Effect of the machine learning-derived Hypotension Prediction Index (HPI) combined with diagnostic guidance versus standard care on depth and duration of intraoperative and postoperative hypotension in elective cardiac surgery patients: HYPE-2 – study protocol of a randomised clinical trial

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ABSTRACT

Introduction Hypotension is common during cardiac surgery and often persists postoperatively in the intensive care unit (ICU). Still, treatment is mainly reactive, causing a delay in its management. The Hypotension Prediction Index (HPI) can predict hypotension with high accuracy. Using the HPI combined with a guidance protocol resulted in a significant reduction in the severity of hypotension in four non-cardiac surgery trials. This randomised trial aims to evaluate the effectiveness of the HPI in combination with a diagnostic guidance protocol on reducing the occurrence and severity of hypotension during coronary artery bypass grafting (CABG) surgery and subsequent ICU admission.

Methods and analysis This is a single-centre, randomised clinical trial in adult patients undergoing elective on-pump CABG surgery with a target mean arterial pressure of 65 mm Hg. One hundred and thirty patients will be randomly allocated in a 1:1 ratio to either the intervention or control group. In both groups, a HemoSphere patient monitor with embedded HPI software will be connected to the arterial line. In the intervention group, HPI values of 75 or above will initiate the diagnostic guidance protocol. In the control group, the HemoSphere patient monitor will be covered and silenced. The primary outcome is the time-weighted average of hypotension during the combined study phases.

Ethics and dissemination The medical research ethics committee and the institutional review board of the Amsterdam UMC, location AMC, the Netherlands, approved the trial protocol (NL76236.018.21). No publication restrictions apply, and the study results will be disseminated through a peer-reviewed journal.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This randomised clinical trial is the first to evaluate the Hypotension Prediction Index algorithm performance within a cardiac surgery population and the first to extend its application to the intensive care unit setting.
⇒ A representative population was used from observational studies within our institution for a precise sample size calculation.
⇒ Laboratory values indicative of organ damage will be collected to assess a possible benefit of hypotension reduction.
⇒ Due to the study design, blinding of the researchers and clinicians is not possible.

INTRODUCTION

Hypotension during cardiac surgery is associated with adverse outcomes, and its occurrence frequently extends to the postoperative intensive care unit (ICU) admission. Current hypotension management often occurs with delay due to the predominantly reactive approach, based on downward blood pressure trends. With a linear association between the duration of a mean
arterial pressure (MAP) below 65 mm Hg and the occurrence of mortality in non-cardiac populations, and it is plausible that a reduction in the severity of hypotension may benefit patient outcomes. In 2018, Hatib et al developed a logistic regression-based model to predict hypotension using continuous invasively measured arterial waveforms. This early warning system, known as the Hypotension Prediction Index (HPI), is embedded in the HemoSphere Advanced Monitoring Platform (Edwards Lifesciences, Irvine, California, USA) and predicts hypotension with high accuracy minutes before blood pressure decreases. Five recent randomised clinical trials (RCTs) evaluated the HPI in non-cardiac surgery populations. In combination with a diagnostic guidance protocol, intraoperative hypotension expressed as a time-weighted average (TWA) was significantly reduced in four of the five trials. In the trial without a significant TWA difference, over a third of HPI alarms were not followed by an intervention. A post-hoc analysis restricted to segments where clinicians intervened based on treatment advice showed a TWA reduction of 57%. This implies that the use of the HPI must be accompanied by an unambiguous implementation protocol, where intervening is preferable to expectant management.

No interventional trial implementing HPI combined with diagnostic guidance has focused on cardiac surgery or any ICU population. We hypothesise that using the HPI algorithm in combination with a guidance protocol will reduce the TWA of hypotension during both the off-pump phases of on-pump coronary artery bypass grafting (CABG) surgery, with or without additional single heart valve surgery and during mechanical ventilation postoperatively in the ICU.

METHODS AND ANALYSIS

Trial design

HYPER-II is an investigator-initiated, single-centre, single-blinded, two-arm, RCT in adult (≥18 years old) elective cardiac surgery patients. The study takes place in the Amsterdam University Medical Centers (Amsterdam UMC), location AMC, a tertiary academic centre in the Netherlands. The planned study duration is 18 months from the first inclusion, which took place on 20 May 2021. This trial paper adheres to the reporting guideline for clinical trial protocols with an artificial intelligence component: SPIRIT-AI extension (online supplemental appendix 1).

Patient and public involvement

It was not deemed feasible to involve patients or a broader public in the design of this trial.

Study population and recruitment

HYPER-II will enrol adult patients scheduled for an elective on-pump CABG procedure with or without additional single heart valve surgery (eg, valve repair or replacement). In addition, both a radial or brachial arterial line and a target MAP of 65 mm Hg are eligibility criteria. This applies both during surgery (excluding the cardiopulmonary bypass (CPB) phase) and during subsequent mechanical ventilation (up to 8 hours) in the ICU. Patients known to have cardiac shunts, severe cardiac arrhythmias (eg, supraventricular tachycardia above 100 beats per minute, ventricular tachycardia or ventricular fibrillation), dialysis-dependent kidney failure and previous cardiac surgery, or patients expected to receive a haemodynamic assist device during surgery (eg, intra-aortic balloon pump), or those with perioperative goal-directed therapy are not eligible. Considering these criteria, patients are only approached if verbal communication with them or their legal representatives can reasonably be conducted (ie, not complicated by a hearing impairment). Additionally, informed consent can only be obtained if they can read the Dutch consent form.

We assume that not all eligible patients can be approached due to various logistical reasons (eg, researchers’ availability, inclusion in competing studies). In the case of a potential study candidate, the involved anaesthetist will be contacted prior to surgery to verify that the MAP threshold will be maintained at 65 mm Hg. If eligible, patients will be contacted by research team members up to 3 days before the surgical procedure to obtain informed consent.

Study procedures and interventions

In order to record the continuous invasively measured arterial waveforms on the HemoSphere patient monitor with software V.2.0 (hereafter referred to as the study monitor), an Acumen IQ sensor with reference number AIQS8R5 (Edwards Lifesciences) is connected to the arterial line by trained researchers and positioned at the phlebostatic axis. The arterial line is zeroed to ambient pressure before surgical incision, after the CPB phase and at ICU arrival. The quality of the arterial waveform is frequently checked. Standard haemodynamic monitoring for CABG patients is displayed on an Intellivue MX800 or Intellivue MP90 patient monitor (Koninklijke Philips N.V., Amsterdam, the Netherlands), hereafter referred to as the standard monitor. It includes systolic blood pressure, diastolic blood pressure, MAP, heart rate and pulse pressure variation. In addition, the study monitor provides, separate from the standard monitor, additional parameters which are only available in the intervention group.

Three separate study phases are distinguished: (1) pre-CPB (from sternotomy until cannulation, 15 min before the start of CPB), (2) post-CPB (starting 30 min after weaning from CPB until wound closure) and (3) during subsequent mechanical ventilation in the ICU. Due to practical reasons, the transfer to the ICU is not included in any study phase. This translates to a 30 min study pause between phases II and III, starting from wound closure until the ICU handover completion. Phase III starts after the handover and lasts until extubation unless transfer to a different ICU takes place beforehand, in any case, for
a maximum period of 8 hours (see figure 1). With this, periods are excluded where permissive hypotension is applied (eg, during cannulation for CPB), ensuring study phases in which diagnostic guidance is most needed and clinicians are receptive to the given advice. After study phase III, the interventional part of the study is completed, but the study monitor remains connected to all patients in both groups for at least 8 hours with a fully covered screen to study potential sustained effects of applied diagnostic guidance.

**Intervention group**

Specific to the intervention group, additional arterial waveform-derived variables are displayed (see figure 2), which include the HPI, MAP, systemic vascular resistance, stroke volume (SV), stroke volume variation, derivative of arterial pressure and dynamic arterial elastance. HPI is expressed as a unitless number ranging from 0 to 100, with higher values indicating a higher likelihood of forthcoming hypotension. During the three study phases, the possible rationale for the impending hypotensive event is explored when the HPI value is in the 50–75 range. This rationale is obtained using a diagnostic guidance protocol incorporating the abovementioned variables (see figure 3). The diagnostic guidance protocol was designed by Wijnberge et al for the HYPER trial and is based on previously published research by Pinsky and

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**Figure 1** Overview of the events delineating the three perioperative study phases. *Period of permitted hypotension occupies at least 15 min before CPB, in some cases initiated earlier by the anaesthetist. †In any case for a maximum of 8 hours. CPB, cardiopulmonary bypass; ICU, intensive care unit.

**Figure 2** HemoSphere screen with additional haemodynamic variables. ART, arterial waveform derived pressures; CO, cardiac output; dP/dt, derivative of arterial pressure; Eadyn, dynamic arterial elastance; HPI, Hypotension Prediction Index; LV, left ventricle; MAP, mean arterial pressure; PPV, pulse pressure variation; PR, pulse rate; SV, stroke volume; SVR, systemic vascular resistance; SVV, stroke volume variation.
This protocol uses relative changes in the additional parameters instead of absolute cut-off values to diagnose the cause of forthcoming hypotension, hereby limiting the influence of possible cardiac arrhythmia and open chest cavity during surgery on the accuracy of the protocol. If HPI reaches and maintains a value ≥75 for at least 1 min, a treatment within 2 min is advised. Therefore, clinicians are trained and qualified to interpret the study monitor in combination with the diagnostic guidance protocol for a timely intervention. Additionally, a researcher is constantly present at the bedside to assist, if needed, in this interpretation and to alert the clinician at the onset of an alert for timely and accurate compliance. Herewith, the treating clinician—either the physician (ie, anaesthetist or intensivist) or nurse (ie, anaesthesia or critical care nurse)—is, if needed, provided with guidance concerning the timing of treatment (HPI≥75 or MAP<65 mm Hg) and assistance in interpreting the cause of the predicted hypotension (eg, hypovolaemia, reduced ventricular contractility or vasoplegia).

The operating room (OR) treatment type and dosage are left to the discretion of the anaesthetist. As a physician is not always present at the bedside in the ICU, a nurse-driven treatment protocol was drafted to enable nurses to initiate quick interventions. This protocol was created by our local ICU cardiology group, consisting of intensivists, cardiac anaesthetists and critical care nurses and is based on current standard hypotension treatment options (see figure 4). Both in the OR and ICU, the clinician may choose to deviate from the study protocol if deemed necessary in both timing and type of intervention. These deviations can be based on medical history (eg, left ventricular hypertrophy), clinical expertise, external factors (eg, vena cava compression by the surgeon) and additional diagnostics (eg, transoesophageal echocardiography (TEE)). Reasons for deviating from the protocol or refraining from treatment when advised will be asked by the researcher and annotated. In case of an ongoing HPI alert, the researcher gives diagnostic advice every 5 min, anticipating a haemodynamic response from the initial intervention (eg, vasopressors, fluids, inotropes or positional changes) within this timespan. Only the interventions given as a direct result of those treatment advices are labelled as study interventions; all subsequent haemodynamic altering interventions within the following 5 min are annotated and considered as interventions initiated by the clinician. Before starting the study, all clinicians were certified to work with the study monitor and were made aware of the limitations of pulse contour analysis-derived parameters.

Control group
In the control group, all clinicians in the OR and in the ICU are provided with standard haemodynamic monitoring for CABG patients to maintain the MAP threshold of 65 mm Hg. The study monitor will be covered and silenced to prevent clinical use of the HPI and additional variables. Similar to the intervention group, a researcher is constantly present at the bedside to annotate all haemodynamic altering interventions.

Randomisation and blinding
The researchers will perform computer-generated permuted block randomisation with varying block sizes of four, six and eight using a dedicated, password-protected, web-based randomisation module. Allocation to
either the intervention group or control group will be done in a 1:1 ratio, concealed from the patient and statistician. However, due to the nature of the interventions, the involved researcher, physician and nurse will not be masked to group allocation.

**Screen failure or patient withdrawal**

Randomised patients will be replaced with new subjects in case the surgical procedure is unexpectedly changed (eg, an off-pump procedure), if haemodynamic monitoring deviates from the necessary conditions (eg, femoral arterial line), if the MAP is below 65 mm Hg prior to surgery, or the target MAP is unexpectedly changed, in case the patient is unexpectedly extubated prior to ICU arrival, and lastly if there is an unexpected placement of a haemodynamic assist device or extracorporeal membrane oxygenation.

Additionally, in the unlikely event that data are not stored correctly on the study monitor device or when a participant withdraws their informed consent, the patient will be replaced.

**Data collection, storage and sharing**

All researchers are trained in using the study-specific standard operating procedures to ensure uniform data collection. Haemodynamic data from the study monitor will be downloaded to a USB flash drive and subsequently extracted to an appropriate password-protected subdirectory at our institutions’ network, only accessible to designated researchers. This haemodynamic data will be available as averaged data points per 20s and as raw-format data files, recorded with a 100 Hz frequency. The source code of the HPI algorithm is not accessible to the researchers.

Additional blood tests needed for exploratory objectives include creatinine, creatine kinase myocardial band, N-Terminal fragment of prohormone of brain natriuretic peptide, central venous oxygen saturation drawn as single samples from the central venous line, complete blood counts and arterial blood gases including lactate (see table 1 for sampling time points). These additional blood tests, along with standard laboratory results, patient characteristics, comorbidities, functional classification, physiological variables and perioperative procedural details, will be collected from electronic patient records and registered in Castor EDC, a GCP-compliant web-based data management system.

SURFfilesender (SURF B.V.25), a web-based service for authenticated users to securely encrypt and send files, will be used to share end-to-end encrypted datasets with Edwards Lifesciences as covered in the informed consent form (online supplemental appendix 2). The decrypting key will be sent separately per email.

**Outcome measures**

The TWA of hypotension during the three combined study phases is the primary outcome. This measure weights the severity of hypotension based on the length of observation periods, facilitating a possible comparison between different durations of measurement and other clinical settings (eg, operating theatre vs ICU). Hypotension is defined as a MAP<65 mm Hg for at least 1 min. Thereby, the TWA of hypotension is calculated taking the depth of hypotension (in mm Hg) below the
To enable comparisons between participants, the corresponding duration of the three study phases by the depth of hypotension (in minutes), providing the area under the threshold of 65 mm Hg multiplied by the time spent in hypotension (in minutes), providing the area under the threshold of 65 mm Hg ($\geq 65$ mm Hg). The secondar y observational studies done in cardiac surgery population. However, a slightly dampened effect is expected resulting from physiological changes caused by the CPB period (eg, systemic inflammatory response) and a likely slower response time to hypotension. For example, the combined length of the three study phases in a patient is 230 min, in which 15 min of hypotension occurs with a MAP of 60 mm Hg ($\Delta 55$ mm Hg). This translates to an AUT of 5x15=75 mm Hg x min. Divided by the total study phases’ duration, it would result in a TWA of 75/230= 0.326 min, in which 15 min of hypotension occurs with a MAP of 60 mm Hg ($\Delta 55$ mm Hg). This translates to an AUT of 5x15=75 mm Hg x min. Divided by the total study phases’ duration, it would result in a TWA of 75/230= 0.326 min.

The secondary outcome measures will be calculated for hypotension, hypertension and HPI alerts and include their incidence, time spent in, percentage of time spent in, AUT (or respectively their area over the threshold (AOT)) and TWA. Hypertension is defined as a MAP>100 mm Hg, and an HPI alert is defined as the number and reasons for deviations from the diagnostic guidance protocol are explored. Furthermore, the treatment behaviour after HPI alerts to which the clinician is blinded (silent alerts) in the control group will be compared with the protocol-guided treatment behaviour based on HPI alerts in the intervention group. These analyses will include the total number of alerts per patient, the percentage of alerts followed by treatment and the timespan from alert to treatment. In case a reduction of the severity of hypotension is present in the intervention group, a possible sustained effect after the three study phases will be assessed on the severity, incidence and time spent in hypotension. Initially, we opted to assess the relation between TEE observations and additional parameters from the study monitor during haemodynamic instability. However, the number of TEE observations in those scenarios proved to be too limited for a thorough comparison. Therefore, this exploratory objective will not be addressed, contrary to what was reported in the trial registry. Finally, biomarker levels will be followed up to see if any clinical effects of HPI implementation are distinguishable. Not all of these exploratory outcomes will be addressed in the main article.

### Sample size calculation

The prior HYPE trial found a median TWA reduction of 77%, favouring HPI with diagnostic guidance in a non-cardiac surgery population. However, a slightly dampened effect is expected resulting from physiological changes caused by the CPB period (eg, systemic inflammatory response) and a likely slower response time to HPI alerts in the ICU setting as the treating personnel is not continuously present at the bedside. Therefore, a 60% reduction in TWA of hypotension was considered both feasible and clinically relevant.

Representative haemodynamic data from two prospective observational studies done in cardiac surgery populations has been provided or in case a hypotensive event occurs.

### Table 1 Timepoints of laboratory values

<table>
<thead>
<tr>
<th>Laboratory values</th>
<th>Timepoints</th>
<th>Baseline</th>
<th>During phases I and II</th>
<th>During phase III</th>
<th>Postventilated ICU phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK-MB</td>
<td>$X^a$</td>
<td>$X^a$</td>
<td>$\dagger$</td>
<td>$\dagger$</td>
<td></td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>$X^a$</td>
<td>$X^a$</td>
<td>$X^a$</td>
<td>$X^a$</td>
<td>$\dagger$</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>$X^S$</td>
<td>$X^S$</td>
<td>$X^S$</td>
<td>$X^S$</td>
<td>$\dagger$</td>
</tr>
<tr>
<td>Arterial blood gas (incl. lactate)</td>
<td>$X^S$</td>
<td>$X^S$</td>
<td>$X^S$</td>
<td>$X^S$</td>
<td>$\dagger$</td>
</tr>
<tr>
<td>Venous blood gas (incl. ScvO$_2$)</td>
<td>$X^S$</td>
<td>$X^S$</td>
<td>$X^S$</td>
<td>$X^S$</td>
<td>$\dagger$</td>
</tr>
<tr>
<td>Creatinine</td>
<td>$X^S$</td>
<td>$X^S$</td>
<td>$X^S$</td>
<td>$X^S$</td>
<td>$\dagger$</td>
</tr>
<tr>
<td>Complete blood count</td>
<td>$X^S$</td>
<td>$\dagger$</td>
<td>$X^S$</td>
<td>$X^S$</td>
<td>$\dagger$</td>
</tr>
</tbody>
</table>

A: 1–4 days preoperative; B: shortly after insertion of the concerning catheter (respectively prior anaesthetic induction and shortly after intubation); C: shortly after the start of CPB and before wound closure; D: directly after ICU arrival; E: shortly after extubation; F: the following day after ICU admission; G: if available, daily from the 2nd to the 28th postoperative day.

$X^a$: laboratory value additional to standard care; $X^S$: laboratory part of standard care.

*Can contain additional samples initi ated by the clinicians.

†If available.

CK-MB, creatine kinase myocardial band; NT-proBNP, N-terminal fragment of prohormone of brain natriuretic peptide; ScvO$_2$, central venous oxygen saturation.

For example, the combined length of the three study phases in a patient is 230 min, in which 15 min of hypotension occurs with a MAP of 60 mm Hg ($\Delta 55$ mm Hg). This translates to an AUT of 5x15=75 mm Hg x min. Divided by the total study phases’ duration, it would result in a TWA of 75/230= 0.326 mm Hg.

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populations at our institution was used for this calculation. The first study, the PREP-trail (ongoing (NL7810 at www.trialregister.nl)), provides intraoperative measurements. The second study, the PHYSIC I trial29 collected data during the postoperative ICU admission. The combined TWA of hypotension was calculated from patients undergoing CABG with or without additional single heart valve surgery in these studies to estimate the current intraoperative and postoperative average for this population (median 1.02 mm Hg, IQR 0.32–2.12). Of all included patients, 94% had hypotension during admission. As expected, the TWA in these patients showed a skewed distribution which was transformed to normality with a Box-Cox procedure.29 This resulted in a mean of 0.983 mm Hg and an SD of 1.15 mm Hg. Anticipating a mean reduction of 60% resulted in a mean difference of 0.59 mm Hg (0.983 mm Hg×0.6). Dividing this mean difference by the SD gives an effect size of 0.51 (0.59/1.15). Using a Student’s t-test with an α=0.05 and 80% power, these parameters translate to a sample size of 80% power, these parameters translate to a sample size of 122. Correcting for the incidence of hypotension in this population resulted in the required sample size of 130 (122/0.94). All statistical analyses were performed using R Project for Statistical Computing (R Core Team, 2017).

Statistical analyses

Continuous data will be presented as medians with IQRs or as means with SDs when normally distributed. Normality of distribution will be visually assessed based on histograms and Q-Q plots. Categorical data will be presented as frequencies and percentages. The level of statistical significance for all tests will be set at an α<0.05.

The primary outcome, the TWA of hypotension for the three combined study phases, will be comparatively analysed with a Student’s t-test or Mann-Whitney U test, whichever is appropriate. In case of a non-normal TWA distribution, additional Hodges-Lehmann analysis will be performed to estimate the median difference with a 95% CI. The TWA of hypotension calculated in the comparable populations of the two aforementioned observational studies at our institution will be used to verify the representativeness of our control group.

The secondary outcomes on hypotension, hypertension and HPI consisting of metric data will be analysed for a difference in either their means or medians with an appropriate two-sided test similar to the primary outcome. In addition, the proportion differences of categorical data will be visualised using the \( \chi^2 \) test or Fisher’s exact test. Generalised mixed-effect models will be employed to assess possible differences in the repeated measurements of each biomarker.

When data are missing, multiple imputation will be used to estimate values missing at random or missing completely at random (MCAR). The mechanism of missingness will be assessed with Little’s MCAR test;28–31 Artefactual waveform data will be removed without subsequent imputation, using an automated algorithm in computational software, excluding absent values or abrupt value changes (eg, blood sampling, flushing and zeroing). All statistical analyses will be performed with R Project for Statistical Computing.

Ethics and dissemination

Ethical approval and registration

The HYPE-2 trial protocol (NL76236.018.21 version 3.0, date: 16 April 2021) is approved by the accredited medical research ethics committee (MREC) and institutional review board (IRB) of the Amsterdam UMC, location AMC, the Netherlands, and drafted according to the principles of the Declaration of Helsinki, and both the Dutch Medical Research Involving Human Subjects Act (WMO) and the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH-GCP). The last approved amendment of the protocol is version 4.0, date: 14 July 2021. All participants have to consent to publication of their data for study participation. They may withdraw from the study at any time.

Monitoring, safety and risks

An independent monitor is appointed to perform study monitoring. During on-site visits, monitoring will be conducted on the following: enrolment progress, presence of informed consent forms for all randomised subjects, accuracy and verifiability of the recorded data from source documents, documentation of protocol deviations, safety reporting and completeness of all other regulatory requirements as specified in the applicable laws (ie, WMO, ICH-GCP and ISO14155).

Regarding safety reporting, all (serious) adverse events related to using the CE-approved HemoSphere device and Acumen IQ sensor will be reported to the MREC and IRB. In addition, an insurance policy has been taken out for all participants that covers damage as a result of medical research. However, as these devices will be used according to their intended indication of use, risks are expected to be negligible.

Dissemination

The study results will only be presented or published per the CONSORT-AI guidelines through a peer-reviewed journal after the last follow-up. No publication restrictions apply, and the funder will have no role in data acquisition. Since all data is pseudo-anonymised, it will not be traceable to any participant. After the publication of the trial results, data and material requests can be sent to the corresponding author.

DISCUSSION

Definition of hypotension

There is no universal consensus on the definition of hypotension, possibly because the margin below which complications arise differs per individual. However, a target MAP of 65 mm Hg is the most commonly reported definition in an international survey conducted among

ICU personnel, making it a feasible study target. It is also the target in current sepsis guidelines. Furthermore, it was the driving force in the development of the HPI algorithm and will for these reasons be maintained in this trial.

**Definition of HPI alert**

In prior RCTs evaluating HPI performance, an HPI alarm was defined as an HPI value ≥85. We lowered this threshold based on a prospective validation study performed at our institution within an ICU population that included 40% post-cardiac surgery patients (PHYSIC I). Lowering the threshold from 85 to 75 resulted in similar sensitivity and specificity but increased the time from alert to hypotension.

**Unintentional influence**

The audible alarm of the study monitor is fixed at an HPI threshold of 85. Since this threshold is higher than the alert threshold of 75 used in our study, a researcher is continuously present to alert the clinician in case of an HPI alert. The continuous presence of a researcher was considered the most robust way to test whether the protocol itself reduces the severity of hypotension, as it guarantees timely recognition of HPI alerts and provides assistance if needed for correct protocol interpretation.

Even in the control group, the study can affect treatment behaviour as the MAP threshold of 65 mm Hg is emphasised prior to inclusion. Furthermore, the researcher’s presence at the bedside can subconsciously increase alertness to blood pressure changes. This potential bias, known as the Hawthorne effect, was not found in the previous HYPE trial. Nevertheless, we will compare the TWA of hypotension in our control group to the TWA obtained from the aforementioned observational studies at our institution, where the clinicians were unaware of an upcoming trial focusing on hypotension reduction.

**Clinical applicability**

Placement of the dedicated sensor on the arterial line to obtain the necessary variables does not constitute an implementation barrier. However, the involved clinicians need to be willing to change their treatment behaviour from mainly reactive to proactive based on a machine learning prediction model whose algorithm is not fully transparent and interpretable. Nevertheless, with a researcher present at the bedside, protocol adherence can be around 80%, as shown in previous trials. Outside clinical trials, it will take time to familiarise all personnel with the additional variables to adequately intervene in an emerging hypotensive event. Especially at our institution’s ICU, where the HPI is not yet registered in the central supervising room for the nurses. Which makes strict incorporation into the workflow difficult, as personnel is not continuously in reach of the visible and audible alarms at the bedside. However, the prediction model is validated for use 5, 10 and 15 min before a hypotensive event providing some room for a delayed response.

**Clinical relevance**

Although we will briefly discuss clinical effects through biomarkers, a subsequent trial should focus on clinical outcome measures (eg, prolonged hospitalisation, myocardial infarction, ischaemic strokes, acute kidney failure and mortality).

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**Contributors**

SRR and JSchuurmans contributed equally to this paper. SRR, JSchuurmans, JSchenk, DPV, BFG and AV were involved in the conception and design of the study. JSchuurmans, TGVC, WKL, PW, DPV and AV contributed to creating the nurse-driven protocol. BJPvdS and JSchenk worked on all technical details and wrote scripts to perform the proposed calculations. AHGD, SE, MVD, HH, LET, WvdV and FP facilitated training days during which all clinicians were informed about the purpose of the study. Their critical feedback helped shape the study protocol for a smooth implementation. SRR and JSchuurmans are responsible for acquiring study materials and patients; they created the electronic database, have full access to all collected data and act as guarantors for the integrity of the data and the accuracy of the subsequent analyses, including the interpretation of the study results. All authors contributed to the writing of this manuscript and gave their final approval. In addition, the corresponding author attests that all listed authors meet authorship criteria.

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**Competing interests**

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**Patient and public involvement**

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication**

Not applicable.

**Provenance and peer review**

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**Supplemental material**

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