

Hemodynamic Management Guided by the Hypotension Prediction Index in Abdominal Surgery: A Multicenter Randomized Clinical Trial

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Postoperative acute kidney injury is a major contributor to the burden of morbidity and mortality associated with major noncardiac surgery
- Intraoperative hypotension and renal hypoperfusion are felt to be major contributing factors
- The proprietary Hypotension Prediction Index (HPI; Edwards Lifesciences, USA) has been promoted as a potential aid in this regard as a potential

ABSTRACT

Background: Postoperative acute kidney injury (AKI) after major abdominal surgery leads to poor outcomes. The Hypotension Prediction Index (HPI; Edwards Lifesciences, USA) may aid in managing intraoperative hemodynamic instability. This study assessed whether HPI-guided therapy reduces moderate-to-severe AKI incidence in moderate- to high-risk elective abdominal surgery patients.

Methods: This multicenter randomized trial was conducted from October 2022 to February 2024 across 28 hospitals evaluating HPI-guided management compared to a wide range of real-world hemodynamic approaches. A total of 917 patients (65 yr or older or older than 18 yr with American Society of Anesthesiologists Physical Status greater than II) undergoing moderate- to high-risk elective abdominal surgery were included in the intention-to-treat analysis. HPI-guided management triggered interventions when the HPI exceeded 80, using fluids and/or vasopressors/inotropes based on hemodynamic data. The primary outcome was the incidence of moderate-to-severe AKI within the first 7 days after surgery. Secondary outcomes included overall complications, the need for renal replacement therapy, duration of hospital stay, and 30-day mortality.

Results: Median age was 71 yr (interquartile range, 65 to 77) in the HPI group and 70 yr (interquartile range, 63 to 76) in standard care group. American Society of Anesthesiologists Physical Status III/IV was 58.3% (268 of 459) in the HPI group and 57.9% (263 of 458) in standard care group. The incidence of moderate-to-severe AKI was 6.1% (28 of 459) in the HPI group and 7.0% (32 of 458) in the standard care group (risk ratio, 0.89; 95% CI, 0.54 to 1.49; $P = 0.66$). Overall complications occurred in 31.9% (146 of 459) of the HPI group and 29.7% (136 of 458) of the standard care group (risk ratio, 1.08; 95% CI, 0.85 to 1.37; $P = 0.52$). The incidence of renal replacement therapy did not differ between groups. Median length of hospital stay was 6 days (interquartile range, 4 to 10) in both groups. The 30-day mortality was 1.1% (5 of 459) in the HPI group *versus* 0.9% (4 of 458) in standard care group (risk ratio, 1.35; 95% CI, 0.36 to 5.10; $P = 0.66$).

Conclusions: HPI-guided hemodynamic therapy did not reduce the incidence of postoperative AKI or overall complications compared to standard care.

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trigger for evaluation of other goal-directed hemodynamic indices that are part of the Acumen IQ software package (Edwards Lifesciences, USA)

- Its impact on acute kidney injury in comparison to standard care in a large, multicenter design has not been previously reported

What This Article Tells Us That Is New

- At 28 hospitals, at-risk patients undergoing major elective abdominal surgery were randomized to a prespecified HPI-guided goal-directed hemodynamic strategy *versus* a standard care approach based on local clinical practice
- The primary outcome was the incidence of moderate-to-severe acute kidney injury according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria within 7 days after surgery
- All sites were required to have previous experience and competence with the HPI package
- No significant difference was noted in the primary outcome between HPI-guided and standard care groups or in overall complications using European Perioperative Clinical Outcome definitions within 30 days after surgery
- Limitations of this study include lack of capture of intraoperative hemodynamic data and lack of adherence data to the HPI-guided protocol

This article is featured in "This Month in ANESTHESIOLOGY," page A1. This article is accompanied by an editorial on p. 593. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has a visual abstract available in the online version.

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*Members of the HYT Group are listed in appendix 2.

More than 300 million surgical procedures are performed annually worldwide.¹ Postoperative acute kidney injury (AKI) is a frequent complication,^{2,3} often associated with intraoperative hypotension, a key factor leading to impaired renal perfusion.⁴

The development of the Hypotension Prediction Index (HPI) represents a novel approach in intraoperative hemodynamic management, enabling clinicians to predict hypotensive events minutes before they occur.⁵⁻⁷ Several studies have demonstrated the efficacy of HPI-guided management in reducing intraoperative hypotension.^{8,9} A recent meta-analysis reported reductions in the time-weighted average of mean arterial pressure (MAP) less than 65 mmHg by -0.21 mmHg (95% CI, -0.33 to -0.09 mmHg) and a reduction in the duration of hypotension by -10.11 min (95% CI, -15.82 to -4.40 min) in HPI-guided groups.¹⁰ However, its performance compared to MAP-based approaches is affected by intrinsic limitations, such as selection bias, which impacts its predictive reliability.¹¹⁻¹³ HPI-guided management aims to optimize organ perfusion and reduce intraoperative hypotension, but its direct impact on improving clinically meaningful outcomes remains uncertain.⁶ Although intraoperative hypotension is associated with adverse postoperative outcomes,¹⁴ whether reducing intraoperative hypotension through interventions like HPI-guided management causally leads to better clinical outcomes remains unclear.¹⁵

We hypothesized that HPI-guided hemodynamic therapy would reduce the incidence and severity of postoperative moderate-to-severe AKI compared to standard care in patients undergoing elective abdominal surgery.

Materials and Methods

We conducted a multicenter, international, open-label, two-arm, parallel-group randomized trial across 27 hospitals in Spain and 1 hospital in Jordan to evaluate HPI-guided management compared to a wide range of real-world hemodynamic approaches.¹⁶ The trial was registered at ClinicalTrials.gov (NCT05569265) before patient enrollment. The study protocol was approved by the Ethics Committee of Clinical Research of the West Valladolid Health Area (CEIM 8/22) and the institutional review board (University of Valladolid, Valladolid, Spain) at each site. Written informed consent was obtained from all participants before enrollment. The study adhered to the Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (Geneva, Switzerland) Good Clinical Practice guidelines,¹⁷ and all relevant laws and regulations. The study was conducted after the completion of a structured Delphi questionnaire by 30 experts in the field in 2022, and promoted by the Fluid Therapy and Hemodynamic Monitoring Working Group of the Spanish Society of Anesthesiology and Critical Care (Madrid, Spain).¹⁸ Edwards Lifesciences (Irvine, California) did not supply any products used in the trial, nor did they play a role in its execution or

data analysis. The trial was centrally monitored by staff at the coordinating center. Research staff collecting and assessing clinical outcomes were not involved in the participants' care and were unaware of study group allocation and study outcomes until the database was locked. The statistical analysis was conducted following the prespecified plan outlined in the original study protocol, which includes the full statistical analysis plan¹⁶ (Supplemental Digital Content, <https://links.lww.com/ALN/D796>). The analysis was performed after the collection of all follow-up data and data cleaning by a researcher not involved in patient management or data collection, ensuring objectivity. Study data were collected, deidentified, and managed using REDCap (Research Electronic Data Capture; Vanderbilt University, USA) electronic data capture tools, a secure, web-based software platform, hosted at Hospital Universitario Infanta Leonor, Madrid, Spain.^{19,20}

Sites and Patients

For inclusion, recruiting sites were required to demonstrate adequate capacity, training, and expertise in hemodynamic monitoring using HPI. This expertise, independent of this study, was evidenced by clinician certification, previous documented experience with the HPI system, initial mentoring by HPI experts, and an audit of early cases to confirm adherence to protocol standards. Sites were also required to have previous experience in performing major elective gastrointestinal surgeries and interventional research. Due to funding limitations, only centers with pre-existing HPI systems were approached for participation. We included adult patients aged 65 yr or older or older than 18 yr with American Society of Anesthesiologists (ASA; Schaumburg, Illinois) Physical Status III or IV, undergoing moderate- to high-risk elective abdominal surgeries, with an anticipated operative duration of at least 2 h and an expected hospital stay of at least 1 day. The specific surgeries included colorectal, pancreatic, gastric, and complex gynecologic-oncologic procedures. Exclusion criteria were clearly defined, including patients undergoing nephrectomy, urgent surgeries, or less extensive laparoscopic procedures (e.g., laparoscopic cholecystectomy). Additionally, patients with pre-existing renal dysfunction requiring dialysis were excluded from the study. Other exclusion criteria are listed in the Methods section of the Supplemental Digital Content (<https://links.lww.com/ALN/D796>). Comorbidities were obtained from patient medical records, verified by research staff, and reviewed by clinicians during preoperative assessments. Standardized protocols ensured consistency, with uncertainties resolved in consultation with the clinical team. All participants provided written informed consent before inclusion in the study. The manuscript adheres to Consolidated Standards of Reporting Trials (CONSORT) reporting standards, and a CONSORT checklist is included as a supplementary document (<https://links.lww.com/ALN/D796>) to ensure transparency and compliance with all relevant guidelines.

Randomization

Randomization was conducted using permuted blocks of four, with stratification by study site, patient age (categorized as younger than 75 yr and 75 yr or older), and surgical risk level (high *vs.* low risk). This approach ensured balanced distribution across treatment groups, addressing potential variations in clinical characteristics such as age and baseline risk factors among participants at different centers.¹⁶ Randomization and allocation were performed *via* the REDCap electronic data capture system to ensure secure and unbiased assignment of patients to either the HPI-guided intervention group or the standard care group. Allocation concealment was maintained by using the REDCap platform, which was only accessible to the study coordinators who were not involved in the clinical care of the patients. Allocation concealment was ensured through a centralized, secure web-based randomization system. Investigators and clinical staff involved in patient care were blinded to the allocation sequence until the moment of randomization, ensuring that the allocation remained concealed until assignment.

HPI-based Goal Directed Hemodynamic Therapy Group

For patients randomly assigned to the HPI-based goal directed hemodynamic therapy group, the team followed the protocol outlined in figure 1, similar to that used previously by our group.⁸ HPI was monitored using an Edwards Lifesciences (USA) system comprising a Hemosphere monitor with either an Acumen cuff (noninvasive) or Acumen IQ (invasive arterial pressure) sensor, depending on the clinician's choice. The hemodynamic protocol triggered intervention when the HPI exceeded 80, guiding fluid and vasopressor/inotrope administration based on the stroke volume variation, the dynamic arterial elastance, $dP/dt_{\max}$ (maximum rate of the arterial pressure rise during systole), and the systemic vascular resistance values to aid in identifying the most common causes of hypotension.²¹ When the hemodynamic algorithm indicated fluid administration, patients received a 250-ml fluid bolus of a balanced crystalloid solution. Ephedrine, administered in bolus doses of 5 to 10 mg, served as the preferred vasopressor. In cases where continuous infusion was warranted, norepinephrine was employed. No additional research staff were present in the operating room to observe HPI use or adherence to protocol in real time. The trial intervention period began at the initiation of surgery, marked by a skin incision, and concluded upon completion of surgery and closure of the skin.

Standard Care Group

Participants in the routine care group were managed according to local clinical practice, allowing anesthesiologists the flexibility to select the intraoperative hemodynamic monitoring method. This could range from basic

blood pressure monitoring to more advanced cardiac output monitors, excluding the HPI. When the Hemosphere system was used, it was paired with the FloTrac sensor (Edwards Lifesciences), which provides standard cardiac output monitoring but does not display advanced parameters such as HPI, dynamic arterial elastance, or $dP/dt_{\max}$. The use of the Acumen sensor, which displays these parameters, was strictly prohibited in the standard care group to ensure no access to HPI-derived data. Some patients in the standard care group were managed with alternative hemodynamic monitors or without advanced monitoring. At no time were two types of monitoring systems (HPI and non-HPI) used simultaneously in the same operating room. This flexibility reflects real-world clinical practice, allowing the study to evaluate HPI-guided therapy in comparison to a broad range of routine hemodynamic management approaches.

Common Perioperative Management in Both Groups

During surgery, key measures were recommended in both groups to maintain oxygenation (oxygen saturation measured by pulse oximetry greater than 94%) and normothermia (body temperature greater than 36°C), and to ensure a heart rate less than 100 beats/min. Mechanical ventilation was adjusted to achieve a P_{aCO_2} range of 35 to 45 mmHg, with a tidal volume of 8 ml/kg of ideal body weight, and a positive end-expiratory pressure between 4 and 6 cmH₂O. Basic monitoring included three-lead electrocardiography, pulse oximetry, and Bispectral Index monitoring. A balanced crystalloid solution was administered at a rate of 1 to 3 ml · kg⁻¹ · h⁻¹ for laparoscopic procedures and 5 to 7 ml · kg⁻¹ · h⁻¹ for open surgeries. After surgery, a balanced fluid therapy regimen was advised to meet ion and glucose requirements, with quantities ranging from 1.75 to 2.75 l every 24 h, determined by the responsible clinician.

Blinding and Data Collection

Given the nature of the intervention, it was not possible to blind the attending anesthesiologists or surgical teams to the use of HPI-guided hemodynamic management during the intraoperative period. However, the research staff responsible for evaluating postoperative complications, including the primary outcome of AKI, were blinded to the group assignments to prevent bias in outcome assessment. Intraoperative data were collected from the electronic health records systems used at each participating site. Postoperative outcomes were assessed by independent research staff who were unaware of the treatment allocation, ensuring blinding in the outcome evaluation process. Deviations from the allocated trial intervention were tracked and reported for both study groups. These deviations occurred when clinical circumstances required an intervention outside the protocol and were consistently

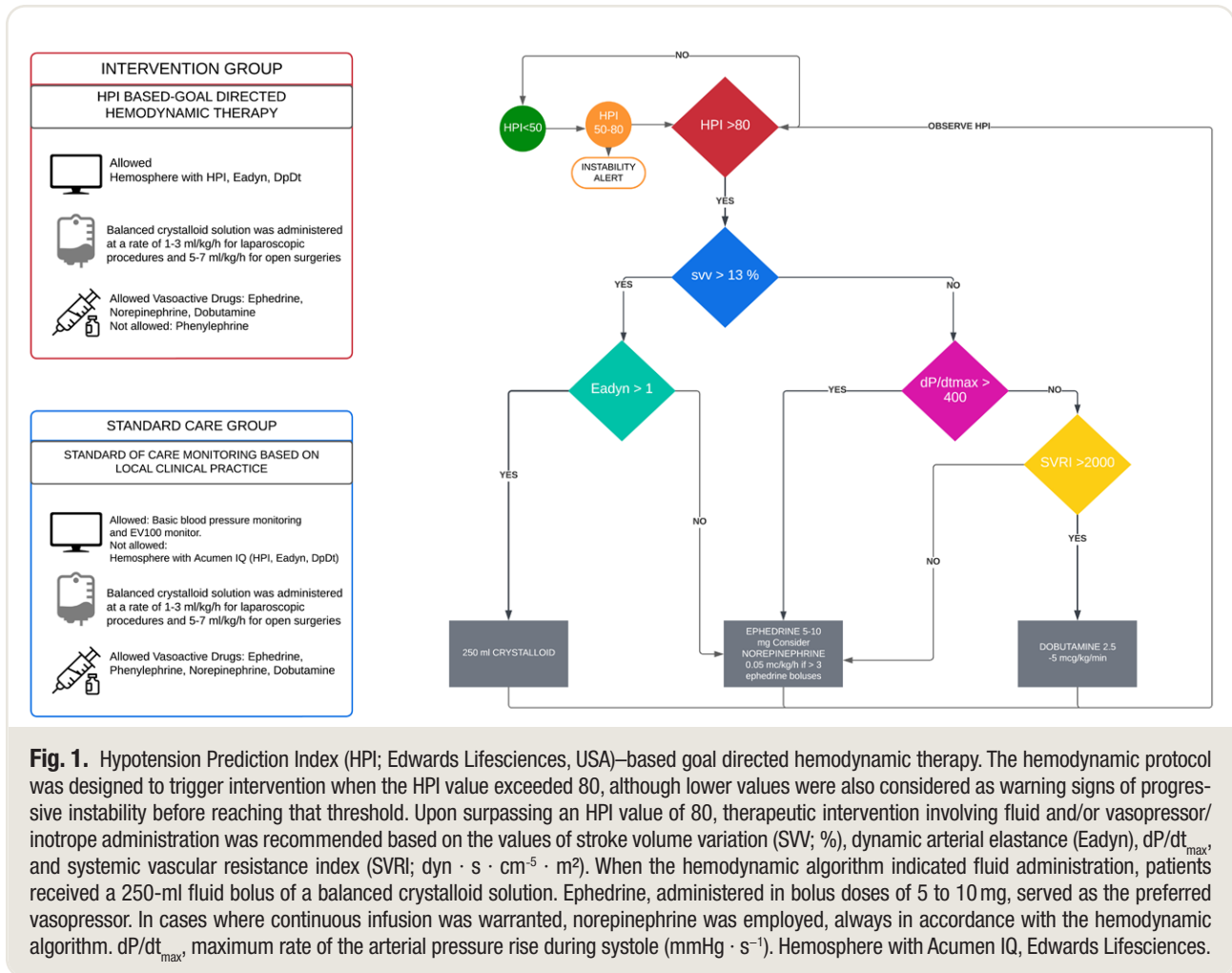


Fig. 1. Hypotension Prediction Index (HPI; Edwards Lifesciences, USA)-based goal directed hemodynamic therapy. The hemodynamic protocol was designed to trigger intervention when the HPI value exceeded 80, although lower values were also considered as warning signs of progressive instability before reaching that threshold. Upon surpassing an HPI value of 80, therapeutic intervention involving fluid and/or vasopressor/inotrope administration was recommended based on the values of stroke volume variation (SVV; %), dynamic arterial elastance (Eadyn), dP/dt_{max} , and systemic vascular resistance index (SVRI; $\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5} \cdot \text{m}^2$). When the hemodynamic algorithm indicated fluid administration, patients received a 250-ml fluid bolus of a balanced crystalloid solution. Ephedrine, administered in bolus doses of 5 to 10 mg, served as the preferred vasopressor. In cases where continuous infusion was warranted, norepinephrine was employed, always in accordance with the hemodynamic algorithm. dP/dt_{max} , maximum rate of the arterial pressure rise during systole ($\text{mmHg} \cdot \text{s}^{-1}$). Hemosphere with Acumen IQ, Edwards Lifesciences.

monitored and discussed with recruiting sites throughout the trial. Independent research staff, not involved in patient care, conducted all data assessments while remaining blinded to treatment groups. Final data cleaning, coding, and statistical analysis were performed by statisticians without access to group allocations.

Outcome Measures

The primary outcome was the occurrence of moderate or severe AKI, defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.²¹ AKI was classified as stage 2 or greater if serum creatinine levels were more than twice the baseline or if urine output was less than $0.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ for 12 h or more (table 1 in the Supplemental Digital Content, <https://links.lww.com/ALN/D796>). These criteria were chosen to ensure an objective and consistent assessment across all study sites. Independent research staff, who were blinded to group allocation, conducted all assessments. Secondary outcomes included the need for renal replacement therapy, AKI occurring between 8 and 30 days postsurgery, and other

postoperative complications, which were graded using the European Perioperative Clinical Outcome definitions²² (Supplemental Digital Content, <https://links.lww.com/ALN/D796>).

Sample Size Calculation

The sample size was calculated to detect an absolute reduction of 5% in the incidence of moderate-to-severe postoperative AKI within 7 days, from an assumed baseline rate of 10%²² to 5%. For the primary analysis, AKI was treated as a binary outcome, and 958 patients were estimated to be required, allowing for a 1:1 allocation ratio, a type I error rate of 5%, and a 10% dropout rate. This calculation provided 80% statistical power.

Statistical Analysis

We conducted primary analyses in the intention-to-treat population, defined as all patients who had undergone randomization. The secondary outcomes were analyzed using the same model. Two-sided *P* values were used throughout, with statistical significance defined as $P < 0.05$. No formal

Table 1. Clinical Characteristics of Patients Included in Analysis

Variable	HPI-based GDHT Group (n = 459)	Standard Care Group (n = 458)
Mean age $\pm$ SD, yr	71.1 $\pm$ 9.4	70.8 $\pm$ 9.9
Male sex, No. (%)	267 (58.3%)	266 (58.1%)
ASA Physical Status, No. (%)		
I/II*	191 (41.6%)	195 (42.5%)
III/IV	268 (58.3%)	263 (57.9%)
Obesity, No. (%)	107 (23.5%)	110 (24.4%)
Comorbidities, No. (%)		
Diabetes mellitus	115 (25.2%)	128 (27.9%)
Hypertension	278 (60.8%)	268 (58.5%)
Chronic pulmonary disease	65 (14.3%)	47 (10.3%)
Ischemic cardiomyopathy	34 (7.4%)	36 (7.9%)
Cirrhosis	7 (1.5%)	14 (3.1%)
Anemia	168 (36.7%)	178 (38.9%)
Preoperative chronic medications, No. (%)		
Diuretics	114 (24.9%)	99 (21.7%)
β Blocker	82 (18.2%)	76 (16.6%)
Statins	170 (37.5%)	177 (38.8%)
Angiotensin antagonist	101 (22.2%)	107 (23.4%)
Oral antihyperglycemic	94 (20.7%)	110 (24.1%)
Nonsteroidal anti-inflammatory	39 (8.5%)	49 (10.7%)
Hemoglobin, g/dl, median [interquartile range]	13.1 [11.8–14.3]	13.0 [11.8–14.4]
Creatinine, mg/dl, median [interquartile range]	0.80 [0.70–0.96]	0.82 [0.70–0.99]
Type of surgery, No. (%)		
Colorectal	261 (56.8%)	270 (59.2%)
Gastric	23 (5.0%)	28 (6.1%)
Pancreatic	57 (12.4%)	53 (11.6%)
Prostatectomy	31 (6.8%)	29 (6.4%)
Cystectomy	14 (3.1%)	15 (3.3%)
Gynecologic	20 (4.4%)	11 (2.4%)
Other	53 (11.6%)	52 (11.2%)
Oncologic surgery, No. (%)	420 (91.5%)	423 (92.7%)
Surgical approach, No. (%)		
Laparoscopic	300 (65.4%)	285 (62.2%)
Open	159 (34.6%)	173 (37.9%)
Median duration of surgery, min [interquartile range]	220 [160–300]	218 [165–285]
Type of anesthesia, No. (%)		
Inhaled	137 (29.9%)	122 (26.8%)
Total intravenous	322 (70.2%)	336 (73.8%)
Epidural analgesia, No. (%)	123 (26.8%)	132 (29.0%)

*ASA I patients comprised 0.7% of the cohort.

ASA, American Society of Anesthesiologists; GDHT, goal directed hemodynamic therapy; HPI, Hypotension Prediction Index (Edwards Lifesciences, USA).

adjustment for multiplicity was applied to the primary and secondary outcomes, while Bonferroni correction was used for the subgroup analyses. Baseline data were summarized descriptively based on the treatment received, without formal statistical comparisons. The treatment effects, 95% CIs, and *P* values were reported for all analyses.

The primary analysis of the primary outcome (AKI) was initially conducted using mixed-effects Poisson regression treating institutions as random intercepts to account for

interinstitutional variability, and the model was adjusted for categorical variables (surgical procedure, sex, ASA Physical Status classification) and continuous variables (age and baseline creatinine). Risk ratios were reported for the primary outcome. Risk ratios presented in the main text are adjusted for prespecified covariates, while crude risk ratios are provided in appendix 1. All the models adhered to the intention-to-treat principle. Detailed reports were generated for both intervention and standard care groups, including absolute frequencies and relative percentages.

Univariate analyses were used to compare the categorical secondary outcomes between the intervention and standard care groups. For each secondary postoperative complication, mixed-effects logistic regression models were employed, again treating the institutions as random intercepts. These models were further adjusted for surgical procedure, age, sex, ASA Physical Status, and baseline creatinine level. Time to discharge was analyzed using time-to-event models, with mortality treated as a competing risk. The effect size for the secondary outcomes was reported using risk ratios. A cause-specific Cox model was applied to account for the influence of mortality on the analysis.

Subgroup analyses were performed by testing for interactions between subgroup characteristics (*e.g.*, age, surgical modality, ASA classification, comorbidities) and treatment allocation using interaction terms in the regression models. Estimates at the subgroup level were also calculated. The use of vasopressors during surgery was recorded for all patients. The total dose and type of vasopressors administered were analyzed as a process measure to compare hemodynamic management between the HPI-guided and control groups.

Sensitivity Analyses

Sensitivity analyses were conducted to evaluate the robustness of the findings. Baseline characteristics and secondary outcomes were imputed using multiple imputation analysis using 10 sets of complete baseline (age, sex, ASA Physical Status classification, surgical procedure) and outcome data for all randomized participants.²³ We also performed other sensitivity analysis by excluding patients who received cardiac output monitoring in the standard care group and those who underwent noninvasive HPI monitoring. Cumulative incidence was used to estimate the occurrence of the primary outcome. Furthermore, AKI status was evaluated daily up to postoperative day 7 while patients remained hospitalized, with time recorded in days. Patients who did not experience an AKI event were censored on day 7.

Protocol Deviations

We preferred to use the mixed-effects Poisson regression analysis to obtain risk ratios rather than odds ratios. In sensitivity analysis, we also designed a time-to-event analysis for our primary outcome, which was analyzed using a mixed-effects Cox hazard regression model with institutions

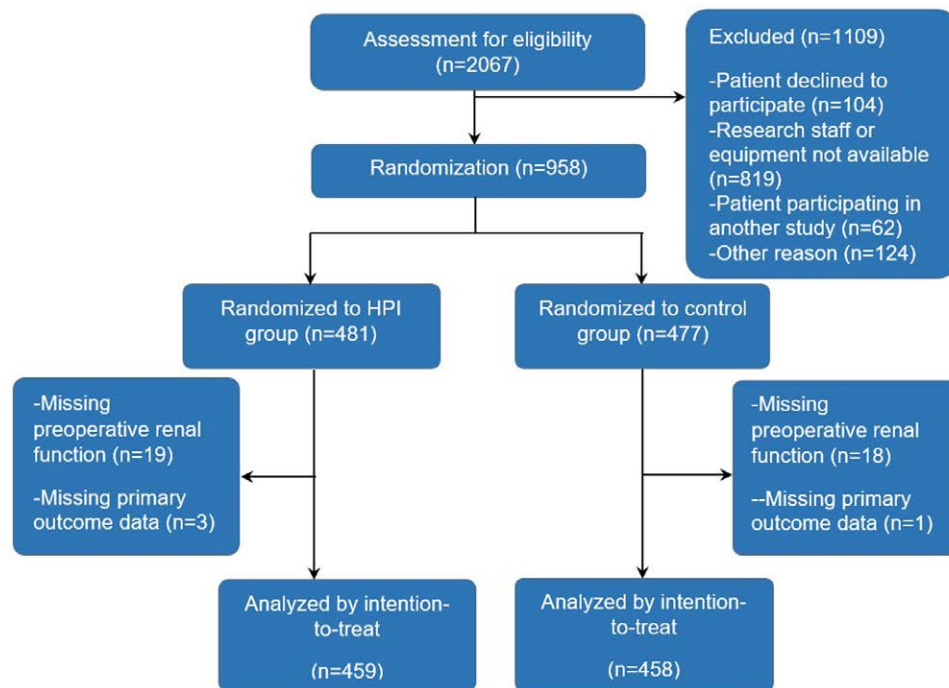


Fig. 2. Consolidated Standards of Reporting Trials (CONSORT) diagram of patient selection. HPI, Hypotension Prediction Index.

as random intercepts and adjusting for the same covariates (surgical procedure, sex, ASA Physical Status classification, age, and baseline creatinine).

All statistical analyses were conducted using Stata version 14.0 (StataCorp LLC, USA).

Results

Study Population

Of the 958 randomized patients, 41 were excluded because of incomplete preoperative and postoperative renal function data. A total of 917 patients were included from October 2022 to February 2024 in the intention-to-treat analysis. Figure 2 shows a flowchart of patient selection in this trial. The mean age of the patients was 71 ± 8 yr, 58% (533 of 917) were male, and 57.9% (531 of 917) were classified as ASA Physical Status III/IV. Most patients underwent laparoscopic abdominal surgery (63.7%; 584 of 917), and colorectal surgery was the most common (58.0%; 532 of 917). There was no evidence of covariate imbalance between groups at baseline (table 1).

Intraoperative Management

Patients allocated to the HPI group received more vasopressor support (89.1% [409 of 459] *vs.* 76.9% [352 of 458]; $P < 0.001$), with a higher utilization of ephedrine (88.2% [405 of 459] *vs.* 68.6% [312 of 458]) and norepinephrine (21.4% [98

of 459] *vs.* 16.7% [76 of 458]; table 2). None of the patients in the HPI group received phenylephrine, while 23.5% (108 of 458) of the patients in the standard care group did. No differences were observed in the fluids administered intraoperatively (table 2). In the HPI group, 20.7% (95 of 459) of the patients were monitored noninvasively (*i.e.*, no arterial line). In the standard care group, 45.9% (210 of 458) of patients underwent cardiac output monitoring during surgery.

Data on protocol deviations, including frequency, nature, and reasons, are provided in table 2 in the Supplemental Digital Content (<https://links.lww.com/ALN/D796>).

Primary Outcome

The incidence of moderate-to-severe AKI was 6.1% (28 of 459) in the HPI group and 7.0% (32 of 458) in the standard care group (risk ratio, 0.89; 95% CI, 0.54 to 1.49; $P = 0.66$). The overall AKI rate was 22.2% (102 of 459) in the HPI group and 25.6% (117 of 458) in the standard care group (risk ratio, 0.87; 95% CI, 0.67 to 1.14; $P = 0.31$; table 3). Crude risk ratios are provided in appendix 1. The time-to-event analysis (fig. 3) did not show significant differences in the overall AKI and moderate-to-severe AKI between the groups. The effect of HPI-guided hemodynamic management on the risk of moderate-to-severe AKI was consistent across prespecified subgroups (fig. 4), except in patients without a history of hypertension. In this subset, the HPI group showed a lower incidence of moderate-to-severe AKI (risk

Table 2. Intraoperative Hemodynamic Management Characteristics

Variable	HPI-based GDHT Group (n = 59)	Standard Group (n = 458)	P Value
Median crystalloid administration [interquartile range], ml	1,650 [1,205–2,500]	1,700 [1,250–2,500]	0.72
Median colloid administration [interquartile range], ml*	250 [100–500]	300 [225–500]	0.43
Blood transfusion, No. (%)	31 (6.8%)	32 (7.1%)	0.86
Median urinary output [interquartile range], ml · kg ⁻¹ · h ⁻¹	1.12 [0.68–1.78]	1.11 [0.67–1.79]	0.82
Median estimated blood loss [interquartile range], ml	200 [100–400]	200 [100–400]	0.72
Vasoactive medications, No. (%)	409 (89.1%)	352 (76.9%)	<0.001
Ephedrine, No. (%)	405 (88.2%)	312 (68.6%)	<0.001
Median dose [interquartile range], mg	30 [16–45]	18 [10–30]	<0.001
Phenylephrine, No. (%)	0 (0.0%)	106 (23.5%)	<0.001
Median dose [interquartile range], mcg	—	300 [200–500]	—
Norepinephrine, No. (%)	98 (21.4%)	76 (16.7%)	0.07
Median dose [interquartile range], mcg	251 [70–625]	400 [140–965]	0.18
Dobutamine, No. (%)	4 (0.9%)	2 (0.4%)	0.69
Median dose [interquartile range], mcg	128 [3–255]	—†	1.00
Noninvasive HPI monitoring, No. (%)	93 (20.7%)	—	—
Cardiac output monitoring, No. (%)	—	207 (45.9%)	—

*Colloids administered in 42 patients in HPI group vs. 80 patients in control group ($P < 0.001$). †Missing dose of dobutamine.

GDHT, goal directed hemodynamic therapy; HPI, Hypotension Prediction Index (Edwards Lifesciences, USA).

ratio, 0.33; 95% CI, 0.12 to 0.89; $P_{\text{interaction}} = 0.021$); however, statistical significance was not reached after correction for multiple hypothesis testing (corrected $P_{\text{interaction}} = 0.11$).

Secondary Outcomes

Renal replacement therapy was required in 1.1% (5 of 459) of patients in the HPI group and 1.1% (5 of 458) in the standard care group (risk ratio, 1.00; 95% CI, 0.30 to 3.67; $P = 0.93$). The rate of kidney injury between 8 to 30 days after surgery was 4.0% (18 of 459) in the HPI group and 4.3% (20 of 458) in the standard care group (risk ratio, 0.98; 95% CI, 0.52 to 1.88; $P = 0.96$). The rate of overall postoperative complications did not differ between the groups (risk ratio, 1.08; 95% CI, 0.85 to 1.37; $P = 0.52$). Crude relative risks are provided in appendix 1.

There were no significant differences in other specific secondary outcomes (table 3) or *post hoc* secondary analyses (fig. 5).

Sensitivity Analysis

After applying multiple imputation to missing data, there were no differences between both groups in the rates of moderate-to-severe AKI (risk ratio, 0.87; 95% CI, 0.51 to 1.48; $P = 0.62$) and overall AKI (risk ratio, 0.84; 95% CI, 0.62 to 1.15; $P = 0.28$). Furthermore, the results of moderate-to-severe AKI did not change significantly after excluding patients who received cardiac output monitoring in the standard care group (6.1% [28 of 459] in the HPI group vs. 5.6% [26 of 458] in the standard care group; $P = 0.78$) or after excluding those who received noninvasive HPI monitoring in the intervention group (7.0% in the HPI group vs. 7.0% in the standard care group; $P = 0.98$).

Discussion

In this international multicenter trial investigating moderate-to-severe postoperative AKI and postoperative complication rates among patients undergoing moderate-to-high-risk elective abdominal surgery, we compared intraoperative goal directed hemodynamic therapy based on HPI versus hemodynamic management not reliant on HPI, reflecting current standard clinical practice. Intraoperative goal directed hemodynamic therapy based on HPI did not reduce the incidence of postoperative AKI within 7 days after surgery. At the 30-day follow-up, no differences in other outcomes were observed.

Previous investigations with limited sample sizes have suggested potential benefits from intraoperative hemodynamic management guided by HPI in mitigating intraoperative hypotension.⁹ While the application of HPI-guided care during surgery resulted in a reduction in both the depth and duration of intraoperative hypotension,⁹ these studies lacked the requisite statistical robustness to comprehensively evaluate patient-centered outcomes. In this study, we focused on patient-centered clinical outcomes such as AKI and postoperative complications. Given the primary interest in postoperative outcomes, we did not specifically assess intraoperative hypotension. Nonetheless, previous research has demonstrated the usefulness of HPI in reducing intraoperative hypotension,⁸ which reinforces the validity of this decision in the context of the trial's objectives. In this large multicenter trial, HPI-guided therapy did not significantly reduce the incidence of postoperative AKI or other complications compared to standard hemodynamic management. While previous smaller studies demonstrated that HPI offers measurable predictive capabilities for managing intraoperative hypotension,^{8,24} our findings suggest

Table 3. Primary and Secondary Outcomes

Outcome	HPI-based GDHT Group (n = 459)	Standard Care Group (n = 458)	Effect Size (95% CI)*	P Value
Acute kidney injury, No. (%)	102 (22.2%)	117 (25.6%)	0.87 (0.67–1.14)	0.31
Moderate to severe, No. (%)	28 (6.1%)	32 (7.0%)	0.89 (0.54–1.49)	0.66
Mild, No. (%)	74 (17.2%)	85 (19.9%)	0.85 (0.62–1.16)	0.33
Renal replacement therapy, No. (%)	5 (1.1%)	5 (1.1%)	1.00 (0.30–3.67)	0.93
Median days of renal replacement therapy [interquartile range], days	2 [1–4]	5 [2–15]	—	0.98
Kidney injury between 8 to 30 days, No. (%)	18 (4.0%)	19 (4.3%)	0.98 (0.52–1.88)	0.96
Overall complications, No. (%)	145 (31.9%)	135 (29.7%)	1.08 (0.85–1.37)	0.52
Moderate to severe, No. (%)	87 (19.2%)	85 (18.7%)	1.02 (0.71–1.43)	0.88
Cardiac complications, No. (%)				
Arrhythmia	9 (2.0%)	10 (2.2%)	0.95 (0.39–2.35)	0.92
Myocardial injury	3 (0.7%)	0 (0.0%)	—	0.12†
Cardiac arrest	3 (1.2%)	0 (0.0%)	—	0.12†
Pulmonary complications, No. (%)				
ARDS	8 (1.8%)	6 (1.4%)	1.21 (0.41–3.57)	0.73
Pneumonia	11 (2.5%)	7 (1.6%)	1.67 (0.65–4.31)	0.29
Pulmonary edema	2 (0.4%)	4 (0.9%)	0.55 (0.10–3.08)	0.50
Pulmonary embolism	1 (0.2%)	2 (0.5%)	0.52 (0.05–5.79)	0.59
Gastrointestinal complications, No. (%)				
Ileus	48 (11.1%)	56 (12.5%)	0.89 (0.61–1.33)	0.59
Bleeding	13 (2.9%)	14 (3.2%)	0.91 (0.54–1.55)	0.74
Other complications, No. (%)				
Surgical site infection	49 (11.1%)	44 (10.1%)	1.12 (0.75–1.70)	0.57
Deep venous thrombosis	4 (0.9%)	1 (0.2%)	4.61 (0.50–42.2)	0.18
Stroke	2 (0.5%)	0 (0.0%)	—	0.25†
Suture dehiscence	27 (6.2%)	30 (6.8%)	0.92 (0.54–1.55)	0.74
Median duration of hospital stay [interquartile range], days	6 [4–10]	6 [4–10]	—	0.45
Readmission, No. (%)	35 (7.8%)	39 (8.6%)	0.88 (0.56–1.39)	0.59
Mortality within 30 days, No. (%)	5 (1.1%)	4 (0.9%)	1.35 (0.36–5.12)	0.66

*Mixed-effects logistic regression was used for analysis of acute kidney injury and secondary outcomes including institutions as random intercepts (reporting risk ratios). †Comparison using Fisher exact test.

ARDS, adult respiratory distress syndrome; GDHT, goal directed hemodynamic therapy; HPI, Hypotension Prediction Index (Edwards Lifesciences, USA).

that these predictive improvements alone do not translate into better postoperative outcomes. Achieving meaningful clinical improvements with HPI-guided management may require therapeutic responses that are tailored to each patient, as the standardized interventions applied in this study may not fully capture the individualized approach necessary to impact in this patient population.

Given the evolving landscape of goal directed hemodynamic therapy,²⁵ integrating these principles into routine care alongside perioperative KDIGO bundles²⁶ may have mitigated the potential benefits observed in earlier studies that focused on alternative goal directed hemodynamic therapy guided by flow optimization.^{25,27,28} Furthermore, strict adherence to perioperative guidelines, even before the introduction of HPI technology, may have contributed to the lack of significant differences between the HPI and standard care groups.

The precise duration of hypotension necessary to cause adverse effects remains unclear, although previous assumptions have implied a graded association between the duration of hypotension and the incidence of postoperative AKI.²⁹ While a trend toward a lower incidence of AKI in the subgroup of patients without chronic hypertension was

observed in the HPI group, this result did not reach statistical significance after correction for multiple hypothesis testing. This finding should be interpreted cautiously, as it does not imply a clinical benefit of HPI-guided therapy in this subgroup. Further research is required to determine whether patient characteristics, such as hypertension, may influence the response to HPI-guided management. Currently, no conclusions regarding the benefit of HPI in hypertensive or nonhypertensive patients can be drawn from these data. Moreover, although the HPI generates alerts regarding the likelihood of hypotension, defined as a MAP less than 65 mmHg, the evidence from the Intraoperative Norepinephrine to Control Arterial Pressure (INPRESS) trial demonstrates that an individualized management approach in patients undergoing abdominal surgery mitigated the risk of postoperative organ dysfunction compared with standard hemodynamic management.²⁸

Conversely, we focused solely on intraoperative HPI-guided care without intervention in postoperative management, potentially explaining the lack of postoperative outcome differences between the HPI and standard care groups. This highlights the importance of postoperative management, especially considering recent findings showing

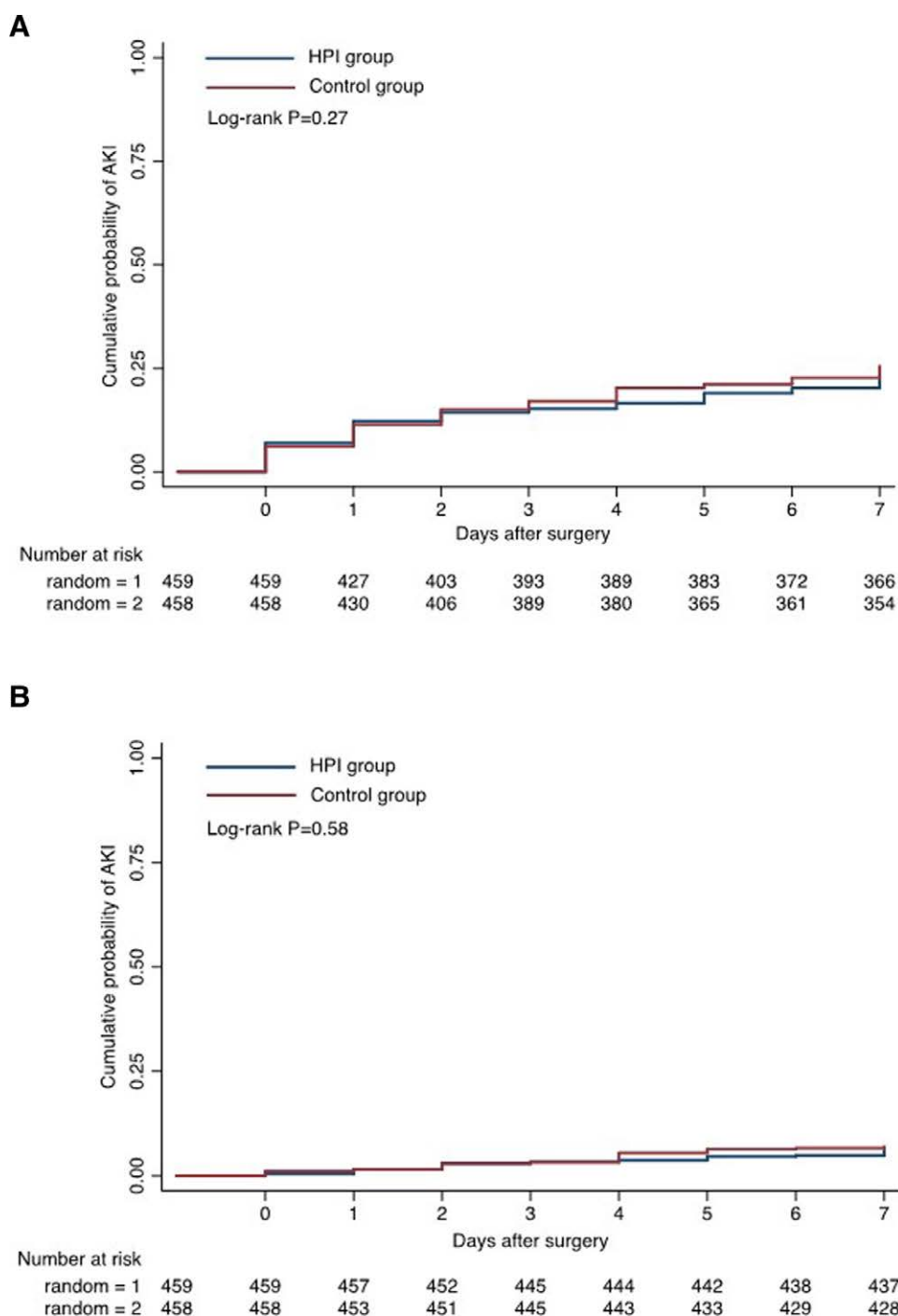
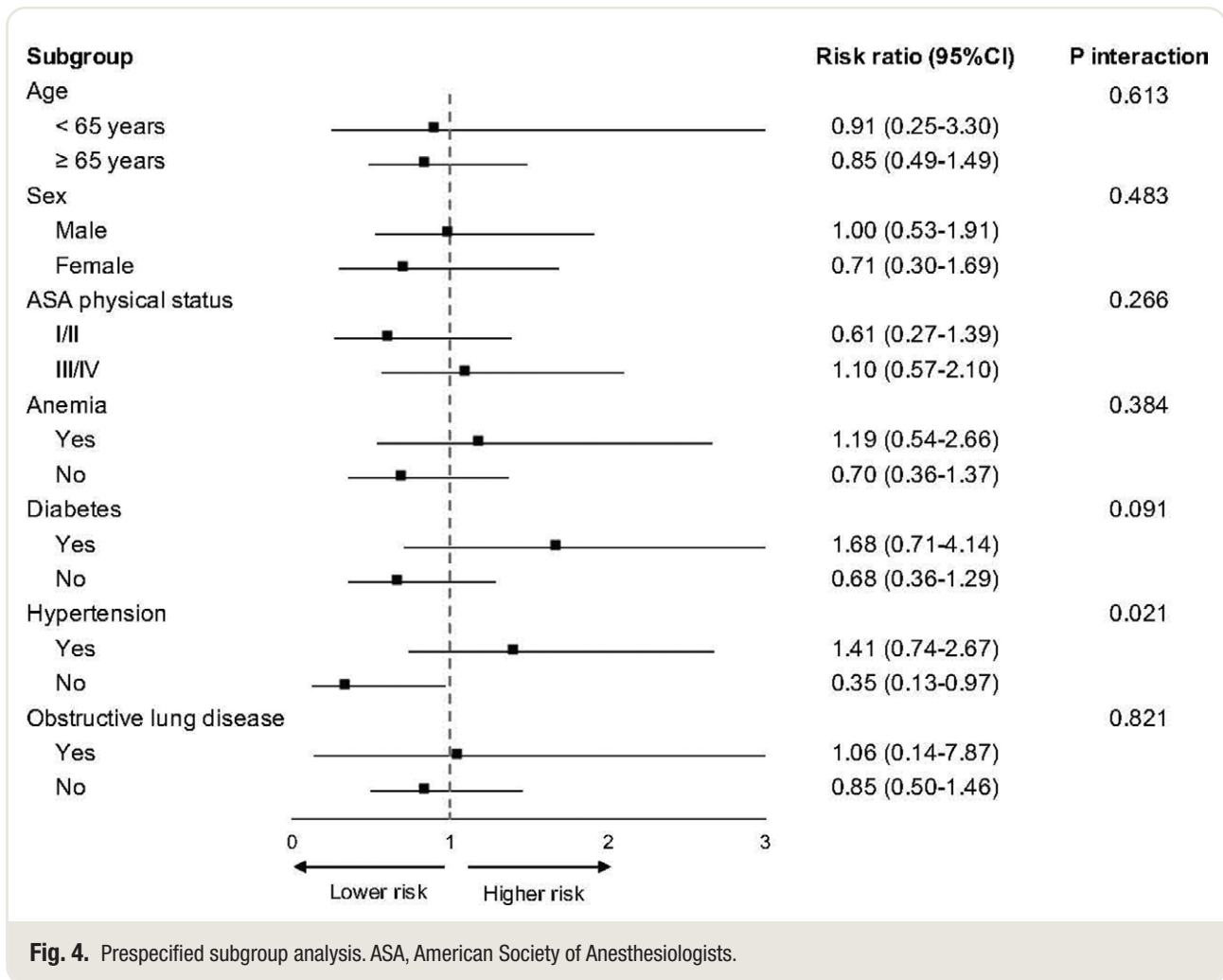


Fig. 3. (A) The cumulative probability of overall acute kidney injury (AKI) within the first 7 days after surgery in the Hypotension Prediction Index (HPI; Edwards Lifesciences, USA) group and the control group. (B) The cumulative probability of moderate-to-severe AKI within the same period is shown. Both panels include the number of patients at risk over time.

that while intraoperative HPI-guided management reduced intraoperative hypotension,³⁰ it had no impact on postoperative hypotension.³¹

In this trial, the limitations of the HPI itself,³² alongside the hemodynamic protocol it triggered, may have contributed

to the lack of significant improvements in outcomes. The HPI's predictive algorithm, while useful for identifying hypotension, may not always translate into meaningful clinical benefits, particularly when applied to a broad patient population. This, combined with the more aggressive



vasopressor management in the HPI group, underscores the need for a more individualized approach to hemodynamic management. Recent retrospective data suggest that prevention and treatment of intraoperative hypotension during abdominal surgery with liberal use of vasopressors at the expense of fluid administration was associated with an increased risk of postoperative AKI.^{33,34} On the other hand, in the intervention group, norepinephrine and ephedrine were used, while phenylephrine was excluded. This difference in vasopressor management may have influenced AKI incidence. Norepinephrine, with its α - and β -adrenergic effects, may preserve renal perfusion more effectively. However, phenylephrine, used in the standard care group, may have sufficiently maintained perfusion pressure to mitigate AKI risk.

Limitations

Our trial had limitations due to the complexity of the intervention, which precluded group allocation blinding and may have introduced bias, particularly favoring the intervention group. However, blinding was not feasible

due to the nature of the hemodynamic monitoring. To mitigate potential bias, the local principal investigator—who remained blinded to group allocation—independently verified the results. Despite the expected bias in favor of the intervention, the absence of clinically meaningful improvements in the HPI group reinforces the conclusion that HPI-guided management did not provide the anticipated benefits. While our power calculation was based on an expected effect size appropriate for a new intervention, the observed variability in patient responses suggests that smaller, more incremental improvements might be more realistic to expect in future studies of similar hemodynamic tools. The trial's nature encompasses various abdominal surgeries and methods of hemodynamic monitoring in the standard care group to ensure generalizability across real-world clinical settings. While certain perioperative care aspects beyond the intervention scope, such as Enhanced Recovery After Surgery protocol adherence,³⁵ lacked uniform standardization, all documented nonprotocolized perioperative care aspects were consistent across the trial groups,

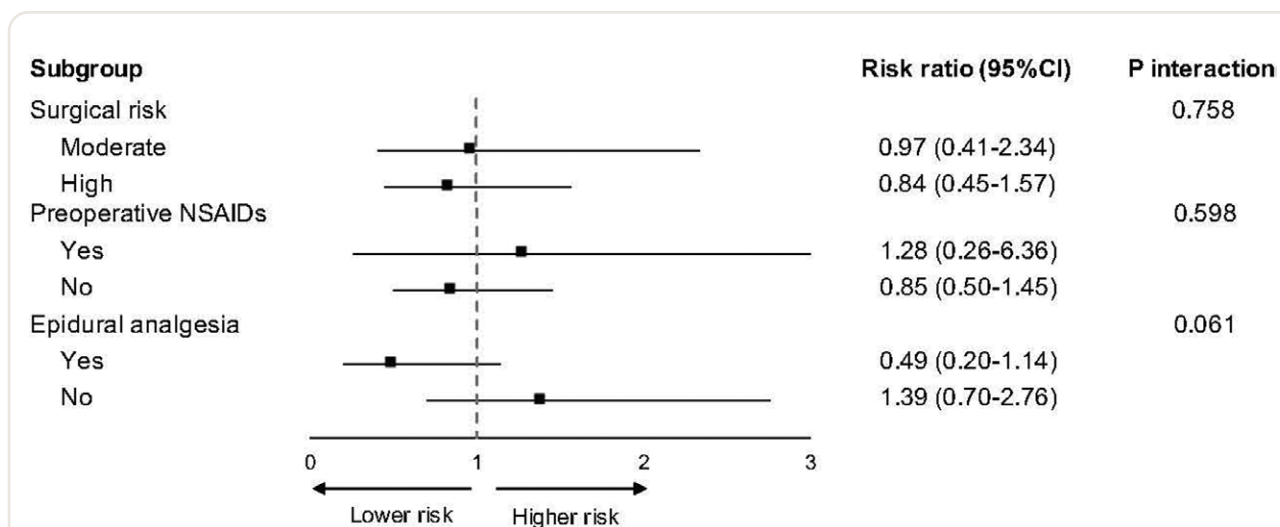


Fig. 5. *Post hoc* subgroup analysis. High surgical risk included pancreatic surgery, total colectomy, rectal surgery, total or subtotal gastrectomy, cystectomy, and complex gynecologic–oncologic surgery. Moderate surgical risk included right hemicolectomy, and prostatectomy. “Other” refers to high-risk abdominal procedures such as cystectomies and combined surgeries involving multiple organ systems, which did not fit into the predefined surgical categories. Comorbidities were obtained from patient medical records, verified by research staff, and reviewed by clinicians during preoperative assessments. Standardized protocols ensured consistency, with uncertainties resolved in consultation with the clinical team. NSAIDs, nonsteroidal anti-inflammatory drugs.

minimizing systemic care differences due to treatment allocation awareness. Another limitation is the absence of intraoperative hemodynamic data. Collecting the real incidence of intraoperative hypotension was not a primary objective of the study, and gathering such data would have introduced significant logistical challenges, especially in the non-HPI group. Moreover, the heterogeneous use of advanced hemodynamic monitoring in this group made standardizing data collection difficult. Additionally, the lack of adherence data to the HPI protocol represents another limitation. Despite all centers receiving thorough training, as suggested by the differences in vasopressor administration, this limits the ability to assess variations in adherence to different components of the protocol, which may influence the generalizability of the study findings. While this decision was aligned with our focus on clinical outcomes, we acknowledge that future studies could benefit from the inclusion of detailed intraoperative data to further explore hemodynamic management during surgery. Due to the sample size calculation being based on a 50% relative risk reduction, the study may have been underpowered to detect smaller yet clinically meaningful differences. The observed lack of improvement across multiple outcomes further suggests that a more individualized therapeutic approach to HPI alerts may be necessary to achieve significant clinical benefits. Moreover, including only sites with pre-existing HPI technology and training may introduce a selection bias favoring the intervention, as familiarity with HPI could enhance implementation. This may limit the generalizability of our findings to centers without previous

HPI experience. Additionally, differences in intervention strategies between the groups, such as the use of cardiac output monitoring, vasopressor choice (norepinephrine in the HPI group *vs.* phenylephrine in the standard care group), and the predictive *versus* reactive management approaches, limit the ability to isolate the specific effect of HPI-guided management on outcomes. These variations make it challenging to attribute the observed results solely to the integration of hypotension prediction by HPI. Finally, although we used single rather than multiple imputation for missing data due to the minimal proportion of missing primary outcomes and the consistency of the observed data, we believe this approach did not compromise the validity of our findings. The robustness of our sensitivity analyses further supports the reliability of these results.

Conclusions

Among patients undergoing major abdominal surgery, intraoperative goal directed hemodynamic therapy based on HPI did not reduce the incidence of postoperative AKI within 7 days after surgery compared with standard hemodynamic management.

Acknowledgments

All listed authors in the HYT Group meet the criteria for authorship. Written permissions were obtained from all individuals named as authors. The corresponding author confirms that such permissions have been secured. Authors agree to make data and materials supporting the results or

analyses presented in their article available upon reasonable request. It is up to the author to determine whether a request is reasonable.

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Competing Interests

Dr. Ripollés-Melchor reports personal fees from Edwards Lifesciences (Irvine, California), Baxter (Deerfield, Illinois), and Fresenius Kabi (Bad Homburg, Germany) outside the submitted work. Dr. Colomina reports personal fees from Octapharma AG (Lachen, Switzerland), Fresenius Kabi, CSL (Melbourne, Australia), and Vifor España (Glattbrugg, Zurich, Switzerland) outside the submitted work. Dr. Lorente reports personal fees from Edwards Lifesciences, BioMérieux (Marcy-l'Étoile, France), Fresenius Kabi, Grifols (Sant Cugat del Vallès, Barcelona, Spain), Vifor Pharma (Glattbrugg, Zurich, Switzerland), and Baxter outside the submitted work. Dr. Carrasco-Sánchez reports personal fees from Edwards Lifesciences outside the submitted work. Dr. Navarro-Pérez reports personal fees from Edwards Lifesciences outside the submitted work. Dr. Pedregosa-Sanz reports personal fees from Edwards Lifesciences outside the submitted work. Dr. Monge-García reports personal fees from Edwards Lifesciences outside the submitted work. The other authors declare no competing interests.

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Supplemental Digital Content

Supplemental Content, <https://links.lww.com/ALN/D796>

1. Study setting, inclusion and exclusion criteria, and common perioperative management in both groups
2. Table 1. Reasons for protocol deviations

3. Table 2. KDIGO criteria
4. European Perioperative Clinical Outcome definitions
5. CONSORT 2010 checklist of information to include when reporting a randomized trial
6. Statistical analysis plan
7. Full study protocol

References

1. Weiser TG, Haynes AB, Molina G, et al.: Estimate of the global volume of surgery in 2012: An assessment supporting improved health outcomes. *Lancet* 2015; 385(suppl 2):S11
2. Zarbock A, Weiss R, Albert F, et al.; EPIS-AKI Investigators: Epidemiology of surgery associated acute kidney injury (EPIS-AKI): A prospective international observational multi-center clinical study. *Intensive Care Med* 2023; 49:1441–55
3. Sun LY, Chung AM, Farkouh ME, et al.: Defining an intraoperative hypotension threshold in association with stroke in cardiac surgery. *ANESTHESIOLOGY* 2018; 129:440–7
4. Lee E-H, Yun S-C, Lim Y-J, Jo J-Y, Choi D-K, Choi I-C: The effects of perioperative intravenous fluid administration strategy on renal outcomes in patients undergoing cardiovascular surgery: An observational study. *Medicine (Baltimore)* 2019; 98:e14383–e1
5. Hatib F, Jian Z, Buddi S, et al.: Machine-learning algorithm to predict hypotension based on high-fidelity arterial pressure waveform analysis. *ANESTHESIOLOGY* 2018; 129:663–74
6. Ripollés-Melchor J, Ruiz-Escobar A, Fernández-Valdes-Bango P, et al.: Hypotension Prediction Index: From reactive to predictive hemodynamic management, the key to maintaining hemodynamic stability. *Front Anesthesiol* 2023; 2. Available at: <https://www.frontiersin.org/articles/10.3389/fanes.2023.1138175>. Accessed October 3, 2024.
7. Lai C-J, Cheng Y-J, Han Y-Y, et al.: Hypotension Prediction Index for prevention of intraoperative hypotension in patients undergoing general anesthesia: A randomized controlled trial. *Perioper Med (Lond)* 2024; 13:57
8. Lorente JV, Ripollés-Melchor J, Jiménez I, et al.: Intraoperative hemodynamic optimization using the hypotension prediction index vs. goal-directed hemodynamic therapy during elective major abdominal surgery: The Predict-H multicenter randomized controlled trial. *Front Anesthesiol* 2023; 2. Available at: <https://www.frontiersin.org/articles/10.3389/fanes.2023.1193886>. Accessed October 3, 2024.
9. Li W, Hu Z, Yuan Y, Liu J, Li K: Effect of Hypotension Prediction Index in the prevention of intraoperative hypotension during noncardiac surgery: A systematic review. *J Clin Anesth* 2022; 83:110981

10. Pilakouta Depaskouale MA, Archonta SA, Katsaros DM, Paidakakos NA, Dimakopoulou AN, Matsota PK: Beyond the debut: Unpacking six years of Hypotension Prediction Index software in intraoperative hypotension prevention – A systematic review and meta-analysis. *J Clin Monit Comput* 2024; 38:1367–77. 1w
11. Mulder MP, Harmannij-Markusse M, Fresiello L, Donker DW, Potters J-W: Hypotension Prediction Index is equally effective in predicting intraoperative hypotension during noncardiac surgery compared to a mean arterial pressure threshold: A prospective observational study. *ANESTHESIOLOGY* 2024; 141:453–62
12. Davies SJ, Sessler DI, Jian Z, et al.: Comparison of differences in cohort (forward) and case control (backward) methodological approaches for validation of the Hypotension Prediction Index. *ANESTHESIOLOGY* 2024; 141:443–52
13. Vistisen ST, London MJ, Mathis MR, van Klei WA, Huzurbazar S, Jacquet-Lagrèze M: Shedding needed light on a black box approach to prediction of hypotension. *ANESTHESIOLOGY* 2024; 141:421–4
14. Wesselink EM, Kappen TH, Torn HM, Slooter AJC, van Klei WA: Intraoperative hypotension and the risk of postoperative adverse outcomes: A systematic review. *Br J Anaesth* 2018; 121:706–21
15. D'Amico F, Fominskiy EV, Turi S, et al.: Intraoperative hypotension and postoperative outcomes: A meta-analysis of randomised trials. *Br J Anaesth* 2023; 131:823–31
16. Ripollés-Melchor J, Carrasco-Sánchez L, Tomé-Roca JL, et al.; HYT Study Group: Hypotension prediction index guided goal-directed therapy to reduce postoperative acute kidney injury during major abdominal surgery: Study protocol for a multicenter randomized controlled clinical trial. *Trials* 2024; 25:288
17. Dixon JRJ: The International Conference on Harmonization good clinical practice guideline. *Qual Assur* 1998; 6:65–74
18. Ripollés-Melchor J, Colomina MJ, Aldecoa C, et al.: Research priorities in perioperative fluid therapy and hemodynamic monitoring: A Delphi Consensus Survey from the Fluid Therapy and Hemodynamic Monitoring Subcommittee of the Hemostasis, Transfusion Medicine and Fluid Therapy Section (SHTF) of the Spanish Society of Anesthesiology and Critical Care (SEDAR). *Rev Esp Anesthesiol Reanim (Engl Ed)* 2023; 70:319–26
19. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG: Research Electronic Data Capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; 42:377–81
20. Harris PA, Taylor R, Minor BL, et al.; REDCap Consortium: The REDCap Consortium: Building an international community of software platform partners. *J Biomed Inform* 2019; 95:103208
21. Ripollés-Melchor J, Valbuena-Bueno MA, Fernández-Valdés-Bango P, et al.: Characterization of intraoperative hemodynamic instability in patients undergoing general anesthesia. *Front Anesthesiol* 2024; 3. Available at: <https://www.frontiersin.org/journals/anesthesiology/articles/10.3389/fanes.2024.1405405>. Accessed November 3, 2024.
22. Bell S, Davey P, Nathwani D, et al.: Risk of AKI with gentamicin as surgical prophylaxis. *J Am Soc Nephrol* 2014; 25:2625–32
23. White IR, Thompson SG: Adjusting for partially missing baseline measurements in randomized trials. *Stat Med* 2005; 24:993–1007
24. Solares GJ, Garcia D, Monge Garcia MI, et al.: Real-world outcomes of the hypotension prediction index in the management of intraoperative hypotension during non-cardiac surgery: A retrospective clinical study. *J Clin Monit Comput* 2023; 37:211–20
25. Jessen MK, Vallentin MF, Holmberg MJ, et al.: Goal-directed haemodynamic therapy during general anaesthesia for noncardiac surgery: A systematic review and meta-analysis. *Br J Anaesth* 2022; 128:416–33
26. Ripollés-Melchor J, Zorrilla-Vaca A, Lorente JV, Weiss R: Is it time to incorporate Kidney Disease Improving Global Outcomes (KDIGO) bundles into Enhanced Recovery After Surgery (ERAS) protocols for colorectal surgery? *Rev Esp Anesthesiol Reanim* 2023; 70:125–8
27. Calvo-Vecino JM, Ripollés-Melchor J, Mythen MG, et al.; FEDORA Trial Investigators Group: Effect of goal-directed haemodynamic therapy on postoperative complications in low-moderate risk surgical patients: A multicentre randomised controlled trial (FEDORA trial). *Br J Anaesth* 2018; 120:734–44
28. Futier E, Lefrant J-Y, Guinot P-G, et al.; INPRESS Study Group: Effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery: A randomized clinical trial. *JAMA* 2017; 318:1346–57
29. Salmasi V, Maheshwari K, Yang D, et al.: Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after noncardiac surgery: A retrospective cohort analysis. *ANESTHESIOLOGY* 2017; 126:47–65
30. Wijnberge M, Geerts BF, Hol L, et al.: Effect of a machine learning-derived early warning system for intraoperative hypotension vs standard care on depth and duration of intraoperative hypotension during elective noncardiac surgery: The HYPE Randomized Clinical Trial. *JAMA* 2020; 323:1052–60

31. Schenk J, Wijnberge M, Maaskant JM, et al.: Effect of Hypotension Prediction Index-guided intraoperative haemodynamic care on depth and duration of postoperative hypotension: A sub-study of the Hypotension Prediction trial. *Br J Anaesth* 2021; 127:681–8
32. Mukkamala R, Schnetz MP, Khanna AK, Mahajan A: Intraoperative hypotension prediction: Current methods, controversies, and research outlook. *Anesth Analg* 2024 [Epub ahead of print]
33. Chiu C, Fong N, Lazzareschi D, et al.: Fluids, vasopressors, and acute kidney injury after major abdominal surgery between 2015 and 2019: A multicentre retrospective analysis. *Br J Anaesth* 2022; 129:317–26
34. Ariyaratna D, Bhonsle A, Nim J, et al.: Intraoperative vasopressor use and early postoperative acute kidney injury in elderly patients undergoing elective noncardiac surgery. *Ren Fail* 2022; 44:648–59
35. Ripollés-Melchor J, Ramírez-Rodríguez JM, Casans-Francés R, et al.; POWER Study Investigators Group for the Spanish Perioperative Audit and Research Network (REDGERM): Association between use of Enhanced Recovery After Surgery protocol and postoperative complications in colorectal surgery: The Postoperative Outcomes Within Enhanced Recovery After Surgery Protocol (POWER) study. *JAMA Surg* 2019; 154:725–11

Appendix 1

1. Crude risk ratios: The crude risk ratio for moderate-to-severe AKI was 0.88 (95% CI, 0.53 to 1.47; $P = 0.64$). For overall AKI, the crude risk ratio was 0.86 (95% CI, 0.66 to 1.13; $P = 0.29$). For overall complications, the crude risk ratio was 1.07 (95% CI, 0.88 to 1.31; $P = 0.47$).
2. Parametrization of baseline covariates was specified as follows: ASA Physical Status (I/II and III/IV), obesity (body mass index greater than 30 kg/m² vs. 30 kg/m² or less), surgical approach (laparoscopic vs. open), and type of anesthesia (inhaled, total intravenous, or combined).

Appendix 2

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