Decision support for intraoperative low blood pressure

The study proposal for an implementation study on decision support for intraoperative hypotension

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Introduction

Recently, there is a growing interest in the relation between intraoperative hypotension (IOH) and the occurrence of various postoperative adverse events. An increasing number of studies show an association between IOH and outcomes such as mortality, acute kidney injury and myocardial infarction.[1–5] However, this does not mean that we now understand 'how low we can go'. For example, heterogeneity in IOH definitions, outcome definitions and study populations makes it difficult to draw firm conclusions about the exact IOH threshold. Nonetheless, the observational nature of the data may be the biggest problem, as residual confounding is still likely to be of great influence.

The main cause of the residual confounding in observational IOH studies may be the current behavior of anesthesia providers. Blood pressure management is a vital part of anesthesia practice, and patients undergoing anesthesia are frequently – if not constantly – being treated for low blood pressures by anesthesia providers. However, blood pressure management is not a one-size-fits-all solution as each patient requires interventions that are tailored his or her needs. This complexity of blood pressure management is very difficult to adjust for during the analysis of IOH. It is very well possible that IOH is merely related to adverse events because it is a symptom of underlying disease severity and comorbidity, rather than being a proof for organ hypoperfusion despite current blood pressure treatment by anesthesia providers. It is thus of

great importance that we improve our understanding of our current circulatory management.

In current clinical practice IOH is quite common. Few anesthesia providers would consider a mean arterial pressure (MAP) below 60 mmHg* to be clinically acceptable for patients undergoing noncardiac surgery.[6] Nonetheless, up to 50% of patients have a MAP below 60 mmHg at any time point during their surgical procedure, adding up to ten minutes or more during the procedure in 15-25% of all patients.[3–5] In view of recent scientific evidence, it thus seems imperative that anesthesia providers adhere more strictly to their own clinically acceptable blood pressure thresholds.

Clinical decision support may help anesthesia providers to adhere more strictly to their own clinically acceptable blood pressure thresholds. An automated notification system may alert the anesthesia providers when the blood pressure of their patient drops below 60 mmHg MAP. A recent randomized trial didn't demonstrate any change in blood pressure management as a result of automated blood pressure notifications.[7] Because of the study design, the authors do not provide a satisfactory explanation of why it didn't change blood pressure management. Although randomization at the patient level may seem the appropriate thing to do, there is a serious risk of contamination. When on a given day an anesthesia provider received notifications for the first patient, is it likely that it the provider will be more aware of the blood pressure threshold during a next case, even when the subsequent patient was randomized to the control group. The contamination could be one explanation for a 'null-result' for the study. Another explanation would be that the authors did not provide sufficient context to the notifications, which has been suggested to be a requirement for the successful implementation of decision support.[8] The recent randomization trial thus by no means provides sufficient scientific evidence that clinical decision support for IOH does not work.

The current study proposal aims to implement a clinical decision support system for IOH that provides both automated notifications and contextual information. The decision support aims to educate anesthesia providers about the risks that are associated with IOH. Their response to that decision support will allow us to study blood pressure management by anesthesia provid-

* a MAP of 60 mmHg corresponds with a blood pressure of systolic 80 over diastolic 50 mmHg

ers, the effect of decision support on that blood pressure management, and the subsequent impact on postoperative adverse events.

Overall research question

Does a more strict treatment of intraoperative hypotension (IOH) encouraged through a clinical decision support system (CDSS) reduce postoperative morbidity and mortality in comparison to care-as-usual?

Specific clinical research questions

Does a lower incidence of IOH reduce postoperative morbidity and mortality?

Assuming that the CDSS resulted in a lower incidence of IOH, the postoperative morbidity and mortality will be compared between the intervention group and the care-as-usual group

How does this relation depend on the anesthetic depth?

Differences in the administration of intraoperative anesthetics and analgesics between the study groups will be determined. Postoperative morbidity and mortality will then be studied conditional on these differences between study groups.

How does this relation depend on other treatment choices?

Differences in the administration of intraoperative vasopressors and inotropes will be compared between study groups. Study groups will also be compared for the differences in total amount of administered intravenous fluids and blood products.

How does this relation depend on intraoperative conditions and patient comorbidity?

The relation between treatment, IOH, and postoperative morbidity and mortality may be studied conditional on other vital signs, blood loss, and various patient comorbidity.

Specific decision making questions

Does a CDSS for IOH result in a lower incidence of IOH?

The incidence of IOH will be compared between study groups, overall and conditional on CDSS activity.

Does a near real-time notification have a greater impact than feedback on performance?

In this study two types of decision support will be compared. One type consists of near real-time notifications that alerts anesthesia providers when the blood pressure drops below a particular threshold. The second type is an email system that provides feedback on what has happened during the anesthetic case and about the possible consequences.

What is the role of teamwork in anesthesia management?

Because the first elements concentrate on the attending anesthesiologist and the latter elements on the in-room providers, this study will provide insight in the anesthesia teamwork. This will be explored by comparing the results according to different roles (e.g. attendings, residents, CRNA, SRNA), years of experience and anesthesia service (multispecialty anesthesia, neuroanesthesia, etc.).

How does the 'directiveness' of the CDSS influence decision making.

The staged elements increase in their degree to which they draw the attention of the attending anesthesiologists and in-room provider to the problem of IOH. Nevertheless, only the last phase provides an actionable recommendation and is thus truly directive.

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How does this relation depend on intraoperative conditions and patient comorbidity?

The relation between treatment and IOH may be studied conditional on other vital signs, blood loss, and various patient comorbidity.

What is the effect of risk education?

The calibration/simulation will not only help to study decisions, but may also train the providers.

Methods

Design and participants

Domain

Adult elderly patients scheduled for a non-cardiac surgical procedure with a moderate to high surgical risk that have a low blood pressure (IOH) during the procedure.

Determinant

A decision support system using two different types of notifications for IOH (for more detailed information see paragraph 'Decision support elements').

Outcome

Postoperative Acute Kidney Injury (AKI, see 'End points').

Study design

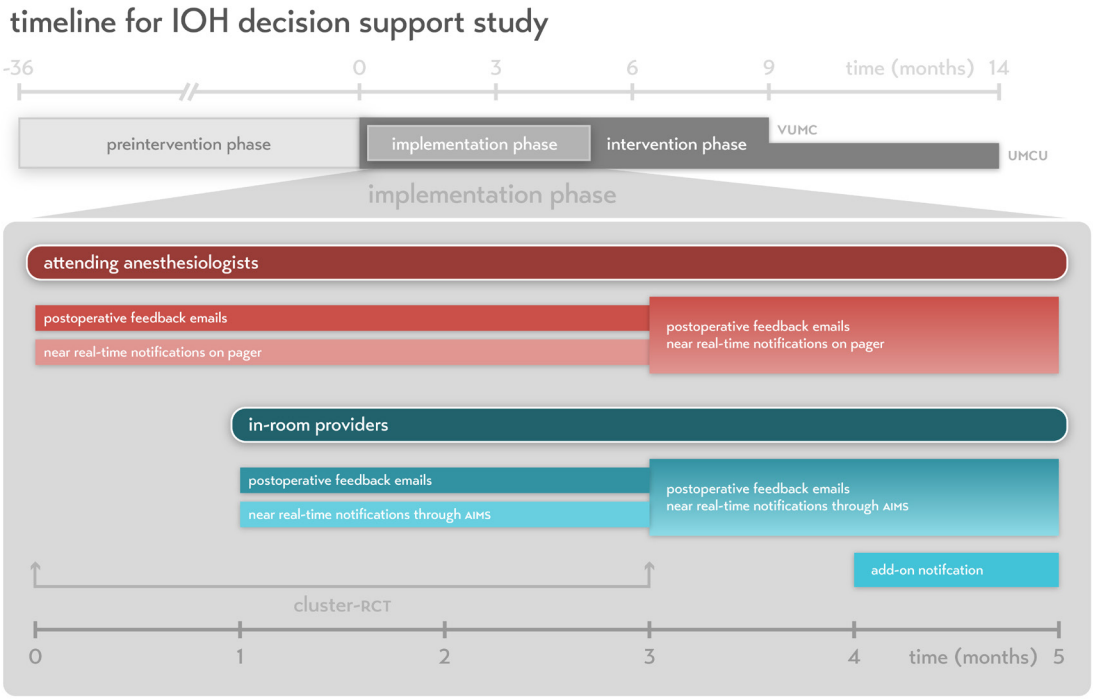
A single center, interrupted time series study with a nested cluster-randomized trial, randomized at the level of the anesthesia provider (see Figure 1). is the study will be performed at Vanderbilt University Medical Center (VUMC). The study will use a 36-month historic cohort of procedures (retrospective data) from the baseline 'off' period, further referred to as the prein-

tervention period. Subsequently, the decision support system is implemented and its effects are recorded during the intervention period using routine clinical data. The decision support system consists of four interventional elements (see paragraph 'Decision support elements'), of which two are aimed at the attending anesthesiologist and two are aimed at the in-room anesthesia provider (the anesthesiology resident, the certified or student nurse anesthetists (CRNA or SRNA)).

The intervention period starts with the nested cluster-randomized trial. At the start of the intervention period, the attending anesthesiologists will be randomized to either of the two elements aimed at the attending. One month later, the in-room providers will be randomized to either of the elements that are aimed at them. The randomization status of the attending anesthesiologists will be maintained. After the third month, all elements will be activated for all users within that user group. This ends the period of the nested cluster-randomized trial. After the fourth month, an add-on for one of the decision support elements will be implemented. The exact nature of this add-on modification is discussed in the section 'Decision support elements'. The entire implementation phase will thus be completed in five months.

The study will then continue to monitor the incidence of the primary end point to reach the estimated sample size. The primary outcome is a routinely collected outcome variable, which enables us to: 1) use a historic cohort as a baseline 'off' period; 2) study the CDSS implementation in a pragmatic setting; and 3) conduct the study in a more cost-effective way. The total intervention period will be 9 months for the VUMC (Figure 1).

Figure 1 - Study design



Study population

All adult inpatients, 60 years and older, scheduled for a non-cardiac surgical procedure under general or central neuraxial anesthesia at the Vanderbilt University Medical Center (VUMC).

Exclusion criteria

Procedures where only a peripheral nerve blockade is used will be excluded, i.e. patients who did not receive either general anesthesia or central neuraxial blockade. Patients with preexisting end-stage renal disease will be excluded, operationalized as excluding all patients with a pre-operative need for dialysis. The following procedures will also be excluded: renal surgery, cardiac surgery, organ transplantation, ophthalmic surgery, endoscopic gastrointestinal procedures, and (interventional) radiologic procedures. Additionally, small non-invasive or minimally-invasive procedures will also be excluded.

Randomization during the nested cluster-randomized trial

Each attending anesthesiologist and in-room provider will be randomized to either of the two interventions that is aimed at their user group. The randomization will occur at the start of the nested cluster-randomized trial period or at the time she/he enters the study within that period. Randomization at the provider level rather than at the patient level aims to prevent contamination and therefore dilution of the implementation effect. Randomization of the attending anesthesiologists will be stratified for the particular anesthesia expertise groups, e.g. vascular surgery anesthesia and neuroanesthesia. In-room providers will also be randomized per participating center, but stratified for being a resident, a CRNA or a SRNA. Randomization of CRNAs will be stratified on the OR-locations within their center where they mostly work. Stratified randomization will be performed using a block size of four.

Patients at risk of IOH

The hypothesis of this study is that prevention of prolonged low blood pressures during anesthesia will reduce the incidence of organ injury, i.e. AKI and myocardial injury. The domain of this study therefore includes patients at risk of IOH. Identification of patients at risk of IOH is not straightforward. In this section we will discuss why identification of patients at risk of IOH is not straightforward and how this complicates the design of this study as compared to a regular randomized trial.

In a classical drug-RCT, you know that everyone in the index group will get the intervention, although you are not sure for which individuals the intervention will work. A more complex intervention often aims to improve patient outcome by implementing an intervention that is targeted to affect behavior and decision making of either healthcare workers or patients. For example, a weight loss program aims to reduce obesity in individuals. The mechanism through which the program achieves weight loss may not have the same effect in all individuals, similar to our drug trial. On top of that, an additional uncertainty is introduced, because the intervention will also depend on the compliance of the individual to the program.

When a complex intervention aims to prevent a particular condition – as in this case of IOH decision support – there is an additional complicating factor besides the two previously men-

tioned factors of uncertainty. When the condition can be completely prevented, the study population becomes difficult to identify. In our study, the decision support can only prevent AKI in patients that would otherwise have had IOH. Thus we should analyze only patients that would have had IOH, not patients that would never have IOH. Since we may not know which patients would have suffered from IOH in the intervention group, there is no simple comparison. Alternatively, we could compare the rates in all patients of both study groups – thus both those that would have had and would not have had IOH. However, as anesthesiologists already aim to prevent low blood pressures, patients with IOH according to our definitions will be relatively rare. Analyzing all patients would thus greatly dilute the effect on AKI and myocardial injury.

A more efficient way would be to compare patients that would be *at risk of IOH* rather than patients that would *definitely have had IOH*. A good example is comparing patients with different predicted risks when a prediction model is implemented to prevent postoperative nausea and vomiting. For IOH there is unfortunately no prediction model available. However, when IOH is prevented from occurring because of the implemented decision support, it is likely that they will have a low blood pressure that is just above the threshold. Patients that have a blood pressure below a higher threshold will thus be at risk of a blood pressure below a lower threshold, if it weren't for the intervention by the anesthesia providers. The next crucial step would be to select that higher threshold. Selecting too high a threshold will dilute the effect, whereas too low a threshold and patients may drop out because they are prevented from reaching that threshold. Although one cannot be sure what would be the best threshold in advance, it seems reasonable that a mean arterial pressure (MAP) below 65 mmHg would be a reasonable indication of MAP below either 60 mmHg or 55 mmHg.

Interventions

The interventions in this study consist of a) the decision support elements; and b) general education.

Decision support elements

The decision support system consists of four elements that aim to notify anesthesia providers of

the risks of organ injury due to organ ischemia when a patient suffers from IOH. The four elements will be implemented during different stages of the nested cluster-randomized trial period. At the end of the trial period all elements will be simultaneously activated (Figure 1).

The decision support system will be custom designed. The VUMC will implement two elements that provide near real-time notifications into GasChart, its anesthesia information management system (AIMS). The two other interventions consist of feedback emails, which be implemented into the email notification system of the Perioperative Data Warehouse (PDW).

One element of each decision support type will be available for each user group. In other words, a near real-time notification system and a feedback email system will be available for the attending anesthesiologists as well as for the in-room providers. During the cluster-randomized trial period, the near real-time elements will only be activated for a specific case when the anesthesia providers were randomized to near real-time decision support within their user group, as registered in the anesthesia information management system.

IOH thresholds associated with organ injury

The thresholds that will trigger decision support intervention are derived from recent literature. The studies were selected based on the results of a systematic review. For AKI, myocardial injury and mortality the two highest ranked studies for that end point were selected. For MAPs below 60, 55 and 50 mmHg and dependent on the duration of hypotension, the results of each study were classified into three risk groups (mild, moderate, high) based on the reported odds ratios or risk ratios. For each end point, the highest risk category for a particular MAP and duration was considered the definitive risk category for that end point. The overall risk of organ injury for a particular MAP and total duration was then considered to be the highest of risks of any of the end points. Risk thresholds for odds ratios and risk ratios were chosen by the investigators so that there was a clinically reasonable incremental increase in risk with lower MAPs and longer durations. The exact classification is shown in Tables 1 and 2.

Table 1 - Risk classification based on the odds ratios as reported in literature

MAP	min	AKI (odds ratios)		Myocardial injury (risk ratios / odds ratios)			30 day Mortality (odds ratios)	
		Sun et al.	Walsh et al.	Van Waes et al.†	Pipanmekaporn et al.†	Walsh et al.	Monk et al.	Mascha et al.
<60	≥1	1.1*		1.1*			1.1*	1.0‡
	>5	1.1*		1.1*			1.1*	1.1‡
	>10	1.8		1.5			1.1*	1.1
	>20	1.7*		1.5	2.6		1.1*	1.2
<55	≥1	1.4*	1.2	1.1*		1.3	1.1*	1.1‡
	>5	1.5*	1.2	1.1*		1.5	1.1*	1.1‡
	>10	2.3	1.3	1.5		1.8	1.1*	1.1
	>20	3.5	1.5	1.5	2.6	1.8	1.1*	1.3
<50	≥1	1.4*	1.2	1.3		1.3	1.2*	1.1‡
	>5	1.5*	1.2	2.0		1.5	2.4	1.1‡
	>10	2.3	1.3	2.0		1.8	2.4	1.2
	>20	3.5	1.5	2.4	2.6	1.8	2.4	1.5

* = not significant; † = the numbers in this column are risk ratios; ‡ = estimated from OR per 10 minutes
yellow = mild risk; light orange = moderate risk; dark orange = high risk
risks from higher MAP groups carry over to lower groups if that particular threshold was not reported in the study

Table 2 - Classification of depth and duration of IOH

MAP	total minutes	overall organ injury*	acute kidney injury	myocardial injury	30 day mortality
<60	≥1	mild risk	mild risk	mild risk	mild risk
	>5	mild risk	mild risk	mild risk	mild risk
	>10	moderate risk	moderate risk	moderate risk	mild risk
	>20	high risk	moderate risk	high risk	mild risk
<55	≥1	mild risk	mild risk	mild risk	mild risk
	>5	moderate risk	moderate risk	moderate risk	mild risk
	>10	high risk	high risk	moderate risk	mild risk
	>20	high risk	high risk	high risk	mild risk
<50	≥1	moderate risk	mild risk	moderate risk	moderate risk
	>5	high risk	moderate risk	high risk	high risk
	>10	high risk	high risk	high risk	high risk
	>20	high risk	high risk	high risk	high risk

* the risk of overall organ injury (2nd column) is determined by the highest risk classification of the individual risks (3rd to 5th columns).
The red bar represents the risks of the current patient.

Postoperative feedback emails

The first two elements consist of the same email notification aimed at different anesthesia providers: the attending anesthesiologists or the in-room providers. The anesthesia providers will be notified within 24 hours after the end of a case, when the patient had an episode of IOH that is associated with an increased risk of organ injury due to organ ischemia. The feedback email will primarily report the risk of AKI at VUMC. In addition, the feedback emails will include a link to a more detailed description of all organ risks (see Table 2 and the Example for the Feedback emails). Moreover, at the end of each week, the anesthesia providers will receive an email that reports which of their patients suffered from postoperative AKI or myocardial injury that week (such a report is already a part of clinical routine at VUMC). As the follow-up for AKI is seven days, the update may contain patients that had their procedure during the previous 14 days.

Near real-time notifications

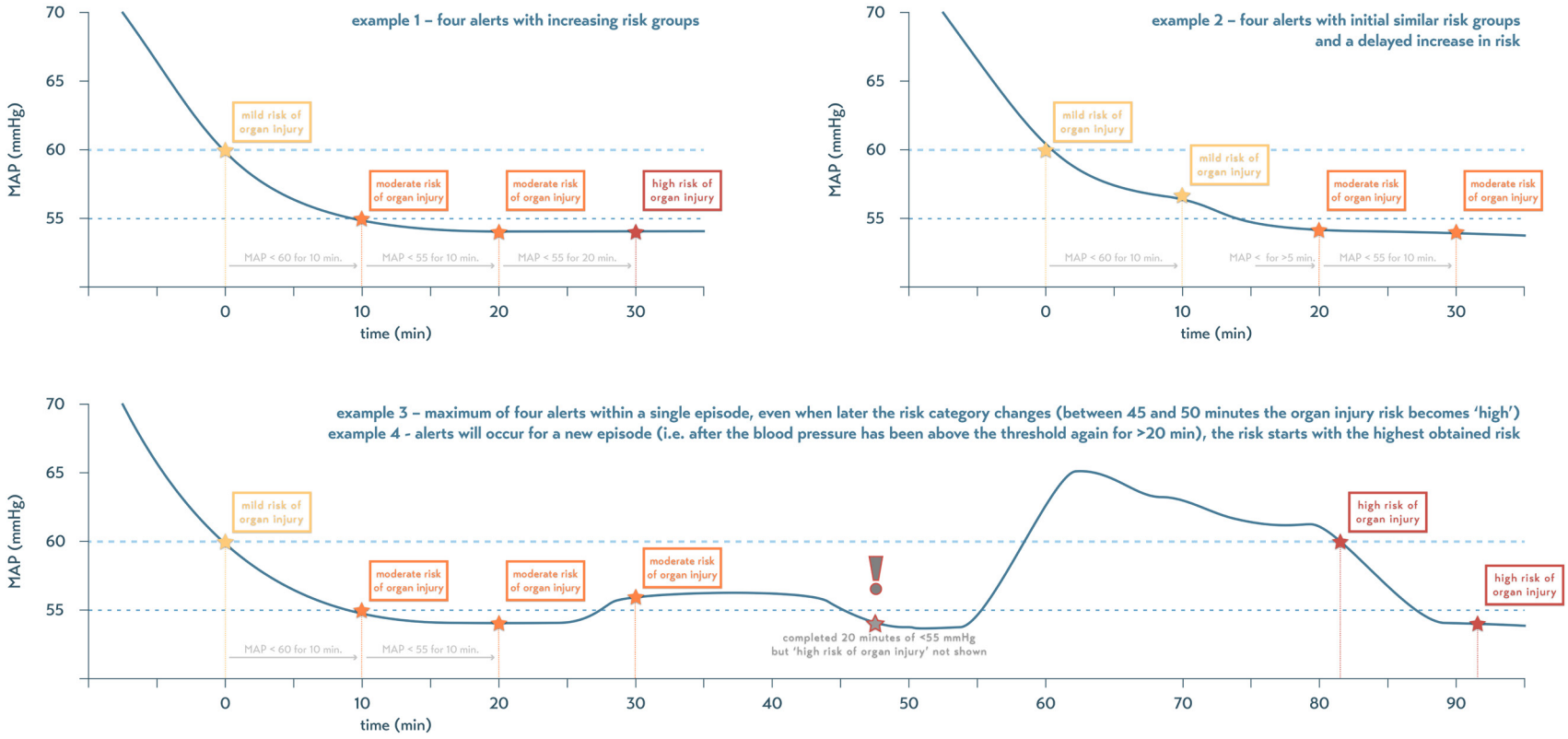
The two near real-time decision support elements will notify the anesthesia provider of a blood pressure drop below one of the IOH thresholds. The near real-time notification for the attending anesthesiologist will be provided through the paging systems (example text: "MAP<50 for 10min, high AKI risk"), whereas the in-room providers receive their notification through the AIMS of the hospital (see attached Example for the AIMS IOH notification).

Triggers of near real-time notifications

The near real-time notifications systems will be triggered by a MAP below 60 mmHg (Figure 2). The decision support system will then provide a notification of the AKI risk at VUMC. Depending on how much time the MAP of an individual patient was below a particular threshold, the notification will display the risk of organ ischemia for that patient (mild, moderate or high, see Table 2). An example in time is shown in Figure 2 – examples 1 and 2.

The near real-time notifications for the in-room providers will be continuously displayed within the AIMS. The near real-time notifications for the anesthesiologists will be sent to their pagers. The pager notifications will repeat with a 10-minute interval. Within a single episode of IOH there will be a maximum of four notifications the paging system (Figure 2 – example 3). An episode of IOH is defined as the time that a patient's MAP drops below 60 mmHg and the first time it reaches a MAP of 60 or higher. When blood pressure has not returned to normal after the four notifications – i.e. after 40 minutes – it is assumed that there is a reason for not increasing the blood pressure. In that instance either the MAP is considered to be appropriate for that patient or the interventions are not sufficiently effective. This prevents anesthesiologists to keep getting notifications throughout the procedure. Even when a new duration threshold is reached, the system will not provide a new notification if four notifications within that episode have already occurred. However, when the blood pressure normalizes for more than 20 minutes, a subsequent IOH episode will again provide notifications to the low MAP. Any risk that is presented, is based on all the previous low MAP values and durations that occurred during the case (Figure 2 – example 4).

Figure 2 - Triggers of near real-time notifications



General education

All attending anesthesiologists and in-room providers will be informed at the start of the nested trial period – or when they enter the study at a later time – of the study's purposes and how the decision support will work. The information will be provided by email as well as during scheduled educational sessions for each provider group. Further educational sessions will be scheduled when required.

End points

The primary end points

The primary end point for the VUMC will be AKI stage I or greater within the first seven postoperative days of surgery. The definition of AKI stage I according to KDIGO (Kidney Disease: Improving Global Outcomes) will be used: an absolute increase in serum creatinine of 0.3 mg/dL or more (≥26.4 µmol/L) from baseline within 48 hours or a percentage increase in serum creatinine to 150% or more from baseline within 7 days. Because of a low availability of information on urine output, this criterion will not be used to diagnose AKI. The baseline serum creatinine value is the last known preoperative value which was recorded within six months prior to the surgical procedure. Preoperative and postoperative creatinine values will be derived from blood samples that are part of routine clinical care. This may be a primary lab request for creatinine or a secondary analysis of blood samples that are otherwise available. No additional blood samples will be drawn for the purpose of this study to determine postoperative AKI at the VUMC.

Secondary end points: patient level

- 30-day mortality
  - combination of in-hospital mortality and 'alive-index' (which checks for visits to the hospital in the electronic healthcare record as indication of being alive)
- In-hospital mortality

- length of hospital stay
- ICU admission
- length of ICU stay (if any)
- readmissions
- AKI stage 2 or greater (to a 200% or more increase in baseline creatinine value)
- postoperative rise in creatinine levels

Secondary end points: process level

- the incidence of IOH
- the depth and duration of IOH
- estimated blood loss
- time to discharge readiness at the PACU

Secondary end points: behavior level

- anesthetic/analgesic drug use
  - average concentrations of inhalational anesthesia during MAP < 65 mmHg episodes
- average use of the following blood pressure interventions during the entire case
  - vasopressor use
  - inotropic use
  - intravenous fluid administration
  - blood products administration
- time to first blood pressure intervention after MAP drops below
  - 65 mmHg
  - 60 mmHg
  - 55 mmHg
  - 50 mmHg

Data collection

Primary and secondary patient end point data are routine clinical data that will be collected from the medical records of the hospital electronic patient record keeping system, which are already linked to the existing perioperative data warehouses. Behavioral end point data will be extracted from the perioperative data warehouse (PDW) of the VUMC. Collection of end point data will automatically be performed, guaranteeing an end point assessment that is independent of the randomization status of providers and procedures.

Data safety monitoring

The principal investigator (PI) will be responsible for data safety and monitoring within the VUMC. Quality control will include regular data verification and protocol compliance checks. Protocol adherence at the VUMC will be monitored by the PI throughout the study. Events determined by the PI to be unanticipated problems involving risks to subjects will be reported by the PI to the VUMC IRB within 10 working days of the Investigator's knowledge of the problem.

All study staff members will be informed about any unanticipated problems involving risks to participants or others associated with the research (such as a breach of confidentiality). If any protocol changes are needed, the PI will submit an amendment request to the VUMC IRB. Protocol changes will not be implemented prior to IRB approval unless necessary to eliminate apparent immediate hazards to the research subjects. In such a case, the IRB will be promptly informed of the change following implementation (within 10 working days).

The PI will permit inspection of all study-related records by the IRB and responsible governmental agencies. Within legal and regulatory restrictions and institutional and ethical considerations, the PI will permit the review of source documents in order to verify data in the study records. The PI will provide oversight during the course of the study. All study data will be handled confidentially.

Sample size calculation

Sample size calculations were performed in *R* software. As mentioned earlier, we calculated

sample sizes for each of the participating centers, because they will use a different primary end point. The required sample sizes were calculated for both primary end points. Sample size calculations assumed a power of 0.8 and a Type 1 error rate (alpha) of 0.05. Based on earlier experiences with decision support intervention studies, we assumed there would be no clustering of primary end point data at the provider level.[9]

Using historic data from the VUMC, the incidence of any MAP below 65 mmHg were estimated at 60% for patients that meet the inclusion criteria. Within this study population – any MAP < 65 mmHg – the incidence of AKI stage I was 9.8%. We derived the assumed treatment effect from the odds ratio (OR) reported by Sun et al. They reported an odds ratio of 1.8 (originally 1.84) for postoperative AKI in patients that had a MAP below 60 mmHg for 10 minutes or more. Thus the possible treatment effect within patients having a MAP < 60 mmHg for 10 minutes or more is then an OR of 0.56 (the inverse of 1.8). Within the study population (any MAP < 65 mmHg), the incidence of MAP < 60 mmHg for 10 minutes was 43%. Applying the OR 0.56 to an incidence of 43% resulted in an overall OR of 0.78 within the study population. The intervention phase (9 months) is four times shorter than the preintervention phase (36 months), resulting in a fraction of 0.20 of the total study period (9 divided by 45). As the intervention might not be as efficient during the nested cluster-randomized trial period, we used only half of the three months trial period, reducing the fraction of the intervention phase to 0.17. Additionally, we included a 20% margin of error to the sample size of the intervention period. The resulting calculated sample size is 2,005 procedures for the intervention phase and 8,019 procedures for the preintervention phase (Table 3). With an average of 275 procedures per month meeting the inclusion criteria, the calculated sample size is feasible within the specified time periods.

The calculations above assume that all episodes of prolonged hypotension will be treated during the intervention phase, which is unlikely. However, it also assumes that preventing shorter amounts of IOH (< 10 minutes) does not have any effect on patient outcome (an OR of 1.0), which is also unlikely. Consequently, the second assumption may compensate for the first assumption. As a sensitivity analysis we calculated the sample sizes for different combination of a different treatment percentage and an OR > 1.0 for patients with a MAP < 60 for 1-10 minutes

(Table 3). This sensitivity analysis shows that the calculated sample sizes indeed include an error margin for the assumption on the IOH treatment percentages.

Table 3 - Sample size calculation with sensitivity analyses

	Sample sizes calculated			
	Center	**n**	**intervention phase**	**preintervention phase**
sample size including 20% error margin	**AKI (VUMC)**	**10024**	**2005**	**8019**
sample size without 20% error margin	**AKI (VUMC)**	9690	1671	8019
80% of hypotension treated OR 1.1 MAP < 60 for 1-10 min.	**AKI (VUMC)**	11432	1971	9461
70% of hypotension treated OR 1.2 MAP < 60 for 1-10 min.	**AKI (VUMC)**	11910	2054	9857

Statistical analysis

Primary end points

The analysis of the primary end point will be performed under the intention-to-treat principle, and only include patients that have had a MAP below 65 mmHg for at least one minute during the procedure. As the study is an interrupted time series design, segmented regression models will be used for both primary end points. The different study groups within the nested cluster-randomized trial will not be separately analyzed because of a too small sample size.

A two-sided alpha of 0.05 will be considered to be statistically significant. Continuous variables will be visually assessed for a normal distribution using histograms and QQ-plots. In descriptive statistics, parametric variables will be expressed as means with standard deviations, nonparametric variables will be expressed as medians with interquartile ranges, and discrete variables will be expressed as numbers with percentages. Missing data will be multiply imputed

using a regression approach. Before multivariable modelling, all continuous variables will be tested for nonlinearity using restricted cubic splines.

Secondary end points: patient outcome

Secondary patient outcomes will be primarily be performed similar to the primary end point. For continuous end points, either a parametric or a nonparametric approach will be used as is appropriate to the distribution of the end points.

Secondary end points: process level

In contrast to the primary end point and other secondary patient outcome, clustering at the attending level is expected for process level end points. Quantitative analysis on process level end points will thus account for clustering using segmented regression models that also included random effects. For these mixed effects models we will exclude attending anesthesiologists with a low case volume of eligible procedures from the analysis.[9]

Secondary end points: behavior

The impact of the decision support system on the blood pressure management of patients will also be studied. This will be done by observing changes in the usage patterns of various treatment options, such as reducing anesthesia, administering vasoactive or inotropic drugs, and administering intravenous fluids. The analysis of fluid administration is expected to be restricted by the accuracy of the AIMS.

Because of the intricate relation between the occurrence of IOH and the timing of various treatment options, there is currently no straightforward method to analyze the effect of the decision support on blood pressure management. Methods for analyzing the behavioral patterns in response to blood pressure thresholds will be explored in a separate observational study. This study has already been initiated through the MPOG initiative[11] and is expected to be completed before the end of the study period. The findings within this study will determine how treatment behavior should be defined and studied within the present decision support study. If necessary, the study proposal will be amended accordingly.

Additional analyses: specific clinical research questions

The previous paragraphs describe the analyses of the differences in various end points between different study periods. The research questions as described in 'Specific clinical research questions' require additional analyses on the relation between depth and duration of IOH and the patient and process level end points. The goal of these additional analyses is to study the relation between IOH, treatment and outcome. The relation between IOH and various end points will be compared between the preintervention and intervention phases. This may seem as a very complex way to study the relation between IOH, treatment and outcome. However, as treatment is an intermediate variable between IOH and outcome, there is no straightforward mathematical way to analyze this relationship using observational data alone. The expected differences between the preintervention and intervention phases will be the changes in blood pressure measurement. The comparison between these phases will thus allow studying of the relation between IOH and various end points may relate to treatment of IOH. As this relation will depend on various preoperative and intraoperative factors, several effect modifiers will be considered (Table 4).

Within the scientific literature there is a large variation in how IOH is defined and analyzed. Different thresholds are used for either systolic, mean or diastolic blood pressure, or even multiple thresholds for a given combination. In addition to a threshold definition, the variable for IOH can also be modelled in several ways. The thresholds often introduce a cut-off: anything above the threshold is considered 'zero'. All values above the threshold are considered to be the same, even when they are close to the threshold. However, everything below the threshold can be modelled in several ways: duration of blood pressure below the threshold, the area under the threshold (AUT), or simply a 'one' – i.e. 'yes' the patient's blood pressure was below the threshold. In a separate observational study we aim to evaluate what the best way is to define and analyze hypotension as an independent variable. This observational study is expected to be completed before the end of the present decision support study. The results of this observational study will be used to guide the analysis of the relation between IOH and patient and process level end points.

Table 4 - Variables that will be considered as effect modifiers during the analysis

Preoperative patient condition
Age
ASA physical status or functional status
Cardiovascular comorbidity
Hypertension
Diabetes Mellitus
History of cardiac disease
History of cardiovascular disease
Non-end-stage renal disease
Intraoperative patient condition
Other vital signs
Heart rate
Oxygen saturation
Pulse pressure variation
Blood loss
Procedural factors
Surgical phase (induction / surgical preparation / surgical)
Type of anesthesia (general anesthesia / central neuraxial blockade)
Type of surgery (vascular, neurosurgery, orthopedic, trauma, ENT)
Emergency surgery
Anesthetic depth
Duration of surgery (stratification for duration < 1 hour, between 1 – 3 hours and > 3 hours)

Additional analyses: specific decision making questions

These additional analyses will main consist of analyzing differences in process level and behavior level end points between the various study phases, including the nested cluster-randomized trial. Effect modification by the variables of Table 4 will also be studied.

References

1. Sessler DI, Sigl JC, Kelley SD, et al. Hospital stay and mortality are increased in patients having a “triple low” of low blood pressure, low bispectral index, and low minimum

alveolar concentration of volatile anesthesia. *Anesthesiology*. 2012;116(6):1195-1203. PMID:22546967.

2. Walsh M, Devereaux PJ, Garg AX, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. *Anesthesiology*. 2013;119(3):507-515. PMID:23835589.

3. Monk TG, Bronsert MR, Henderson WG, et al. Association between Intraoperative Hypotension and Hypertension and 30-day Postoperative Mortality in Noncardiac Surgery. *Anesthesiology*. 2015;123(2):307-319. PMID:26083768.

4. van Waes J a. R, Nathoe HM, de Graaff JC, et al. Myocardial Injury After Noncardiac Surgery and its Association With Short-Term Mortality. *Circulation*. 2013;127(23):2264-2271. doi:10.1161/CIRCULATIONAHA.113.002128.

5. Sun LY, Wijeysundera DN, Tait GA, Beattie WS. Association of Intraoperative Hypotension with Acute Kidney Injury after Elective Noncardiac Surgery. *Anesthesiology*. 2015;(3):515-523. PMID:26181335.

6. Bijker JB. Intraoperative Hypotension.2011.

7. Panjasawatwong K, Sessler DI, Stapelfeldt WH, et al. A Randomized Trial of a Supplemental Alarm for Critically Low Systolic Blood Pressure. *Anesth Analg*. 2015;121(6):1500-1507. PMID:26465928.

8. Kappen TH. Prediction Models and Decision Support: Chances and Challenges.2015.

9. Kappen TH, Moons KGM, Van Wolfswinkel L, Kalkman CJ, Vergouwe Y, Van Klei WA. Impact of risk assessments on prophylactic antiemetic prescription and the incidence of postoperative nausea and vomiting. *Anesthesiology*. 2014;120(2):343-354. doi:10.1097/ALN.0000000000000009.

10. van Waes JA, van Klei W a, Wijeysundera DN, Wolfswinkel L Van, Lindsay TF, Beattie WS. Association between Intraoperative Hypotension and Myocardial Injury after Vascular

Surgery. *Anesth Analg*. 2016;(1).

11. Kheterpal S. Clinical research using an information system: the multicenter perioperative outcomes group. *Anesthesiol Clin*. 2011;29(3):377-388. PMID:21871400.