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Study protocol

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The Hypotension Prediction Index versus standard advanced haemodynamic monitoring in patients undergoing major aortic surgery (HYPE-AORTA): study protocol for a prospective randomised controlled trial

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Abstract

Purpose: Intraoperative hypotension is associated with postoperative organ dysfunction and mortality, particularly in high-risk vascular surgery. The Hypotension Prediction Index (HPI) is a machine learning algorithm designed to predict hypotensive events before they occur, potentially enabling preemptive intervention. While HPI has been associated with reductions in hypotension burden in heterogeneous surgical populations, its efficacy and safety in major aortic surgery remain uncertain. Our retrospective analysis identified clinically relevant

trends toward reduced hypotension with HPI but also increased intraoperative hypertension, suggesting a need for protocol refinement and prospective validation. **Methods:** The **HYPE-AORTA trial** is a single-centre, parallel-group, prospective randomised controlled trial that will enrol 200 patients (ASA III–IV) undergoing elective major abdominal aortic surgery with an expected duration exceeding 2 hours. Participants will be randomised in a 1:1 manner to receive either HPI-guided haemodynamic management (Acumen IQ sensor) or standard arterial pressure-derived cardiac output monitoring (FloTrac sensor). Both groups will follow structured haemodynamic algorithms designed to maintain MAP $\geq$75 mmHg while avoiding excessive hypertension (MAP $\leq$100 mmHg). The primary outcome is the time-weighted average of mean arterial pressure below 65 mmHg (TWA-MAP $<$65 mmHg). Key secondary outcomes include a composite of postoperative organ complications (acute kidney injury, myocardial injury, stroke, respiratory failure, circulatory failure), intraoperative hypertension metrics, and 90-day mortality. Statistical analysis will follow the intention-to-treat principle with multiplicity correction applied to outcome families.
Discussion: This trial will provide prospective evidence on whether predictive haemodynamic monitoring is associated with clinically meaningful differences in haemodynamic control and safety outcomes over reactive monitoring in major vascular surgery. Regardless of outcome, the results will inform optimal perioperative blood pressure management strategies in this high-risk population. The trial design incorporates lessons from our retrospective analysis, including enhanced monitoring of hypertensive exposure as a safety outcome and balanced haemodynamic targets to minimise overcorrection.
Trial Registration: ClinicalTrials.gov [NCT07510451]

Keywords: hypotension, major vascular surgery, aortic abdominal surgery, haemodynamic monitoring, Hypotension Prediction Index, Acumen IQ, FloTrac, randomised controlled trial, HYPE-AORTA

Protocol version {2}

This manuscript describes protocol version 1.0, dated 14 December 2025. Recruitment is anticipated to commence in April 2026 following ethics approval and trial registration. We estimate recruitment will be completed by March 2028, with final 90-day follow-up completed by June 2028 and results expected by December 2028.

Roles and responsibilities

Author contributions {3a}

MG (Mariusz Gezela) is the principal investigator at the University Hospital in Poznań and the coordinating investigator with JS (Jakub Szrama); they both led the study design and protocol development in close collaboration, and serve as co-corresponding authors. ŁŻ (Łukasz Żurański), KK (Katarzyna Kulas), MG (Michał Gajda), AK (Anna Kłos) and PP (Piotr Przybylski) contributed to the study design and protocol

development. PS (Paweł Sobczyński) is the trial sponsor; he contributed to all phases of the study protocol development, drafted and revised the manuscript. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

Name and contact information for the trial sponsor {3b}

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Role of the sponsor {3c}

The sponsor is the initiator of the study and has a role in the study design, management and reporting of the study. Positive, negative and inconclusive results will be published by the author group, of which the sponsor is part of, but does not have ultimate authority over.

Composition, roles and responsibilities of the coordinating site and steering committee {3d}

The author group functions as the trial steering committee. The coordinating/principal investigators (MG and JS) will monitor the trial, recruitment and data on an ongoing basis, and will be responsible for the day-to-day running of the trial in collaboration with the other investigators and the sponsor. The entire group will meet every three months or as needed, depending on the trial's phase. The principal investigator, coordinating investigator and the sponsor will meet weekly during the first months of inclusion and monthly thereafter. Additional meetings will be held as necessary. An independent Data Safety Monitoring Committee (DSMC) is described in Section 6.1.

1 Introduction

1.1 Background and rationale {9a}

Perioperative haemodynamic instability remains a significant contributor to adverse outcomes following major surgery. Episodes of low mean arterial pressure (MAP) during the intraoperative period have been consistently associated with postoperative organ dysfunction, increased hospital stay, and mortality [1, 2]. The relationship between reduced tissue perfusion pressure and cellular injury is particularly pronounced in patients with pre-existing cardiovascular disease undergoing high-risk procedures [3, 4].

Vascular surgical patients represent a population at heightened risk for perioperative complications. Open abdominal aortic reconstruction, whether for aneurysmal or occlusive disease, is associated with major adverse cardiovascular and cerebrovascular event (MACCE) rates approaching 8%, substantially exceeding those observed in other non-cardiac surgical populations [5, 6]. Myocardial injury following vascular surgery carries early mortality rates exceeding 16%, while perioperative stroke, though less

frequent, contributes significantly to morbidity and prolonged hospitalisation [7, 8]. These complications are mediated in part by the unique physiological stresses of aortic surgery, including haemorrhage, aortic cross-clamping with acute afterload changes, reperfusion injury, and large-volume fluid shifts.

Advances in perioperative monitoring have enabled clinicians to measure not only arterial pressure but also derived indices of cardiac function and tissue perfusion. Goal-directed therapy (GDT), which utilises dynamic parameters such as stroke volume variation (SVV), cardiac index (CI), and systemic vascular resistance (SVR) to guide fluid and vasopressor administration, has demonstrated benefit in selected surgical cohorts by reducing postoperative complications and hospital length of stay [10–12]. However, the evidence supporting GDT specifically in vascular surgery remains inconsistent. Meta-analyses have shown that while GDT reduces morbidity in cardiac surgery, comparable benefits have not been reliably demonstrated in peripheral vascular or aortic procedures [13, 14]. This discrepancy may reflect the distinct pathophysiology and co-morbidity burden of vascular surgical patients, as well as the unpredictable haemodynamic fluctuations inherent to aortic manipulation.

Current haemodynamic monitoring strategies, including arterial pressure-derived cardiac output (APCO) systems such as the FloTrac sensor (Edwards Lifesciences, Irvine, CA, USA), operate on a fundamentally *reactive* paradigm. Clinicians respond to observed hypotension or reduced cardiac output after these events have already occurred. Although such systems provide valuable real-time physiological data, their utility is constrained by the lag between haemodynamic deterioration and clinical intervention. This reactive approach may contribute to cumulative hypotensive burden, defined as the integration of depth and duration of low blood pressure, which has been associated with organ injury even when individual hypotensive episodes are brief [1].

Recent technological advances have introduced the possibility of *predictive* haemodynamic monitoring. The Hypotension Prediction Index (HPI; Acumen IQ sensor, Edwards Lifesciences) is a machine learning-derived algorithm that analyses high-fidelity arterial waveform characteristics to forecast impending hypotension up to 15 minutes in advance [15]. The HPI value, scaled from 0 to 100, reflects the probability of MAP falling below 65 mmHg in the near future. When HPI exceeds 85, clinicians are prompted to initiate preemptive interventions—such as fluid boluses, vasopressor titration, or reduction of anaesthetic depth—before hypotension manifests. Early clinical trials in non-cardiac surgery demonstrated that HPI-guided management reduced both the time-weighted average (TWA) of MAP below 65 mmHg and the total duration of hypotensive episodes compared with standard care [16, 17].

Despite these promising findings, several critical knowledge gaps remain. First, the majority of HPI validation studies have focused on heterogeneous surgical populations, with limited data specific to major vascular surgery. The applicability of HPI during aortic cross-clamping and declamping—phases characterised by abrupt, mechanically induced haemodynamic shifts—has been questioned [18, 19]. Second, while HPI has been shown to reduce hypotensive burden, no randomised trial has definitively demonstrated a reduction in clinically meaningful postoperative outcomes such as acute

kidney injury (AKI), myocardial injury after non-cardiac surgery (MINS), or mortality. Third, emerging evidence suggests that overly aggressive hypotension avoidance may inadvertently increase the incidence and duration of intraoperative hypertension, which itself has been associated with adverse outcomes including AKI and myocardial strain [20, 21].

Fourth, there are some doubts regarding the HPI technology, due to high correlation between the mean arterial pressure and the HPI values, known as the "mirror effect" [36, 41]. The HPI value of 85, which is considered the threshold for a clinical intervention aimed at avoidance of hypotension episodes, corresponds to a MAP of 72–76 mmHg. There are some assumptions that making these MAP values the trigger for clinical intervention aimed at avoidance of hypotension, might be as effective as the HPI algorithm and might be considered also a proactive management [37, 42].

We recently completed a retrospective analysis of 100 patients undergoing major aortic vascular surgery at our institution, comparing outcomes between patients monitored with standard APCO (FloTrac) and those managed with HPI-guided algorithms [22]. While the primary endpoint—TWA-MAP below 65 mmHg—did not differ significantly between groups (medians 0.26 vs 0.22 mmHg, $p = 0.27$ from Mann–Whitney; corresponding means 0.48 vs 0.33 mmHg, yielding a mean ratio of 0.68 (95% CI 0.45–1.05) estimated using a Gamma regression model with robust standard errors), the HPI group demonstrated clinically relevant trends toward reduced total hypotension time (5 vs 10 minutes; $p = 0.03$) and shorter mean episode duration (2 vs 3 minutes; $p = 0.02$), although these did not remain significant after correction for multiple comparisons. Importantly, patients managed with HPI spent significantly more time with MAP exceeding 90 mmHg (38% vs 25% of monitored time; $p = 0.006$) and 100 mmHg (18% vs 9%; $p = 0.006$), suggesting potential overcorrection. No differences in postoperative organ complications were observed, though the study was underpowered for these outcomes.

These retrospective findings informed the design of the present prospective randomised controlled trial. The **HYPE-AORTA trial** extends the program of research initiated by previous HPI investigations (HYPE [16], HYPE-2 [32]) into a high-risk vascular surgery population. We hypothesise that HPI-guided haemodynamic management, when implemented with protocol refinements to mitigate hypertensive overcorrection, will reduce the burden of intraoperative hypotension compared with standard APCO monitoring in patients undergoing major abdominal aortic surgery. Secondary objectives include evaluation of postoperative organ injury, assessment of intraoperative hypertension as a safety outcome, and characterisation of fluid and vasopressor requirements. By testing this hypothesis in a rigorously designed, adequately powered trial, we aim to clarify whether predictive haemodynamic monitoring offers clinically meaningful advantages over current reactive approaches in this high-risk population.

1.2 Study Objectives {10}

The primary aim of this trial is to determine whether HPI-guided haemodynamic management reduces the time-weighted average of mean arterial pressure below 65 mmHg (TWA-MAP <65 mmHg) compared with standard arterial pressure-derived

cardiac output monitoring in patients undergoing elective major abdominal aortic surgery.

Secondary aims include:

- To compare the incidence of postoperative organ complications (composite of AKI, MINS, stroke, respiratory failure, and circulatory failure) between HPI-guided and standard monitoring
- To evaluate intraoperative hypertension (MAP >90 and >100 mmHg) as a safety outcome
- To compare total hypotension time, number and duration of hypotensive episodes, and severity metrics at multiple MAP thresholds (<50, <65, <75 mmHg)
- To assess differences in fluid administration, vasopressor and inotrope use, and blood product transfusion
- To determine effects on hospital and intensive care unit length of stay
- To compare 90-day all-cause mortality between groups

This trial will provide prospective, controlled evidence regarding the efficacy and safety of predictive versus reactive haemodynamic monitoring in a well-defined, high-risk surgical population, addressing critical gaps in the current evidence base.

2 Methods: patient and public involvement, trial design

This protocol is reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2025 statement [23].

2.1 Trial Design {12}

This is a single-centre, prospective, parallel-group, randomised controlled trial with a 1:1 allocation ratio comparing HPI-guided haemodynamic management (HPI group) with standard arterial pressure-derived cardiac output monitoring (FloTrac group) in patients undergoing major abdominal aortic surgery.

2.2 Patient and public involvement {11}

Patient representatives were not involved in the design of this protocol. However, feedback from participants in our previous retrospective study informed the choice of patient-centred outcomes (e.g., hospital length of stay, 90-day mortality). Study results will be disseminated to patient advocacy groups in vascular surgery through institutional channels.

3 Methods: participants, interventions, and outcomes

3.1 Study Setting {13}

The trial will be conducted at the Department of Anaesthesiology and Intensive Care, University Hospital in Poznań, Poland.

3.2 Eligibility Criteria {14a}

3.2.1 Inclusion Criteria

Patients will be eligible for inclusion if they meet all of the following criteria:

1. Age $\geq$ 18 years
2. American Society of Anesthesiologists (ASA) physical status classification III or IV
3. Scheduled for elective major abdominal aortic surgery (open or endovascular repair) with an expected surgical duration exceeding 2 hours
4. Able to provide written informed consent

3.2.2 Exclusion Criteria

Patients meeting any of the following criteria will be excluded:

1. Emergency or urgent surgery
2. Pregnancy or breastfeeding or positive/uncertain pregnancy test
3. Haemodynamically significant valvular heart disease:
   - Severe aortic stenosis (aortic valve area < 1.5 cm^2)
   - Moderate to severe aortic regurgitation
   - Moderate to severe mitral regurgitation
   - Moderate to severe mitral stenosis
4. Severe heart failure with left ventricular ejection fraction $< 35\%$
5. Permanent atrial fibrillation (reduces accuracy of pulse contour analysis)
6. Inability to provide informed consent
7. Participation in another interventional trial that may influence haemodynamic management or study outcomes

The cardiac exclusions are based on conditions that compromise the reliability of arterial pulse contour-derived cardiac output monitoring for both FloTrac and HPI systems, as documented in manufacturer guidelines and prior validation studies.

3.3 Intervention and comparator {15a}

All patients will receive general anaesthesia according to institutional protocols, with or without regional anaesthesia (epidural analgesia) at the discretion of the attending anaesthesiologist. Invasive arterial blood pressure monitoring via radial artery cannulation will be established in all patients before induction of anaesthesia. The choice of anaesthetic agents (volatile or intravenous), opioids, and neuromuscular blocking agents will be left to the clinical judgement of the anaesthesia team.

3.3.1 Standard APCO Monitoring (FloTrac Group)

Patients allocated to the FloTrac group will receive haemodynamic monitoring using the FloTrac sensor (Edwards Lifesciences, Irvine, CA, USA) connected to the radial arterial line. The FloTrac system provides continuous measurements of cardiac output (CO), cardiac index (CI), stroke volume (SV), stroke volume index (SVI), stroke

volume variation (SVV), systemic vascular resistance (SVR), and systemic vascular resistance index (SVRI) based on arterial pressure waveform analysis.

Haemodynamic management in the FloTrac group will follow a structured protocol (Figure 1) designed to maintain MAP $\geq$ 75 mmHg while avoiding excessive hypertension (target MAP $\leq$ 100 mmHg). The protocol incorporates the following decision pathways:

- **MAP $<$ 75 mmHg with SVV $>$ 12%:** Administer fluid bolus (250–500 mL crystalloid or 250 mL of colloid over 5–10 minutes) and reassess
- **MAP $<$ 75 mmHg with SVV $\leq$ 12% and SVRI $<$ 1700** $\mathrm{dyn \cdot s \cdot cm^{-5} \cdot m^2}$ **with CI $\geq$ 2.5 L/min/m^2:** Initiate or increase noradrenaline infusion (target MAP 75–90 mmHg)
- **MAP $<$ 75 mmHg with SVV $\leq$ 12% and CI $<$ 2.5 L/min/m^2:** Consider inotropic support (dobutamine 2–5 μg/kg/min) and reassess fluid status
- **MAP $>$ 100 mmHg:** Reduce vasopressor infusion rate; if MAP remains $>$ 100 mmHg despite minimal vasopressor support, consider deepening anaesthesia or administering antihypertensive medication

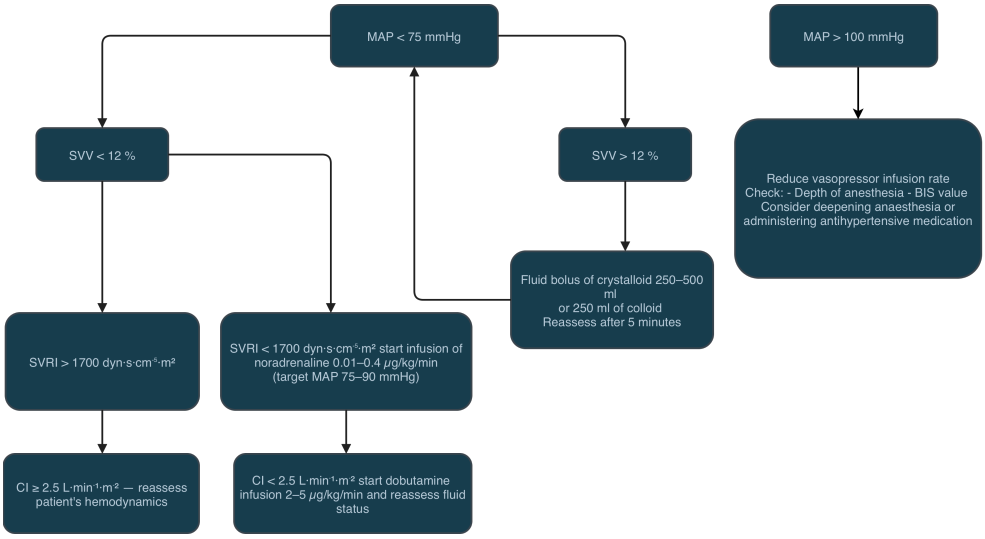


Fig. 1 Institutional FloTrac algorithm for fluids, vasopressors and inotropes.

3.3.2 HPI-Guided Monitoring using Acumen IQ sensor (HPI Group)

Patients allocated to the HPI group will receive haemodynamic monitoring using the Acumen IQ sensor (Edwards Lifesciences, Irvine, CA, USA) connected to the radial arterial line. The Acumen IQ system provides all parameters available with the FloTrac sensor, plus additional advanced metrics including dynamic arterial elastance ($\mathrm{Ea_{dyn}}$),

the rate of ventricular pressure change (dP/dt), and the Hypotension Prediction Index (HPI).

The HPI is a machine learning-derived value ranging from 0 to 100 that represents the probability of MAP falling below 65 mmHg within the next 15 minutes. When HPI exceeds 85, the system generates an alert and displays a secondary screen presenting real-time haemodynamic parameters and suggested interventions. Haemodynamic management in the HPI group will follow a structured protocol (Figure 2) incorporating both predictive (HPI-triggered) and reactive (MAP-based) components:

- **HPI $\geq$ 85 (hypotension prediction alert):**
  - If SVV $>$ 12%: Administer fluid bolus (250–500 mL crystalloid or 250 mL of colloid over 5–10 minutes) and reassess
  - If SVV $\leq$ 12% and SVRI $<$ 1700 dyn $\cdot$ s $\cdot$ cm^{-5} $\cdot$ m^2 with $\frac{dP}{dt} > 400$ mmHg/s : Initiate or increase noradrenaline infusion (target MAP 75–90 mmHg)
  - If SVV $\leq$ 12% and SVRI $>$ 1700 dyn $\cdot$ s $\cdot$ cm^{-5} $\cdot$ m^2 with $\frac{dP}{dt} < 400$ mmHg/s: Consider inotropic support
- **MAP $<$ 75 mmHg despite HPI-guided interventions:** Implement reactive management as per FloTrac protocol
- **MAP $>$ 100 mmHg:** Reduce vasopressor infusion rate; consider deepening anaesthesia or antihypertensive medication if MAP $>$ 100 mmHg persists

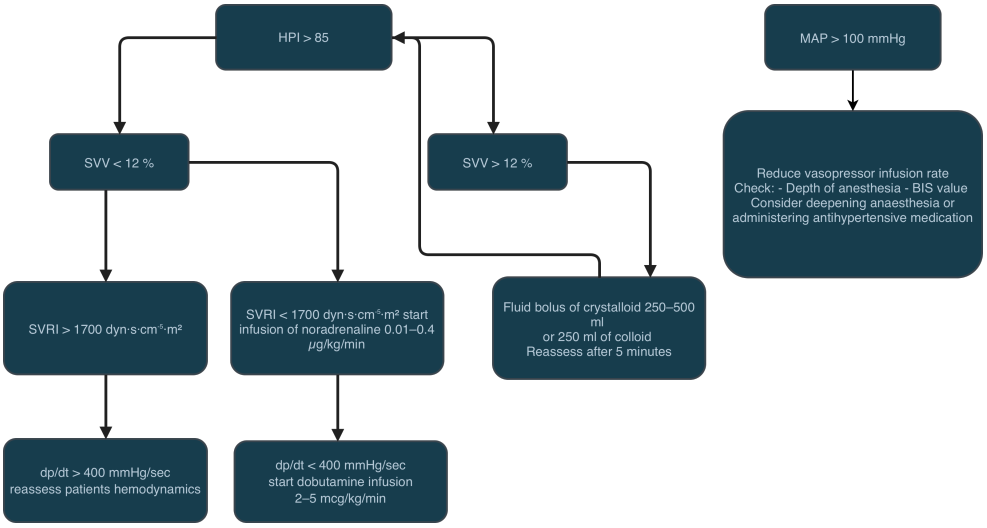


Fig. 2 HPI-based haemodynamic treatment protocol (institutional).

In both groups, fluid administration will be guided by clinical assessment, haemodynamic parameters, and an estimated blood loss replacement protocol. Blood product transfusion will follow institutional guidelines based on haemoglobin concentration,

coagulation parameters, and clinical bleeding. All vasoactive drug doses, fluid boluses, and timing of interventions will be recorded electronically.

Haemodynamic monitoring will be discontinued upon completion of surgery and transfer of the patient from the operating theatre. Postoperative care will follow standard institutional protocols and will not differ between groups.

3.3.3 Criteria for discontinuation or modification of allocated interventions {15b}

Both haemodynamic monitoring modalities are considered standard-of-care and of comparable quality; therefore, crossover between groups is not anticipated under routine conditions.

If clinical circumstances require additional haemodynamic assessment or management (e.g., echocardiography or other advanced monitoring), this will be performed at the discretion of the treating physician in the interest of patient safety. Such cases will be considered protocol deviations but will not result in exclusion from the study.

Similarly, if the actual duration of surgery or haemodynamic monitoring is shorter than the anticipated two hours, participants will not be excluded after randomisation. These cases will be retained in the primary analysis population, with handling of incomplete data described in the statistical analysis plan (Section 5.2.10).

All randomised participants will be analysed according to their allocated group (as-randomised principle), with per-protocol analyses conducted as sensitivity analyses (Section 5.2).

3.3.4 Strategies to improve adherence to intervention protocols {15c}

All the care providers will undergo repeated training regarding the hemodynamic monitoring and hemodynamic protocols. Protocol adherence will be reviewed during the regular steering committee meetings.

3.3.5 Concomitant care permitted or prohibited during the trial {15d}

If clinically indicated, haemodynamic monitoring and management may be intensified at the discretion of the treating physician, including the use of additional modalities such as echocardiography or other advanced monitoring techniques. Similarly, the haemodynamic management protocol may be modified if the patient remains haemodynamically unstable despite protocol-guided treatment. All such deviations from the protocol will be recorded and reported. These modifications will not result in exclusion from the study and will be handled as protocol deviations in the analysis.

3.4 Outcomes {16}

3.4.1 Primary Outcome

The primary outcome is the **time-weighted average of mean arterial pressure below 65 mmHg (TWA-MAP $<$ 65 mmHg)** during the period from induction

of anaesthesia to departure from the operating theatre. TWA-MAP is calculated as the area under the threshold (AUT, integrated over time) divided by total monitoring time:

$$\text{TWA-MAP}_{<65} = \frac{\text{Area below 65 mmHg (mmHg·min)}}{\text{Total monitoring time (min)}}$$

This metric integrates both the depth and duration of hypotension, providing a comprehensive measure of hypotensive burden [24].

3.4.2 Key Secondary Outcomes

1. **Composite postoperative organ complications within 7 days:** At least one of the following:
   - **Acute kidney injury (AKI)** according to KDIGO criteria
   - **Myocardial injury after non-cardiac surgery (MINS)**, defined as troponin elevation $\geq$ assay-specific 99th percentile upper reference limit
   - **Stroke** (new focal neurological deficit confirmed by neuroimaging)
   - **Postoperative respiratory failure** will be defined as a composite endpoint reflecting clinically relevant impairment of gas exchange or ventilation in the early postoperative period. It will be considered present if at least one of the following criteria is met within 7 days after surgery or before ICU discharge:
     (a) Prolonged invasive mechanical ventilation, defined as failure to extubate within 48 hours after the end of surgery;
     (b) Unplanned reintubation with initiation of invasive mechanical ventilation due to respiratory failure (hypoxaemia, hypercapnia, or inability to maintain adequate ventilation) after initial extubation; or
     (c) Unplanned initiation of non-invasive ventilation or high-flow nasal oxygen for respiratory failure, maintained for at least 6 hours after extubation.
   - **Postoperative circulatory failure** will be defined as a composite endpoint reflecting clinically relevant cardiovascular instability in the early postoperative period. It will be considered present if at least one of the following criteria is met within 48 hours after surgery:
     (a) sustained requirement for vasopressor support, defined as continuous norepinephrine infusion $\geq$0.1 μg/kg/min for $\geq$6 hours despite adequate fluid resuscitation;
     (b) initiation or escalation of inotropic therapy (dobutamine, milrinone, or epinephrine at inotropic doses) for signs of tissue hypoperfusion;
     (c) need for mechanical circulatory support (intra-aortic balloon pump, extracorporeal membrane oxygenation, or equivalent).
2. **Intraoperative hypertension:**
   - Total time with MAP $>$ 90 mmHg (minutes and % of monitoring time)
   - Total time with MAP $>$ 100 mmHg (minutes and % of monitoring time)
   - TWA-MAP $>$ 90 mmHg and TWA-MAP $>$ 100 mmHg
3. **All-cause mortality at 90 days**

3.4.3 Other Secondary Outcomes

- Total hypotension time (MAP $<$ 65 mmHg) in minutes and as percentage of monitoring time
- Number of hypotensive episodes (MAP $<$ 65 mmHg lasting $\geq$ 1 minute)
- Mean duration per hypotensive episode
- Area under threshold (AUT) for MAP $<$ 65 mmHg (mmHg·min)
- Number and severity of episodes at alternative thresholds: MAP $<$ 50 mmHg and MAP $<$ 75 mmHg
- Intraoperative fluid administration: total crystalloids, colloids, and blood products (units)
- Vasopressor and inotrope use: maximum dose and total infusion time for noradrenaline and dobutamine
- Estimated blood loss (mL)
- Duration of surgery and anaesthesia
- Length of stay in post-anaesthesia care unit (hours)
- Length of stay in hospital (days)
- Incidence of surgical complications requiring re-operation

Detailed definitions of all postoperative outcomes are provided in the Supplementary Material.

3.5 Harms {17}

The trial is conducted within the framework of standard anaesthetic care for patients undergoing major aortic surgery and uses established advanced haemodynamic monitoring techniques. No substantial additional risks related to study participation are anticipated beyond those inherent to the surgical and anaesthetic care.

Nevertheless, potential risks related to protocolised haemodynamic management — including possible overcorrection leading to hypertensive exposure — will be specifically monitored as part of the study safety outcomes.

All adverse events (AEs) and serious adverse events (SAEs) occurring during the perioperative period will be systematically recorded and reported. Several of these events constitute pre-specified study outcomes (Section 3.4).

3.5.1 Adverse Event Reporting

All adverse events (AEs) and serious adverse events (SAEs) occurring within 30 days of surgery will be recorded.

Serious adverse events are defined in accordance with ICH E2A criteria and include:

- Death
- Life-threatening events
- Hospitalisation or prolongation of existing hospitalisation
- Persistent or significant disability/incapacity
- Important medical events that may require intervention to prevent one of the above outcomes

Expected postoperative complications — including known complications of major aortic surgery in this patient population (e.g., haemorrhage, vessel rupture or injury, hypotensive episodes requiring vasopressor support, acute kidney injury [AKI], myocardial injury after non-cardiac surgery [MINS], stroke, respiratory or circulatory failure, ICU-level support requirements, surgical site complications, mortality) and known complications of general anaesthesia — will be recorded as AEs and study outcomes. These events will not be subject to expedited reporting unless they are considered unexpected (i.e., not a known complication of the surgical/anaesthetic care) or related to the study intervention.

All SAEs will be reported to the Principal Investigator immediately and reviewed by the independent Data Safety Monitoring Committee (Section 6.1) in accordance with the predefined safety monitoring plan.

SAEs that are considered related to the study intervention or are unexpected will be reported to the institutional ethics committee within 24 hours of the investigator becoming aware of the event, in accordance with local regulatory requirements. Follow-up reports will be submitted until resolution or clinical stabilisation.

The relationship of each AE/SAE to the study intervention will be assessed by the investigator as unrelated, possibly related, or related. Severity will be classified according to standard clinical criteria (mild, moderate, severe).

Non-serious adverse events will be recorded and summarised descriptively.

Several adverse events correspond to pre-specified study outcomes (Section 3.4) and will be analysed accordingly.

All adverse events will be reviewed periodically by the Data Safety Monitoring Committee.

3.5.2 Stopping Rules

The trial may be considered for early termination under the following pre-specified circumstances.

1. Safety boundary. At the planned DSMC safety review (after enrolment of approximately 100 participants; Section 5.2.11), early termination for harm will be considered if there is a clinically important between-group difference in any key safety outcome:

- 30-day all-cause mortality
- Composite organ injury within 7 days
- Serious haemodynamic-related adverse events

exceeding a Haybittle–Peto stopping boundary (two-sided $p < 0.001$; corresponding $Z \approx 3.29$), based on the statistical model appropriate for each outcome. This conservative boundary is specified to preserve the overall type I error rate and does not require formal alpha adjustment at the final analysis.

2. Other safety concerns. The DSMC may recommend trial modification or termination based on emerging safety concerns not captured by formal statistical stopping boundaries, including but not limited to:

- Unexpected clustering of adverse events

- Device-related technical failures affecting patient safety
- Signals of harm in clinically relevant subgroups

All such recommendations will be formally documented, including the underlying rationale.

3. Recruitment feasibility (futility). The trial may be considered for termination if recruitment is deemed infeasible, defined as:

- <30% of the planned sample size achieved after 12 months of active recruitment,
- despite documented and reasonable efforts to improve enrolment.

4. External evidence. The trial may be stopped if compelling external evidence emerges that adequately and conclusively addresses the primary research question, such as results from a large, methodologically robust randomised controlled trial.

Decision process. The DSMC will review accumulating data and issue written recommendations to the trial sponsor. The final decision regarding trial continuation, modification, or termination will be made by the sponsor in consultation with the principal investigators, taking into account DSMC recommendations.

Any decision to stop the trial early will be communicated to:

- the Bioethics Committee (resolution 808/25),
- all participating investigators,
- the trial registry (ClinicalTrials.gov identifier NCT07510451),
- and, where appropriate, enrolled participants.

3.6 Participant timeline {18}

The schedule of enrolment, interventions and assessments is shown in Table 1.

Table 1 Schedule of enrolment, interventions and assessments (SPIRIT figure).

	Enrolment	**Study period**			
Timepoint	d_{-1}	d_0	d_0–d_7	d_{hd}	d_{90}
Enrolment					
Eligibility screen	X				
Written informed consent	X				
Project explanation	X				
Demographics & comorbidities	X				
Allocation		X			
Interventions					
Group A (FloTrac, APCO)		X			
Group B (HPI, Acumen IQ)		X			
Assessments					
Primary outcome (TWA-MAP)		X			
Secondary outcomes		X	X	X	X

d_{-1}: day before surgery; d_0: surgery day; d_0–d_7: in-hospital follow-up; d_{hd}: hospital discharge; d_{90}: 90-day follow-up (telephone).

3.7 Sample Size {19}

Sample size determination was based on the primary outcome (TWA-MAP <65 mmHg) and informed by our retrospective cohort as well as simulation-based power analysis using a generalized linear model with Gamma distribution and log-link.

In the retrospective study, TWA-MAP <65 mmHg demonstrated a markedly right-skewed distribution with substantial inter-individual variability. Therefore, the primary estimand in the present trial is defined as the ratio of mean TWA-MAP values between groups (HPI vs. FloTrac), and power calculations were performed accordingly.

Monte Carlo power simulations were performed by bootstrap resampling from the empirical distribution of TWA-MAP <65 mmHg observed in the FloTrac group of our retrospective cohort, assuming a clinically meaningful relative reduction of 30% (mean ratio 0.70) in the HPI group.

The choice of 30% as the target effect was informed by three considerations. First, randomised trials of HPI-guided haemodynamic management in other surgical populations have reported substantially larger reductions in intraoperative hypotension burden, ranging from 33% to 63% across non-cardiac and cardiac surgery cohorts [16, 32]; 30% therefore represents a conservative target relative to the broader HPI evidence base. Second, the retrospective cohort point estimate suggested a 32% relative reduction in mean TWA-MAP <65 mmHg (mean ratio 0.68, 95% CI 0.45–1.05, estimated using a Gamma regression model with robust standard errors), broadly consistent with the present trial's pre-specified target effect of a 30% reduction (mean ratio 0.70). However, this retrospective estimate was imprecise because of the limited sample size (n=50 per group, p=0.27 from non-parametric comparison; the wide confidence interval includes both the null effect and the pre-specified target) and should therefore be interpreted as hypothesis-generating. The present trial incorporates pre-specified protocol refinements, including explicit upper MAP limits and balanced haemodynamic targets, and is designed to estimate this effect prospectively and with greater precision. Third, 30% was pre-specified as the minimal clinically important difference. This threshold reflects both the prior literature on HPI-guided management and the magnitude of effect considered clinically meaningful in the context of hypotension-associated organ injury, based on prior observational evidence [1, 2].

Should the true effect prove smaller (e.g., 15–20%), the achieved power and precision will be lower than estimated; this possibility is acknowledged in the estimation-focused framing of the trial and is reflected in the planned reporting of effect sizes with 95% confidence intervals as the primary inferential output, rather than reliance on dichotomous hypothesis testing.

Simulation-based calculations using Gamma parameters fitted to the retrospective dataset (shape = 0.896, scale = 0.551) indicated approximately 65–70% power to detect a mean ratio of 0.70 with 100 participants per group (200 total) under a two-sided significance level of 0.05. This corresponds to an expected reduction in mean TWA-MAP <65 mmHg from approximately 0.49 to 0.34 mmHg under the Gamma data-generating model. Sensitivity analyses using alternative zero-handling assumptions, including a Gamma model fitted to positive observations only and a two-part data-generating process, yielded power estimates approximately 65–80%, supporting the interpretation of the primary estimate as a conservative scenario. A pre-generated

randomisation list of 240 allocations (20% buffer above the analysable target) will be used to accommodate post-randomisation exclusions (see Section 4.1).

This power is below the conventional 80% threshold used in confirmatory trials. However, the present study is designed within an estimation-focused framework, where the primary objective is to obtain a precise estimate of the treatment effect rather than to reject or accept a null hypothesis. At the planned sample size, the expected 95% confidence interval for the mean ratio will have sufficient precision to distinguish clinically meaningful effects from negligible ones and to inform the design and sample size calculations for future multicentre confirmatory trials. This approach is consistent with recommendations for single-centre hypothesis-generating trials, where effect size estimation with adequate precision is prioritised over dichotomous significance testing [40]. A secondary objective is to comprehensively characterise the safety profile of HPI-guided haemodynamic management, particularly with respect to hypertensive exposure.

3.8 Recruitment {20}

Study participants will be recruited from patients meeting the eligibility criteria undergoing elective major abdominal aortic surgery at the University Hospital in Poznań. Based on the volume of scheduled aortic procedures at the centre, a recruitment period of 24 months should be sufficient to enroll the planned 200 participants. Anaesthesiologists from the Department of Anaesthesiology and Intensive Therapy will be involved in participant identification and recruitment.

4 Methods: assignment of interventions

4.1 Randomisation and Allocation Concealment {16, 21a, 21b, 22, 23}

Eligible patients who provide informed consent will be randomly allocated to FloTrac or HPI group in a 1:1 ratio using permuted block randomisation with variable block sizes (4, 6, 8). The randomisation list comprises 240 pre-generated allocations (200 target analysable participants plus a 20% buffer to account for protocol deviations, withdrawals, and participants randomised but not treated). The sequence was computer-generated in R (R Foundation for Statistical Computing, Vienna, Austria; version 4.5.2(2025-10-31)) prior to trial initiation using a fixed random seed to ensure reproducibility (complete code provided as Supplementary File S1). Enrolment will continue until 200 analysable participants have been obtained, at which point allocation will cease; any unused pre-generated slots will be discarded at database lock. In the unlikely event that the pre-generated list is exhausted before reaching 200 analysable participants, an extension of the list will be generated using a new documented seed and implemented as a protocol amendment (Section 7.2). No stratification will be applied, as this is a single-centre trial with a relatively homogeneous patient population.

Central allocation concealment is implemented through an Interactive Web Response System (IWRS) developed in R/Shiny with SQLite database backend, hosted

on a secure server with HTTPS/TLS encryption and individual user authentication. Following informed consent and eligibility confirmation on the morning of surgery, authorised study personnel log into the IWRS and enter the participant's unique study identifier. The system automatically assigns the next sequential allocation from the pre-generated master randomisation list. The allocation is recorded in the database using atomic SQL transactions with complete audit trail including timestamp, user ID and assignment details. The treatment assignment remains concealed from site personnel until surgery initiation, when it is revealed to the attending anaesthesiologist to enable implementation of the appropriate haemodynamic management protocol.

The planned flow of participants through the trial—including pre-randomisation screening, allocation to either group, follow-up, and analysis populations—is illustrated in Figure 3 as a CONSORT 2010 template flowchart. Numbers will be completed at trial closure and reported in the primary results manuscript.

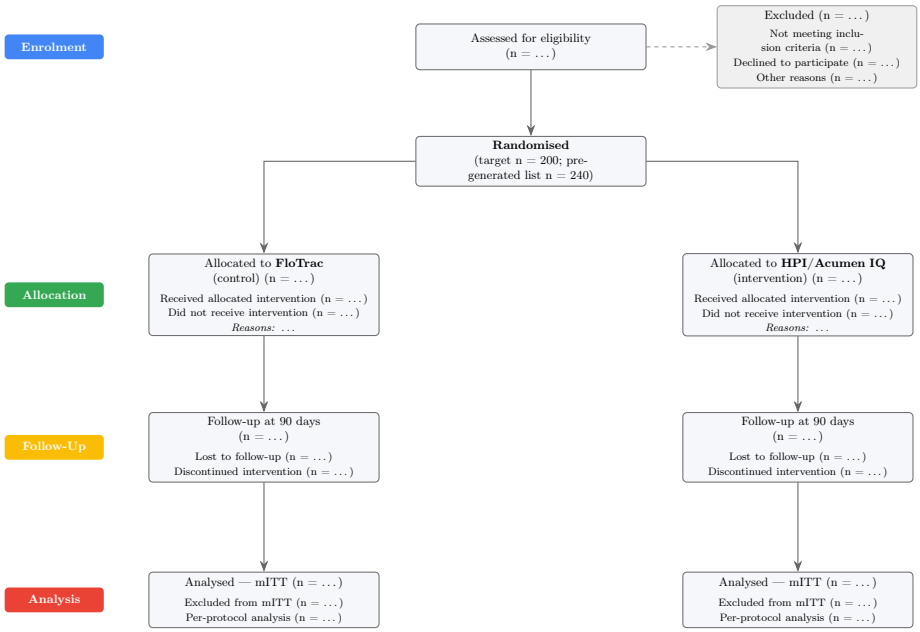


Fig. 3 CONSORT 2010 template flowchart of the trial.

4.2 Blinding {24}

Due to the nature of the intervention, blinding of the anaesthesia team is not feasible. However, the following measures will be implemented to minimise detection bias:

- Outcome assessors adjudicating postoperative complications (AKI, MINS, stroke, respiratory failure, circulatory failure) will be blinded to group allocation.
- Outcome assessors analysing biomarkers (troponin, creatinine) will be blinded to group allocation.

- Data analysts will remain blinded to group allocation until completion of the primary analysis.

5 Methods: data collection, management, and analysis

5.1 Data management and monitoring

5.1.1 Data Collection and Storage {25a, 27}

All intraoperative haemodynamic data will be exported from the HemoSphere monitoring platform (Edwards Lifesciences) and analysed using Acumen Analytics Software (version 1.0 or later). All data will be collected using REDCap (Research Electronic Data Capture) hosted at Poznan University of Medical Sciences, a secure web-based data entry platform with role-based access control, automated data validation and range checks, and complete audit trail of all data entries and modifications. Source documents include electronic anaesthesia records, laboratory information system and hospital electronic medical records.

Data quality will be ensured through weekly review by the study coordinator for missing data and inconsistencies, with queries generated and resolved in REDCap. All data will be stored in compliance with European Union General Data Protection Regulation (GDPR) and institutional data protection policies. Individual patient data will be de-identified and linked to a unique study identification number. Only members of the research team will have access to the dataset. De-identified study data will be retained for 15 years in accordance with institutional policy and applicable Polish data protection regulations.

5.1.2 Plans to promote participant retention and complete follow-up {25b}

All study outcomes, except 90-day mortality, can be ascertained during the participant's hospitalisation. Before patients discharge, a follow-up telephone call will be scheduled for the 90th day after surgery to evaluate vital status and any rehospitalisations.

5.2 Statistical Analysis {27}

5.2.1 General Principles {27a, 27b}

Analysis populations. Three analysis populations are pre-specified:

- **Intention-to-treat (ITT):** All randomised participants, analysed in the group to which they were allocated, regardless of intervention received or protocol deviations. The ITT population includes participants who were randomised but did not undergo surgery. As intraoperative data are not available in such cases, the ITT population will be used primarily for outcomes ascertainable without intraoperative measurements, including 90-day all-cause mortality, as a sensitivity analysis.
- **Modified intention-to-treat (mITT):** All randomised participants who received the allocated monitoring intervention (defined as connection of the assigned sensor

to the arterial line before induction of anaesthesia). Participants will be analysed according to their randomised allocation (as-randomised principle). Availability of outcome data does not define inclusion in the mITT population; handling of missing or incomplete intraoperative data is described in Section 5.2.10. The mITT population constitutes the primary analysis population for the primary outcome, composite organ injury, 90-day mortality, and intraoperative secondary outcomes. The target enrolment of n = 200 participants refers to the mITT population.

- **Per-protocol (PP):** A subset of the mITT population excluding participants with major protocol deviations, defined a priori as: (a) substantial failure to follow the assigned haemodynamic management algorithm; (b) crossover to the alternative monitoring system during surgery; or (c) other major deviations identified through trial monitoring. The PP population will be used for sensitivity analyses of the primary outcome and the composite organ injury endpoint.

Reasons for exclusion from each population will be documented in the CONSORT participant flow diagram (Figure 3).

Descriptive statistics.

For outcomes with pre-specified regression-based analyses, these model-based approaches will constitute the primary inferential framework; summary statistics and non-parametric comparisons described in this section are provided for descriptive and supportive purposes.

Continuous variables will be summarised using measures appropriate to their expected distributional characteristics, informed by the retrospective cohort and the nature of the measurement. Hypothesis tests of normality (e.g., Shapiro–Wilk) will not be used as gating decisions, as such tests are sensitive to sample size and may lead to data-dependent analytic choices.

Variables with approximately symmetric distributions (e.g., baseline demographics such as age, BMI, baseline mean arterial pressure) will be summarised as mean ± standard deviation and compared between groups using Welch's two-sample t-test, with mean differences and 95% confidence intervals reported.

Variables with positively skewed distributions (e.g., TWA-MAP <65 mmHg, total hypotension time, hypotensive episode counts, vasopressor doses, intraoperative blood loss, length of stay) will be summarised as median [interquartile range, IQR] and compared using the Mann–Whitney U test, with median differences and 95% confidence intervals derived from the Hodges–Lehmann estimator.

Graphical inspection (histograms, box plots, Q–Q plots) will be performed to assess agreement with expected distributional characteristics. Substantive deviations will be reported descriptively; pre-specified analytical approaches will not be modified post hoc.

Categorical variables will be presented as counts and percentages and compared using the chi-square test or Fisher's exact test (when expected cell frequencies are <5). Relative risks (RR) with 95% CI will be calculated for binary outcomes. All primary and safety analyses will prioritise estimation using effect sizes and confidence intervals over dichotomous hypothesis testing. Confidence intervals will be interpreted in relation to clinically meaningful effect sizes rather than solely null-hypothesis significance testing.

5.2.2 Primary Outcome Analysis

The primary outcome (TWA-MAP <65 mmHg) will be analysed using a **generalized linear model with Gamma distribution and log-link**, with treatment group as the main explanatory variable. Results will be reported as **mean ratios** (HPI vs. FloTrac) with 95% confidence intervals.

This modelling approach was selected *a priori* due to the positively skewed distribution of TWA-MAP observed in the retrospective study and allows direct interpretation of treatment effects on a relative (percentage) scale.

To accommodate the expected zero values in TWA-MAP <65 mmHg (approximately 7% of patients in the retrospective dataset had no intraoperative hypotension), a small constant (epsilon = 0.01) will be added solely for model fitting purposes, without altering the clinical interpretation of the outcome. This pragmatic offset avoids undefined values under the log-link while preserving the underlying treatment estimand on the original scale.

A two-part hurdle model (zero-adjusted Gamma; ZAGA family) will be fitted as a pre-specified sensitivity analysis to assess robustness to the zero-handling approach, allowing separate modelling of (i) the probability of any hypotension and (ii) the magnitude of hypotension burden among patients with non-zero TWA-MAP values. This approach provides a pragmatic primary estimand, while the hurdle model represents the fully specified data-generating process accounting for excess zeros. Consistency of the primary and sensitivity analyses will be reported, with the epsilon-offset Gamma GLM result serving as the primary estimand.

Model fit will be assessed using residual diagnostics and goodness-of-fit measures.

5.2.3 Key Secondary Outcome Analysis: Composite Organ Injury

The composite postoperative organ injury endpoint (occurrence of at least one of the following within 7 days: acute kidney injury [KDIGO Stage 1–3], myocardial injury after non-cardiac surgery [MINS], stroke, postoperative respiratory failure, or circulatory failure; defined in Section 3.4) will be analysed as a binary outcome at the participant level.

Primary analysis: The treatment effect will be estimated using a generalized linear model with binomial distribution and log-link to directly estimate risk ratios (RR) with 95% confidence intervals. The model will include treatment group as the main explanatory variable and the following pre-specified covariates: age (continuous), ASA physical status (III vs IV), baseline mean arterial pressure (continuous), coronary artery disease (binary), and procedure type (open vs endovascular repair). Log-binomial regression is preferred to allow direct estimation of risk ratios, which are more clinically interpretable for outcomes with moderate to high incidence. If the log-binomial model fails to converge, a modified Poisson regression with robust standard errors will be used.

Unadjusted analysis: Group incidence proportions will be presented as count (%), along with unadjusted risk ratios and 95% confidence intervals for descriptive comparison.

Component-level analysis: Each component of the composite will be analysed separately and reported as incidence proportions with corresponding effect estimates and 95% confidence intervals. These analyses are exploratory and intended to aid interpretation of the composite endpoint.

Multiplicity: The composite organ injury endpoint is considered a single outcome and no adjustment for multiplicity will be applied. As a secondary outcome, results will be interpreted with emphasis on point estimates and confidence intervals; p-values will be reported but not used as binary decision thresholds.

5.2.4 Mortality Analysis (90-day all-cause mortality)

Ninety-day all-cause mortality will be analysed as a time-to-event outcome to account for both event timing and censoring.

Primary analysis: Given the expected limited number of events, the primary analysis will be based on an unadjusted Cox proportional hazards model with treatment group as the sole explanatory variable, to minimise the risk of overfitting. Results will be reported as hazard ratios (HR) with 95% confidence intervals. Survival probabilities will be estimated using the Kaplan–Meier method and presented as survival curves with 95% confidence intervals. The log-rank test will be reported for completeness.

Adjusted analysis (exploratory): A multivariable Cox model including prespecified covariates (age, ASA physical status, baseline mean arterial pressure, coronary artery disease, and procedure type) will be fitted and interpreted with caution given the limited number of events.

If the proportional hazards assumption is violated, restricted mean survival time (RMST) at 90 days will be used as an alternative summary measure.

Secondary analysis: Ninety-day mortality will additionally be analysed as a binary outcome using log-binomial regression (or modified Poisson regression with robust standard errors if convergence fails), reporting risk ratios with 95% confidence intervals.

Censoring: Participants lost to follow-up before day 90 will be censored at the date of last known vital status. The planned 90-day follow-up telephone call (Section 5.1.2) is intended to minimise missing outcome data.

Multiplicity: Mortality analyses will be considered exploratory, with emphasis on effect sizes and confidence intervals rather than formal hypothesis testing.

5.2.5 Sensitivity Analyses {27d}

Sensitivity analyses will be performed to evaluate the robustness of the primary analysis under alternative modelling assumptions and analytical approaches.

1. **Covariate-adjusted primary model.** A pre-specified adjusted Gamma generalized linear model with log-link will be fitted, using the same covariate set as the composite organ injury and mortality analyses (age, ASA physical status, baseline mean arterial pressure, coronary artery disease, procedure type). Adjusted mean ratios with 95% confidence intervals will be reported and compared with the unadjusted estimates.

2. **Per-protocol (PP) analysis.** Conducted on the PP population defined in Section 5.2, excluding major protocol deviations. Results will be compared with the mITT analysis to assess the impact of adherence on treatment effect estimates.
3. **Non-parametric analysis.** Mann–Whitney U test as a distribution-free comparison; Hodges–Lehmann estimator with 95% confidence interval to quantify the location shift between groups.
4. **Quantile regression at the median** ($\tau = 0.5$). Evaluates group differences in the central tendency of TWA-MAP <65 mmHg, providing an estimate at the median (rather than the mean) that is robust to extreme values.
5. **Multiplicative-scale sensitivity.** Analysis using log-transformed values ($\log[\text{TWA} + 0.01]$) to verify consistency of results on a multiplicative scale and to reduce the influence of extreme values and skewness.
6. **Zero-handling sensitivity.** The two-part hurdle model (zero-adjusted Gamma, ZAGA family) described in Section 5.2.2 will additionally serve as a sensitivity analysis for the primary epsilon-offset Gamma GLM, evaluating robustness to the assumed handling of zero values.

Consistency of direction, magnitude, and statistical inference across these pre-specified sensitivity analyses will be interpreted as evidence of robustness of the primary findings. Divergence between approaches will be explored descriptively and considered in the context of distributional assumptions and clinical plausibility.

5.2.6 Secondary Outcome Analyses

For secondary outcomes, multiplicity will be addressed within predefined outcome families using the Holm–Bonferroni procedure. The primary outcome is analysed separately and is not included in multiplicity adjustments.

Hypotension-related and hypertension-related secondary outcomes (as listed in Section 3.4) will be grouped into two clinically coherent families. The hypotension-related family comprises 5 comparisons (total hypotension time, number of episodes, mean episode duration, area under threshold, and counts at alternative thresholds <50 and <75 mmHg, considered as a single construct), and the hypertension-related family comprises 4 comparisons (time and TWA-MAP above 90 and 100 mmHg). The Holm–Bonferroni procedure will control the family-wise error rate at $\alpha = 0.05$ within each family. Within each family, adjusted p-values will be reported alongside unadjusted p-values.

Effect sizes (e.g., mean ratios, risk ratios, or median differences, as appropriate) will be presented for all outcomes together with 95% confidence intervals.

For closely related metrics (e.g., absolute time and percentage time above/below the same threshold), a single primary metric per construct (pre-specified as absolute time) will be used for multiplicity adjustment, while related measures will be reported descriptively.

Postoperative adverse events and harms are analysed in detail in Section 5.2.7 (Harms Analysis).

Given the exploratory nature of these analyses, interpretation will focus primarily on effect sizes and confidence intervals rather than strict statistical significance thresholds.

5.2.7 Harms Analysis {27a}

Harms analyses are pre-specified across three categories and will be conducted in the mITT population; analyses in the ITT population will be performed as sensitivity analyses for outcomes ascertainable without intraoperative data.

1. **Individual organ injury components** of the composite endpoint (acute kidney injury, MINS, stroke, postoperative respiratory failure, postoperative circulatory failure; Section 3.4) will each be analysed separately as binary outcomes using log-binomial regression (or modified Poisson regression with robust standard errors if convergence fails), reporting risk ratios with 95% confidence intervals. Results will be presented in a forest plot. These component analyses are exploratory and are not adjusted for multiplicity, to aid interpretation of the composite endpoint (Section 5.2.3).
2. **Hypertensive exposure** (time and TWA-MAP above 90 and 100 mmHg) is a pre-specified safety outcome capturing potential overcorrection associated with HPI-guided management. It is analysed within the hypertension-related secondary outcome family (Section 5.2.6) using the Holm–Bonferroni-adjusted framework, but will be interpreted primarily as a safety signal.
3. **Other adverse events** — including serious adverse events (SAEs) and non-serious adverse events occurring within 30 days of surgery (definitions in Section 3.5.1) — will be reported descriptively as group incidence counts and proportions, with risk ratios and 95% confidence intervals estimated using log-binomial regression (or modified Poisson regression with robust standard errors if required). Appropriate exact or asymptotic methods will be used as required. For rare events or small cell counts, estimates will be interpreted with caution.

No formal multiplicity correction will be applied across distinct adverse event types, as these represent clinically distinct safety endpoints.

In line with the estimation-focused framework of the trial, all harms analyses will emphasise effect sizes (risk ratios, risk differences, and number needed to harm/benefit where estimable) with 95% confidence intervals rather than p-value-driven inference. Particular attention will be given to clinically meaningful safety signals regardless of statistical significance.

5.2.8 Adjusted Analyses {27d}

Multivariable regression models will be used in secondary analyses to adjust for potential confounders and assess robustness of findings. For skewed continuous outcomes (e.g., total hypotension time, hypertension exposure metrics), quantile regression will be applied, adjusting for the same pre-specified covariate set as the composite organ injury and mortality analyses (age, ASA physical status, baseline mean arterial pressure, coronary artery disease, and procedure type; see Section 5.2.3). For the key secondary binary outcome (composite organ injury), the pre-specified adjusted log-binomial regression model described in Section 5.2.3 serves as the primary analysis.

5.2.9 Subgroup Analyses {27d}

Pre-specified subgroup analyses will be conducted to explore potential heterogeneity of treatment effect for the primary outcome (TWA-MAP <65 mmHg) and the key secondary composite organ injury endpoint.

Pre-specified subgroups. Treatment effect modification will be evaluated according to the following pre-specified subgroups:

- Type of surgical procedure (open vs endovascular repair)
- Baseline cardiovascular risk (coronary artery disease present vs absent)
- Baseline renal function (eGFR $\geq$60 vs <60 mL/min/1.73 m^2)

Statistical analysis. For each outcome, subgroup effects will be estimated using regression models consistent with the primary analyses, including the same pre-specified covariates (age, ASA physical status, baseline mean arterial pressure, coronary artery disease, procedure type):

- For TWA-MAP <65 mmHg, a Gamma generalized linear model with log-link will be used.
- For the composite organ injury endpoint, a log-binomial regression model will be applied.

Effect modification will be evaluated by inclusion of a treatment-by-subgroup interaction term in each model. Interaction p-values will be reported. Within each subgroup, treatment effects will be reported as adjusted effect estimates (mean ratio or risk ratio, as appropriate) with corresponding 95% confidence intervals.

Continuous moderator analyses (exploratory). For continuous baseline moderators (notably eGFR; supplementary exploratory analyses for age and baseline mean arterial pressure will also be conducted), the treatment-by-moderator interaction will additionally be modelled as a continuous function using restricted cubic splines (three knots placed at the 10th, 50th, and 90th percentiles of the observed distribution) within the same regression framework. This complements the binary subgroup analyses by preserving the full information content of the moderator, increases power to detect effect modification, and may reveal non-linear patterns.

Presentation. Results will be presented graphically as forest plots displaying subgroup-specific effect estimates alongside confidence intervals and interaction statistics; for continuous moderator analyses, smoothed effect curves with 95% confidence intervals will be presented to enable visual assessment of effect modification patterns.

Interpretation. All subgroup analyses are pre-specified and exploratory, and will be interpreted as hypothesis-generating.

In line with the estimation-focused framework of the trial (Section 3.7), primary interpretation will emphasise the magnitude and precision of subgroup-specific effect estimates rather than statistical significance testing. P-values for interaction terms will be reported but will not be used as binary decision criteria, given their limited statistical power and known limitations in detecting true effect modification.

Given the overall sample size (n = 200 in the modified intention-to-treat population), subgroup analyses are expected to be underpowered, with relatively small

numbers of participants within subgroup-by-treatment strata and correspondingly wide confidence intervals. Accordingly:

- Lack of statistical evidence for interaction will not be interpreted as evidence of absence of treatment effect heterogeneity.
- Apparent subgroup differences will be interpreted cautiously in the context of multiple comparisons and imprecision.
- Any observed patterns will be considered exploratory and require confirmation in future adequately powered studies specifically designed to assess effect modification.

5.2.10 Missing Data {27c}

The proportion and pattern of missing data will be described separately for the primary outcome and for each secondary outcome.

Minimal missing data are anticipated for the primary outcome (TWA-MAP <65 mmHg), as haemodynamic monitoring is a core component of intraoperative care and will be recorded continuously by the HemoSphere platform.

For any analysed outcome with >5% missing data, multiple imputation by chained equations (MICE) will be performed under the missing-at-random (MAR) assumption, using predictive mean matching for continuous variables and logistic regression for binary variables. Imputation models will include treatment group, the pre-specified baseline covariates used elsewhere in the analysis (age, ASA physical status, baseline mean arterial pressure, coronary artery disease, procedure type), and any auxiliary baseline variables showing strong association with the missing variable or with its missingness mechanism. The number of imputations will be set to at least 20, with results pooled using Rubin's rules.

The primary analysis will be based on the imputed dataset if the proportion of missing data exceeds 5%; otherwise, complete-case analysis will be used.

Imputed values for continuous outcomes will be checked to ensure plausibility and consistency with the distributional assumptions of the primary analysis model. For outcomes with a substantial proportion of zero values (e.g., TWA-MAP <65 mmHg), imputation models will account for this distributional feature where appropriate, while the primary analysis will use a zero-adjusted modelling approach as specified in Section 5.2.2.

Sensitivity analyses will compare complete-case and imputed estimates for the primary outcome and key secondary outcomes (composite organ injury, 90-day mortality). Where informative missingness is suspected (e.g., proportion missing >10% or correlation between missingness and outcome), additional analyses under departures from MAR (pattern-mixture or tipping-point analyses) will be considered.

All multiple imputation analyses will be performed in R using the `mice` package.

5.2.11 Interim Analyses {28b}

No formal interim analyses for efficacy are planned. The independent Data Safety Monitoring Committee (DSMC; composition described in Section 6.1) will conduct a single planned safety review after enrolment of 100 participants. The DSMC will

have access to unblinded safety data (treatment allocation unblinded) and may recommend trial modification, suspension, or termination according to the pre-specified stopping rules (Section 3.5.2), which include a Haybittle–Peto safety boundary (two-sided $p < 0.001$) for key safety outcomes. Trial investigators, the sponsor, and the primary outcome data analyst will remain blinded to all interim treatment-group comparisons throughout recruitment and until the primary analysis lock.

6 Methods: monitoring

6.1 Data Safety Monitoring Committee {28a}

An independent Data Safety Monitoring Committee (DSMC) comprising two anaesthesiologists and one biostatistician, none of whom are investigators in the trial, will review safety data at regular intervals. The DSMC will have access to unblinded data and may recommend trial modification, suspension, or termination based on safety concerns. Any protocol modifications will be submitted to the ethics committee for approval before implementation. Amendments will be documented in a protocol version log and updated on the trial registry (ClinicalTrials.gov).

6.2 Trial monitoring {29}

An independent research nurse, not involved in the intraoperative management of participants, will act as an independent reviewer for the duration of the trial. Audits will be conducted weekly and will include verification of case report forms (CRFs), trial registry entries, and missing data. Audit findings will be reported to the principal investigator and to the DSMC.

7 Ethics

7.1 Ethical approval {30}

This trial has been approved by the Bioethics Committee of Poznan University of Medical Sciences (resolution number 808/25, dated 8 January 2026). The trial will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

7.2 Plans for communicating important protocol amendments to relevant parties {31}

No protocol amendments will be implemented without prior approval from the Bioethics Committee. Any substantial modifications to the protocol will be reviewed and signed by the principal investigators (MG and JS) before formal submission to the Bioethics Committee. Approved amendments will be communicated to all investigators, the trial sponsor, the DSMC, the ClinicalTrials.gov registry and, where relevant, to enrolled participants.

7.3 Who will take informed consent {32a}

Participants meeting the eligibility criteria will be identified by the anaesthesiologist from the Department of Anaesthesiology and Intensive Therapy at the University Hospital. The investigator will obtain written informed consent from each participant on the day before surgery during the preoperative assessment visit. The consent form and patient information sheet will describe the study objectives, procedures, potential risks and benefits, and the right to withdraw at any time without affecting clinical care. Participants will have adequate time to consider participation and ask questions.

7.4 Confidentiality {33}

All paper documentation related to the study will be assigned a unique study identification number and will not contain personally identifying patient data. These documents will be stored in a locked cabinet in the anaesthesiology office under the supervision of the principal investigator. Access will be restricted and granted only under exceptional circumstances. De-identified data will be entered into a password-protected REDCap database hosted at Poznan University of Medical Sciences. Access to the electronic database will be restricted to authorised study investigators. All data handling complies with the European Union General Data Protection Regulation (GDPR) and institutional data protection policies.

7.5 Provisions for post-trial care {34}

Participants will receive any additional care required beyond the scope of the trial. Any adverse events or complications arising from participation in the trial will be addressed promptly, with any necessary medical interventions provided free of charge.

8 Open science

8.1 Trial registration {4}

This trial was prospectively registered with ClinicalTrials.gov under identifier **NCT07510451** prior to enrolment of the first participant. The trial registry entry includes all protocol elements required by the World Health Organization Trial Registration Data Set.

8.2 Protocol and statistical analysis plan {5}

Given the relative simplicity of the planned analyses, the statistical analysis plan is included as an integral component of this study protocol (Section 5.2).

8.3 Data sharing {6}

Due to privacy regulations, individual participant data will not be shared publicly. However, de-identified data may be shared with other researchers upon reasonable request, following approval by the trial steering committee and the institutional review board.

8.4 Funding and conflict of interest {7a, 7b}

This trial received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. All study materials, including the Acumen IQ and FloTrac sensors, are purchased through the institutional procurement system. The authors declare no competing interests.

8.5 Dissemination policy {8}

Results will be disseminated through:

- Publication in a peer-reviewed journal (target: within 12 months of trial completion)
- Presentation at national and international scientific conferences
- Update of the trial registry record with summary results
- Communication of findings to patient advocacy groups if results have implications for perioperative care standards

Supplementary information. Supplementary File S1: R code for randomisation sequence generation.

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Declarations.

- **Funding:** This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. All study materials, including the Acumen IQ and FloTrac sensors, are purchased through the institutional procurement system.
- **Competing interests:** The authors declare that they have no competing interests.
- **Ethics approval and consent to participate:** This study was approved by the Bioethics Committee of Poznan University of Medical Sciences (resolution 808/25, dated 8 January 2026). Written informed consent will be obtained from all participants prior to enrolment.
- **Consent for publication:** Not applicable.
- **Data availability:** The datasets generated during and/or analysed during the current study will be available from the corresponding authors on reasonable request following publication of the main trial results. The study protocol, statistical analysis plan and informed consent form will be publicly available via the ClinicalTrials.gov registry.
- **Materials availability:** Not applicable.
- **Code availability:** The R code for randomisation sequence generation is provided as Supplementary File S1.
- **Author contributions:** MG (Mariusz Gezela) is the Principal Investigator. MG and JS (Jakub Szrama) are co-corresponding authors and contributed equally to this work. MG and JS conceived the study and drafted the protocol, and will oversee data collection. ŁŻ (Łukasz Żurański), KK (Katarzyna Kulas), MG (Michał Gajda), AK

(Anna Kłos) and PP (Piotr Przybylski) contributed to study design and protocol development. PS (Paweł Sobczyński) is the trial sponsor and contributed to all phases of the study protocol development. MG will perform the statistical analysis. All authors contributed to manuscript preparation, reviewed and approved the final protocol, and agree to be accountable for all aspects of the work.

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