.176	.540	2.562
Surgery min. invasive	.338	2.732	.350	21.318
Open	.988	.991	.288	3.404
Endoscopic	.423	.627	.200	1.965
Rate Control CCB <1d	.517	1.421	.491	4.114
Dihydrop. CCB <1d	.487	.785	.398	1.552
ACEI/ARB <1d	.647	1.136	.658	1.959
Beta-blocker <1d	.113	1.540	.903	2.626
Gender Male	.000	.387	.246	.610

Adjusted Logistic regression for VIF>2 – excluding spinal s, endoscopic s, spinal anes. (SBP<80mmHg)

Variable	Sign.	OR	95% CI	
hx CHF	.863	1.076	.468	2.470
hx of Tobacco use	.217	1.332	.845	2.099
hx AF	.844	1.116	.374	3.333
hx CAD	.238	1.409	.797	2.490
hx DVT/PE	.177	1.514	.829	2.768
hx CVE	.068	1.974	.950	4.104
hx PVD	.632	.828	.382	1.795
hx HTN	.791	.926	.524	1.635
hx COPD	.844	1.067	.558	2.042
hx Diabetes	.052	.556	.308	1.006
hx Dialysis	.293	2.447	.461	12.980
Thoracic Combined	.494	.592	.132	2.656
Abdominal surgery combined	.001	2.761	1.555	4.903
Orthopedic surgery combined	.010	2.481	1.247	4.936
Vascular surgery combined	.666	1.247	.458	3.395
BMI (kg/m2)	.942	.999	.970	1.029
Age (y)	.916	.999	.976	1.022
General anaesth.	.749	1.138	.517	2.505
Surgery min. invasive	.267	3.184	.411	24.652
Open	.041	1.959	1.029	3.728
Rate Control CCB <1d	.505	1.424	.504	4.022
Dihydrop. CCB <1d	.420	.758	.387	1.485
ACEI/ARB <1d	.764	1.086	.635	1.858
Beta-blocker <1d	.107	1.543	.910	2.616
Gender Male	.000	.408	.261	.638