

# Intraoperative Hemodynamic Optimization Using The Hypotension Prediction Index And Its Impact Of Tissular Perfusion. Protocol For The Predict H Trial

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**Study protocol**

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# Abstract

*Background:* Intraoperative arterial hypotension is associated with poor postoperative outcomes. The Hypotension Prediction Index, developed from machine learning, predicts the occurrence of arterial hypotension from the analysis of the arterial pressure waveform. The use of this index can reduce the duration and severity of intraoperative hypotension in adults undergoing noncardiac surgery.

*Methods:* We will conduct a multicenter, randomized, controlled trial (N=80) in high-risk surgical patients scheduled for elective major abdominal surgery. All participants will be randomly assigned to a control or intervention group. Hemodynamic management in the control group will be based on standard hemodynamic parameters. Hemodynamic management of patients in the intervention group will be based on functional hemodynamic parameters provided by the HemoSphere platform (Edwards Lifesciences Corp.), including dynamic arterial elastance,  $dP/dt_{max}$  and the Hypotension Prediction Index. Tissue oxygen saturation will be non-invasively and continuously recorded by using near-infrared spectroscopy technology. Biomarkers of acute kidney stress (cTIMP2 and IGFBP7) will be obtained before and after surgery. The primary outcome will be intraoperative time-weighted average of a mean arterial pressure < 65mmHg.

*Discussion:* The aim of the study is to determine whether a goal-directed algorithm based on the prevention of arterial hypotension using the Hypotension Prediction Index reduces the duration and severity of intraoperative hypotension when compared with the recommended standard therapy and if this intraoperative strategy is associated with better tissue oxygenation and organ perfusion.

*Trial registration:* ClinicalTrials.gov, NCT04301102. Registered on March 10, 2020.

## Background

Intraoperative monitoring of usual hemodynamic parameters, such as heart rate or blood pressure, are insufficient for ensuring an adequate oxygen delivery ( $DO_2$ ) to the tissues and prevent organ hypoperfusion [1]. Moreover, tissue hypoxia is a significant determinant of a surgical patient's outcome [2]. Hemodynamic strategies aimed to optimize  $DO_2$  and prevent organ hypoperfusion, also known as goal-directed therapies (GDT), have demonstrated to be superior to the traditional care of patients undergoing surgery. This perioperative hemodynamic optimization has been associated with a significant reduction in morbidity and mortality [3].

On the other hand, arterial hypotension is a frequent phenomenon during the intraoperative period and has been related to the development of organ hypoperfusion and poor postoperative outcomes [4]. Both the duration and severity of arterial hypotension are significant determinants of the postoperative outcome [5]. Particularly, intraoperative arterial hypotension significantly increases acute kidney and myocardial injury [6].

The Hypotension Prediction Index (HPI) is a recently available index developed from machine learning that predicts the occurrence of arterial hypotension from the analysis of the arterial pressure waveform. The HPI value indicates the likelihood of an arterial hypotension event in the following 5–10 minutes [7]. This index has demonstrated to reduce intraoperative hypotension in adults undergoing noncardiac surgery patients [8] [9] [10].

Since tissue oxygenation depends not only on  $DO_2$  but also on perfusion pressure, hemodynamic optimization should be targeted to achieve an adequate blood flow and arterial pressure that ensures normal organ function. We, therefore, hypothesize that an HPI-based therapeutic protocol will reduce the overall duration of arterial hypotension and improve tissue oxygenation and organ perfusion during noncardiac surgery.

## Methods And Design

This manuscript was written according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline (Additional file 1) on reporting of interventional trial protocols [11].

A double-blind, multicentre, randomized controlled trial, with daily follow-up of patients until hospital discharge and mortality censured at 30 days after surgery will be conducted. The study will be carried out at five different Spanish hospitals: Juan Ramón Jiménez University Hospital (Huelva), Virgen del Rocío University Hospital (Sevilla), Infanta Leonor University Hospital (Madrid), Hospital Universitario SAS de Jerez (Jerez de la Frontera) and Infanta Cristina University Hospital (Badajoz).

Ethics Committee approval was obtained from the Ethics Committee of Hospital Gregorio Marañón (Meeting of 27 July 2020, minutes 18/2020, Madrid, Spain). The trial was registered in the ClinicalTrials.gov database on March 10th, 2020 (NCT04301102) by the main investigator (JVL).

Written informed consent will be obtained from all included patients. Patients will be informed that they may decline to participate or withdraw from the study at any time. Enrolled patients will be at least 65 years old and/or American Society of Anesthesiologist (ASA) physical status III/IV, scheduled for elective major surgery (general surgery, urology, or gynecology, through laparoscopic or open approach), with general or combined anesthesia. Surgery will be considered to be major if the expected duration is > 2 h, or the estimated blood loss is > 15% of blood volume, or if the expected required transfusion is  $\geq 2$  packed red blood cells.

Exclusion criteria will be pregnancy, surgery performed only under regional anesthesia, preoperative glomerular filtrate < 60 ml/min/1.73 m<sup>2</sup> according to the CKD-EPI 2009 formula, persistent atrial fibrillation, known cardiac shunts or if the patient received a kidney transplant, and refusal of the patient to participate in the study.

## Study protocol

Researchers will examine all patients who present for elective, noncardiac surgery. Patients will be contacted by the principal investigator (PI) of each hospital and informed if they are eligible. The patient's informed consent will be obtained the day before surgery. Patient demographics and comorbidities will be collected before randomization. Patients will be assigned by the local PI to the intraoperative HPI algorithm (intervention group) or a GDT algorithm (control group). We will use a computer-generated, variable block randomization method through age strata.

All principal investigators and collaborators will receive specific training with the monitoring used for hemodynamic management.

A Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the study is shown Fig. 1. All data will be entered using an electronic Clinical Report Form build in Castor EDC, a Good-Clinical-Practice-compliant data management system [12].

## **Common perioperative measures**

Before the induction and during surgery, all subjects will receive standard of care with five-lead electrocardiogram, pulse oximetry, a peripheral intravenous line and an indwelling radial arterial catheter.

All subjects will receive general or combined anaesthesia, neuraxial analgesia technique (epidural or intradural) will be performed according to the preference of the anaesthesiologist before induction. For pragmatic reasons, the administration of the drugs used in induction of anaesthesia and neuromuscular relaxants will be at the discretion of the anaesthesiologist. Bispectral index monitoring (BIS; Medtronic, Dublin, Ireland) will be used to monitor the depth of anaesthesia. Sevoflurane will be used for hypnosis maintenance, with a BIS target range of 40–60. All patients will received invasive and continuous arterial pressure monitoring with an indwelling radial arterial catheter connected to a FloTrac® sensor in the control group or an Acumen IQ® sensor in the intervention group (Edwards Lifesciences Corp., Irvine, CA, USA).

All subjects will receive standard measures to maintain oxygen saturation by pulse oximetry > 94%, normothermia (> 36°C), and heart rate < 100 beats/min. Ventilation with an inspired oxygen fraction of 60% will be mechanically controlled to maintain PaCO<sub>2</sub> between 4.7 and 6.0 kPa, with a positive end-expiratory pressure of 4–6 mmHg and a tidal volume of 8 ml/kg. As maintenance fluid therapy, a balanced crystalloid (Isfundin®/Plasmalyte®) will be administered at 1–3 ml/kg/h for laparoscopic surgery and 5–7 ml/kg/h for open surgery. The stroke volume will be optimized with hydroxyethyl starch (Voluven®). Packed red blood cells will be transfused if the haemoglobin level is < 8 g/dL.

Tissue oxygen saturation (StO<sub>2</sub>) will be non-invasively recorded every 2 seconds in the brachioradial muscle by using near-infrared spectroscopy (NIRS) technology and hidden from the main screen in both study groups, so trends in StO<sub>2</sub> will be internally recorded into the HemoSphere system but unavailable for the anaesthesiologist.

The hemodynamic optimization algorithm will begin 15 minutes after the start of surgery, once the hemodynamic impact of anaesthesia and surgery have been stabilized. Meanwhile, the hemodynamic goal in both groups will be to achieve a MAP > 65 mmHg with the administration of boluses of vasopressors at the choice of the anaesthesiologist. In both groups, hemodynamic data will be recorded every 20 seconds in the HemoSphere monitor after starting the hemodynamic optimization protocols and download after surgery for offline analysis

During the surgery, any procedure carried out with repercussions for the hemodynamic status of the patient will be marked and adequately labelled for further identification.

Biomarkers of acute kidney stress in the perioperative period will be measured by the PI and blinded for the rest of the researchers. Urinary [TIMP-2]-[IGFBP7] will be measured with the Astute140 Meter (BioMérieux). This device applies a sandwich immunoassay technique and converts the fluorescent signals from each of the two immunoassays (TIMP-2 and IGFBP7) contained within the Nephrocheck test cartridge into a single numerical risk result (AKIRisk). The result is calculated as the product of the measured concentrations of the two cell-cycle arrest biomarkers and can quantify the stress developed by kidney epithelial cells during surgery, identifying patients at risk of postoperative Acute Kidney Injury (AKI) [13] [14] [15].

The first urine sample will be collected when performing the bladder catheterization after induction. The first postoperative sample will be collected 4 hours after the patient's admission to the Intensive Care Unit for postoperative stay. If the value of this sample is in the grey zone, between 0.3 and 2, a second postoperative sample will be collected 12 hours after the first one [16].

Arterial blood analyses will be performed after induction of anaesthesia, midway through the surgery, immediately after admission to the Intensive Care Unit, and daily from postoperative day 1 to day 5 inclusive.

## **Hemodynamic management**

### **Control group**

Hemodynamic management will be based on the functional hemodynamic parameters provided by the HemoSphere platform® with the FloTrac® sensor, including cardiac output (CO), stroke volume (SV), and stroke volume variation (SVV). The hemodynamic optimization algorithm on this group is shown in Fig. 2.

### **Intervention group**

Hemodynamic management will be based on the functional hemodynamic parameters provided by HemoSphere platform with the Acumen IQ sensor, including cardiac output, stroke volume, SVV and Acumen IQ specific parameters: maximal arterial pressure rise ( $dP/dt_{max}$ ), dynamic arterial elastance ( $Ea_{dyn}$ ) and HPI. The hemodynamic optimization algorithm on this group is shown in Fig. 3.

# Study outcome

## Primary Outcomes

- Intraoperative Time-Weighted Average of Mean Arterial Pressure under a threshold of 65 mmHg (TWA-MAP < 65), calculated as the area between 65 mmHg threshold and the curve of the MAP measurements divided by the total continuous reading time [17]:

$$TWA - MAP < 65 = \frac{\sum_{i=1}^k (area_{i < 65}) + (area_{i < 65} + \dots + area_{k < 65})}{Total\ time\ of\ measurements}$$

The advantage of using TWA-MAP instead of using just MAP is that the former combines the severity and duration of the hypotension to the overall duration of the intervention.

-Intraoperative StO<sub>2</sub> as an indicator of tissue oxygenation and wellness of the microcirculation. StO<sub>2</sub> will be non-invasively and continuously recorded in the brachioradial muscle in the arm opposite to the arterial line. We calculated the time averaged StO<sub>2</sub> per patient and identified the minimum StO<sub>2</sub>, defined as the minimum value sustained (+ 1%) over at least 5 min [18] [19].

- Postoperative measurements of the TIMP-2 and IGFBP7 (postoperative AKIRisk).

## Secondary Outcomes

The secondary outcome measures include intraoperative incidence of arterial hypotension, defined as an event of MAP < 65 mmHg of at least 1-minute duration, the total time of hypotension per case, and the Average Real Variability of Mean Arterial Pressure (*aVR-MAP*) [20], defined as:

$$aVR = \frac{1}{\sum t} \sum_{k=1}^{n-1} t [MAP(k+1) - MAP(k)]$$

At the end of the surgery, data regarding the total fluid therapy during surgery, the accumulated dose of opioids during the intraoperative period, accumulated dose of vasoactive agents during the intraoperative period, accumulated dose of inotropic drugs during the intraoperative period, other drugs with a hemodynamic impact not included in previous groups, total intraoperative diuresis, and transfusion of total blood products during surgery, will be collected.

Secondary outcomes will also include postoperative complications in accordance with the European Perioperative Clinical Outcome (EPCO) definitions [21], length of hospital stay, and 30-day mortality. Post-

operative follow-up of patients will be performed by a collaborating investigator from each centre, blinded for the randomization. For an overview of the outcome assessments see Fig. 4

## Sample Size and Data Analysis

The literature indicates that a cumulative hypotension time of more than 10 minutes during surgery is clinically relevant [22]. Given the novelty of the HPI parameter and the lack of publications during the design of this study, a pilot study in 31 patients undergoing major surgery was performed at the Virgen del Rocío Hospital. In this preliminary study, two groups were defined: a control group with invasive and continuous arterial pressure monitoring but without the use of HPI; and an intervention group with invasive and continuous blood pressure monitoring, in which the anaesthesiologist also had access to the HPI value and the additional parameters during surgery. In both groups, the hemodynamic objective during the intraoperative period was to maintain the MAP above 65 mmHg. The results from this preliminary study revealed that in the control group (15 patients), 68.75% of the patients accumulated more than 10 minutes of hypotension (11 patients), while in the intervention group with HPI (16 patients), only 31.25% of the patients accumulated periods of a MAP < 65 mmHg more than 10 minutes (5 patients).

Based on this pilot study, to achieve a 90% power, and a significance level of 1%, 72 patients will be required (36 in each group). Assumed a drop-out rate of 10%, a total of 80 patients will be required (40 patients per group).

## Statistical Analysis

The normality of data distribution was assessed by the D'Agostino-Pearson test and confirmed by inspection of a Q-Q Plot. The results are expressed as the mean  $\pm$  standard deviation (SD) when normally distributed or the median (25th to 75th interquartile). Categorical data were given as frequencies with percentages.

Comparison of quantitative variables between control and intervention group will be performed with the Mann-Whitney U test or the independent  $t$  test, and the Chi-square test ( $\chi^2$ ) for categorical variables. To establish a relationship between changes intraoperative hypotension management and tissue perfusion, a regression analysis will be performed between TWA-MAP and the perfusion indexes (StO<sub>2</sub> and AKI<sub>risk</sub>).

A  $p$  value < 0.05 will be considered statistically significant. The statistical analyses will be performed with the SPSS software, version 23.0.

## Discussion

Our goal is to determine whether a goal-directed algorithm based on the prevention of arterial hypotension using the HPI and the aid of the additional parameters, such as arterial  $dP/dt_{max}$  and  $Ea_{dyn}$ , reduces the duration and severity of intraoperative hypotension when compared with the recommended standard therapy. We also aim to determine whether this optimization of the systemic perfusion pressure

is associated with a better intraoperative tissue perfusion and decreased postoperative complications. To achieve this objective, we will include patients with a higher risk of intraoperative hypoperfusion (> 65 years old and/or ASA III/IV).

Considering the significant impact of intraoperative arterial hypotension on patient outcome [23], arterial pressure can be considered as a critical element. This definition derives from the field of engineering, where critical elements are deemed crucial to the outcome and a small error is not allowed due to the high direct and indirect costs. Consequently, different security mechanisms have been developed to predict the failure of these critical elements. This anticipation would allow the crucial element to be replaced before the breakdown, even if there is no apparent sign of malfunction since the potential cost of total failure is much higher than the replacement of the part [24].

The definition of blood pressure as a critical element justifies, therefore, that maintaining blood pressure within a physiological range that ensures tissue perfusion should be considered not as an option, given the high impact of intraoperative hypotension on mortality and morbidity [25]. Furthermore, this definition also implies a paradigm shift in the current treatment of intraoperative arterial hypotension from a reactive attitude to a proactive action based on predictors, such as HPI. If this proactive attitude associates with a better patient's outcome still needs to be proven clinically. Moreover, the proper correction of arterial hypotension also depends on the adequate identification of the pathophysiological mechanisms leading to low blood pressure and the choice of the optimal treatment [9]. Accordingly, the clinical benefit of an artificial parameter based on machine learning, such as HPI, should be analyzed coupled with the hemodynamic protocol that determines the best treatment according to those physiological mechanisms involved in the development of arterial hypotension. Therefore, if this preemptive hemodynamic protocol is associated with better tissue perfusion is also one of the main goals of our study.

## Trial Status

Protocol version 1.0; March 2019. Recruitment will begin September 1, 2020, and will be completed January, 2021

## Abbreviations

- **AKI:** Acute Kidney Injury
- **AKIRisk:** Acute Kidney Injury risk.
- **ASA:** The American Society of Anaesthesiologists (ASA) physical status classification system.
- **AUC:** Area Under the Curve.
- **aVR-MAP:** Average Real Variability of the Mean Arterial Pressure.
- **CKD-EPI:** Chronic Kidney Disease Epidemiology Collaboration.
- **Ea<sub>dyn</sub>:** Dynamic Arterial elastance.

- **EPCO**: European Perioperative Clinical Outcome.
- **HPI**: Hypotension Prediction Index.
- **ICU**: Intensive Care Unit.
- **IGFBP-7**: Insulin Growth Factor Binding Protein 7.
- **MAP**: Mean Arterial Pressure.
- **MINS**: Myocardial Injury after Non-cardiac Surgery.
- **NIRS**: Near Infrared Light Spectrophotometry.
- **StO<sub>2</sub>**: Tissue Oxygen Saturation.
- **SV**: Stroke Volume.
- **TIMP-2**: Tissue Metalloproteinase Inhibitor 2.
- **TWA-MAP < 65**: Time Weighted Average of Mean Arterial Pressure under 65 mmHg.
- **SVV**: Stroke Volume Variation.

## Declarations

### Funding

This study has been funded thanks to a grant provided by Edwards Lifesciences, after presenting the study to a competitive international call through its Grant Portal

The design of the study, the writing of this manuscript and the collection and interpretation of data are being carried out independently by the research team, without any intervention from the funding body.

### Availability of data and materials

Not applicable

### Authors` contributions

Concept, study design and first draft of manuscript: JVL, IJ, JRM, FH, PC, MIM.

Manuscript review and data collection: JVL, IJ, JRM, MIM, AIB, IM, MAF, AAM, EA.

Editing and critical review: JVL, IJ, JRM, MIM, WW, FH, PC, JB, FR.

### Monitoring

The study has been classified by the Spanish Agency for Medicines and Healthcare Products as a "Non-observational study without medicines", being applicable to it the provisions of Law 14/2007, of July 3rd, on Biomedical Research. Therefore, not need to be monitored by a Data Monitoring Committee.

### Ethics approval and consent to participate

Ethics Committee approval was obtained from the Ethics Committee of Hospital Gregorio Marañón (Meeting of 27 July 2020, minutes 18/2020, Madrid, Spain) and informed consent will be obtained from all patients who will be enrolled to this study

Serious adverse effect of the product which, by its nature, incidence, intensity or consequences has not been identified in the updated version of the risk analysis report.

**Consent for publication:** Not applicable

### **Competing interest**

JVL: Edwards Lifesciences, Fresenius Kabi, Vifor Pharma and bioMérieux conference fees, financial support for Edwards Lifesciences research obtained through the Grant Portal of the company. Economic research support from bioMérieux.

IJ: Edwards Lifesciences conference fees

JRM: Edwards Lifesciences, MSD, Fresenius Kabi and Dextera Medical conference fees

MIMG: Clinical consultant for Edwards Lifesciences and Dextera Medical.

WW: Employed by Edwards Lifesciences

The rest of the authors declare no conflict of interest.

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## Figures

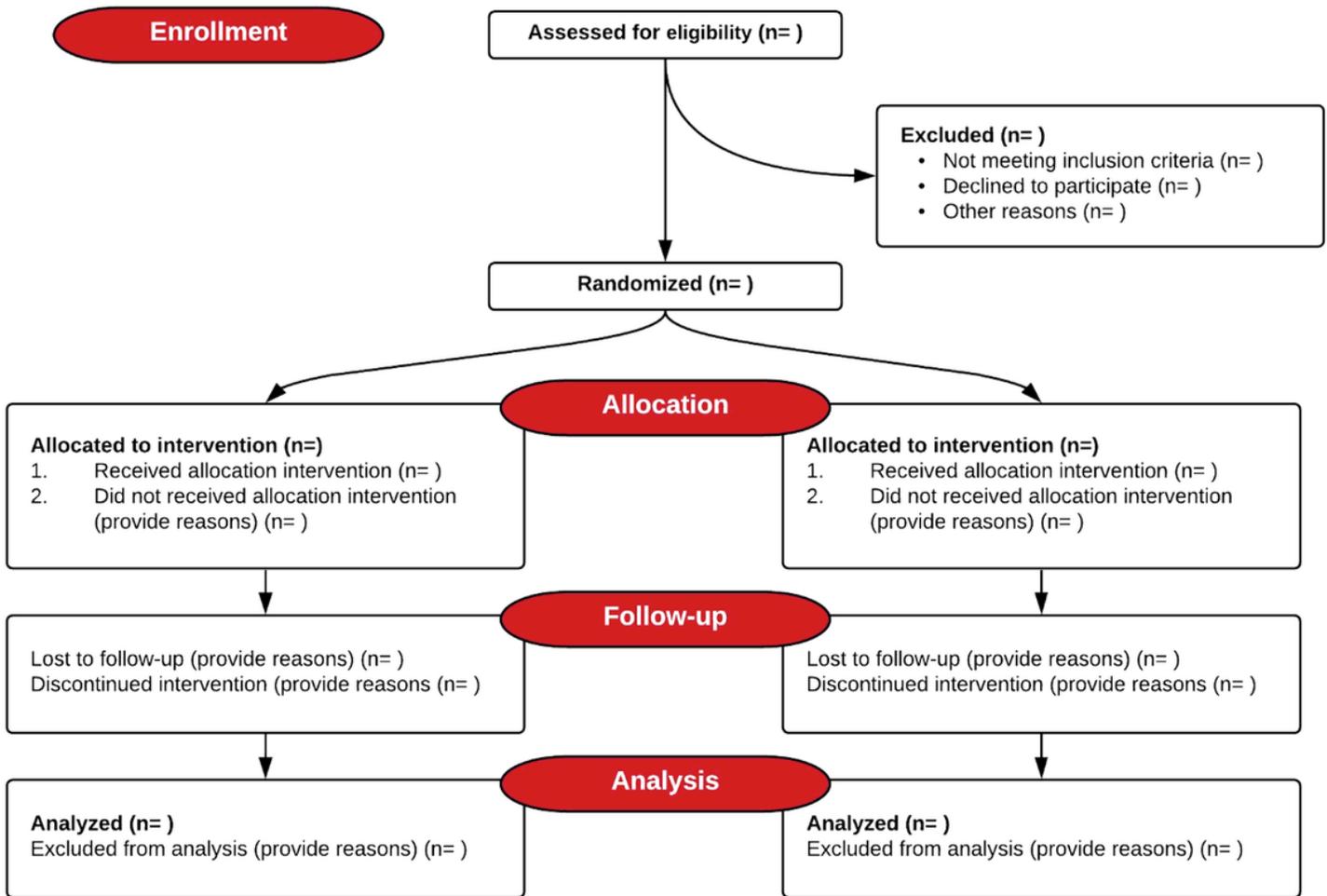
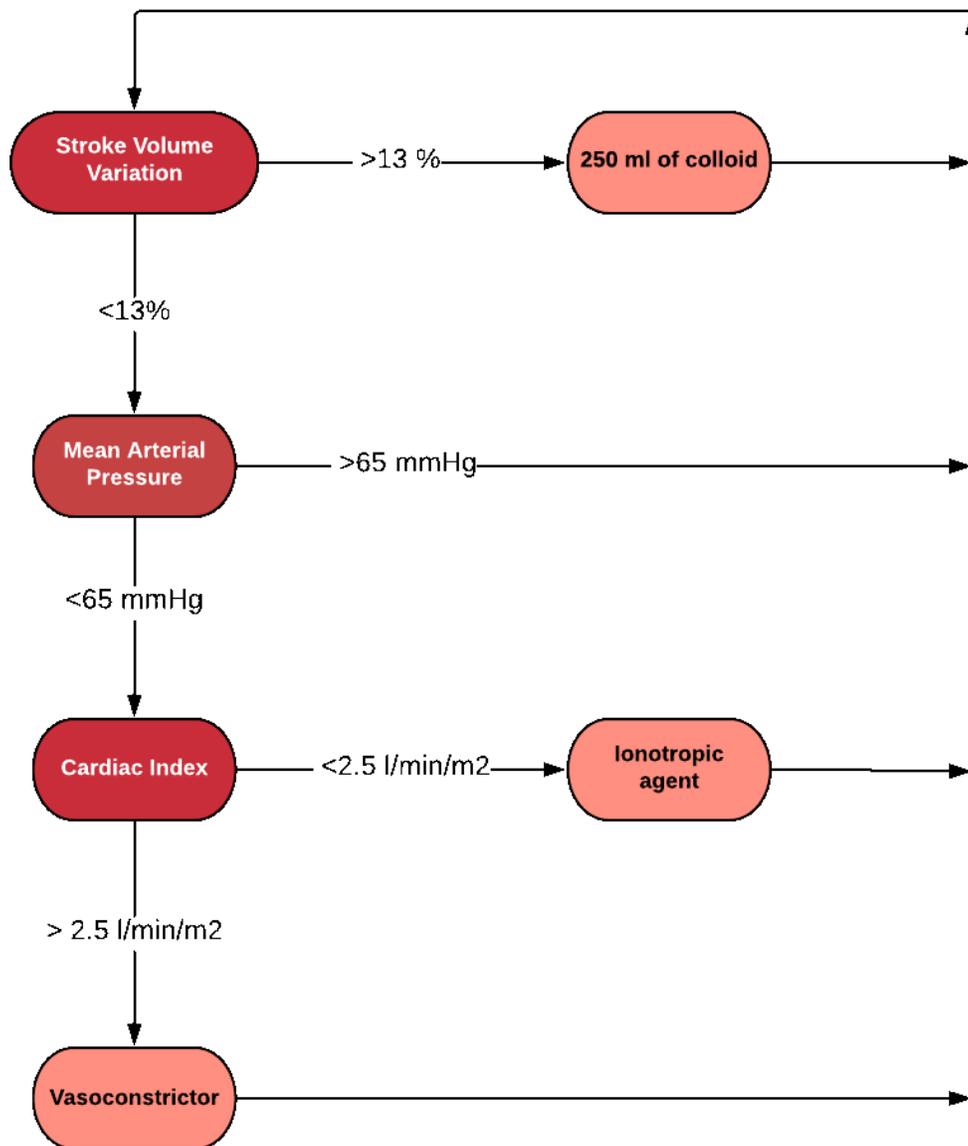


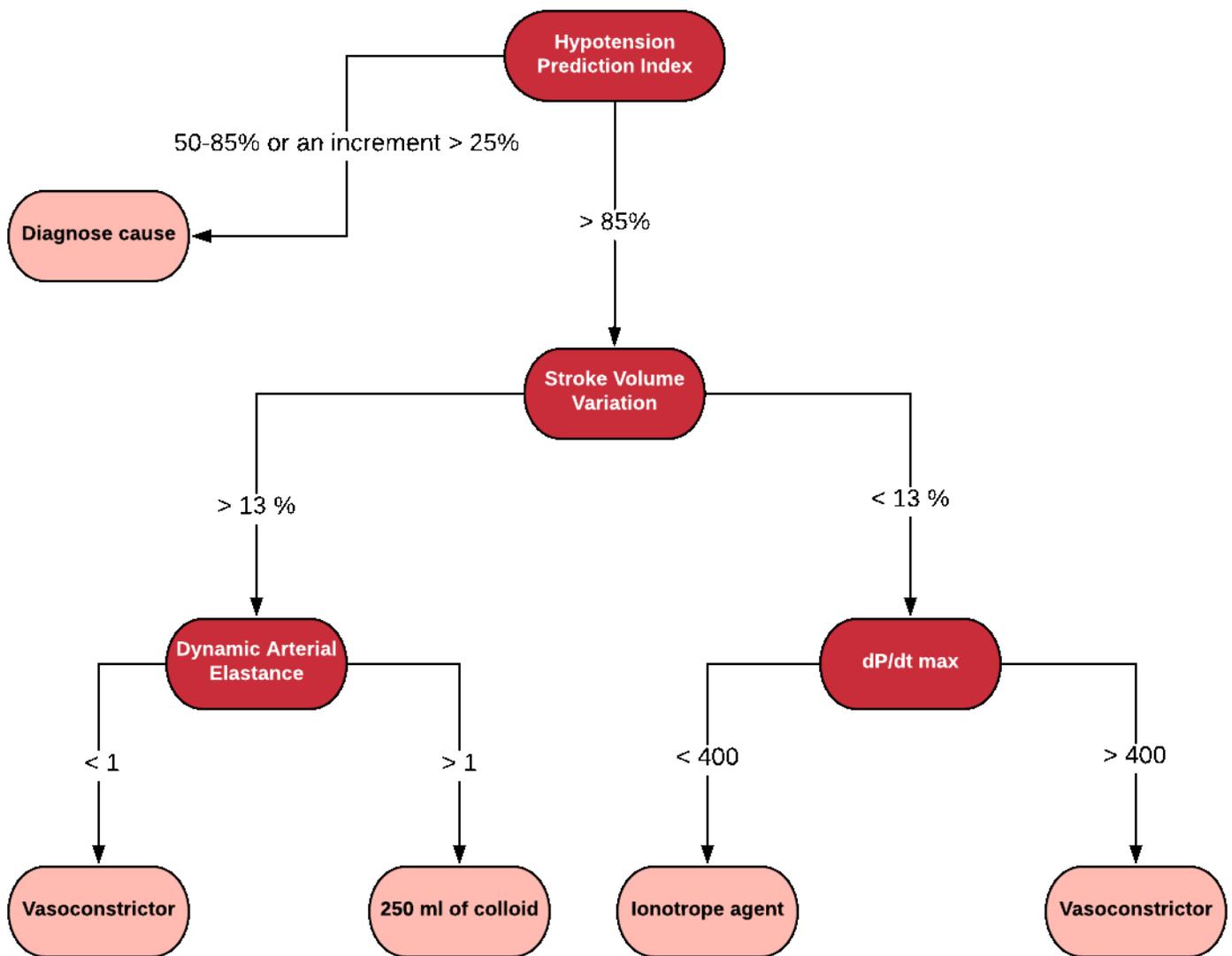
Figure 1

Consort Flow diagram



**Figure 2**

Control group hemodynamic optimization algorithm



**Figure 3**

Intervention group hemodynamic optimization algorithm

	STUDY PERIOD				
	Enrolment	Study Intervention			
TIMEPOINT**	<i>d<sub>-1</sub></i>	<i>Surgical day (d<sub>0</sub>)</i>	<i>Daily follow-up (d<sub>1</sub>-d<sub>hd</sub>)</i>	<i>Hospital discharge (d<sub>hd</sub>)</i>	<i>Follow-up (d<sub>30</sub>)</i>
<b>ENROLMENT:</b>					
Eligibility screen	X				
Written and oral project explanation	X				
Written Informed consent	X				
Allocation		X			
Patient demographic/comorbidities	X	X			
<b>INTERVENTIONS:</b>					
<i>Control group</i>		X			
<i>Intervention group]</i>		X			
<b>ASSESSMENTS:</b>					
<i>Primary outcomes</i>		X			
<i>Secondary outcomes</i>		X	X	X	X

Figure 4

Schedule of enrolment, interventions and assessments

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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