Circulation

ORIGINAL RESEARCH ARTICLE

Ivabradine in Patients Undergoing Noncardiac Surgery: A Randomized Controlled Trial

Wojciech Szczeklik, MD, PhD; Jakub Fronczek, MD, PhD; Zbigniew Putowski, MD, PhD; Anna Włudarczyk, MD, PhD; Jacek Górka, MD, PhD; Bożena Seczyńska, PhD; Dominika Gryszówka, MSc; Agnieszka Widawska, MSc; Szymon Białka, MD, PhD; Piotr Palaczyński, MD, PhD; Michał Borys, MD, PhD; Paweł Kutnik, MD, PhD; Tomasz Czarnik, MD, PhD; Anna Szczepańska, MD, PhD; Marcin Możański, MD, PhD; Marcin Mieszkowski, MD, PhD; Katarzyna Kotfis, MD, PhD; Janusz Trzebicki, MD, PhD; Łukasz Sadowski, MD; Joanna Sołek-Pastuszka, MD, PhD; Paweł Grudzień, MD; Wojciech Mudyna, MD; Agnieszka Misiewska-Kaczur, MD, PhD; Radosław Owczuk, MD, PhD; Bartosz Kudliński, MD, PhD; Dorota Studzińska, MD, PhD; Jarosław Pawlik, MD; Adam Makowski, MD; Mirosław Ziętkiewicz, MD, PhD; Mikołaj Przydacz, MD, PhD; Waldemar Goździk, MD, PhD; Wojciech Gola, MD, PhD; Przemysław Jasiewicz, MD; Zhiguo Zhao, MS; Yu Shyr, PhD; P.J. Devereaux, MD, PhD, on behalf of the PERI-CRIT Investigators*

BACKGROUND: Perioperative beta blockade lowers heart rate and decreases the risk of myocardial infarction but increases the risk of hypotension, death, and stroke. Ivabradine, a selective heart rate–lowering agent, may prevent prognostically important myocardial injury after noncardiac surgery (MINS) without causing hemodynamic instability.

METHODS: In this multicenter, double-blind, placebo-controlled trial, we assigned patients ≥45 years of age with, or at risk of, atherosclerotic disease undergoing noncardiac surgery to receive ivabradine (5 mg orally twice daily for up to 7 days, starting 1 hour before surgery) or placebo. The primary outcome was MINS within 30 days from randomization.

RESULTS: All of the 2101 participants who underwent randomization were included in the intention-to-treat population. MINS occurred in 178 of 1050 patients (17.0%) in the ivabradine group and in 159 of 1051 patients (15.1%) in the placebo group (relative risk, 1.12 [95% CI, 0.92 to 1.37]; *P*=0.25). Enrollment was halted at the prespecified interim analysis because of a conditional power of 6%, below the futility boundary of 20%. The intraoperative mean heart rate was lower in the ivabradine group by 3.2 beats per minute than in the placebo group (95% CI, −4.07 to −2.36), with no difference in intraoperative mean arterial pressure.

CONCLUSIONS: Among patients undergoing noncardiac surgery, ivabradine did not reduce the occurrence of MINS.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT05279651.

Key Words: ivabradine ■ myocardial injury after noncardiac surgery ■ perioperative care ■ troponin

Myocardial injury after noncardiac surgery (MINS) is a common complication associated with short- and long-term morbidity and had an attributable fraction (ie, potential proportion of deaths attributable to this complication provided a causal relationship exists) of 13% for death within.[1] One of the proposed mechanisms contributing to MINS is perioperative tachycardia, which increases myocardial oxygen consumption and leads to a supply-demand mismatch that may result in prognostically important myocardial injury.[2–4]

Correspondence to: Wojciech Szczeklik, MD, PhD, Jagiellonian University Medical College, Centre for Intensive Care and Perioperative Medicine, ul Wrocławska 1-3, 30–901 Krakow, Poland. Email wojciech.szczeklik@uj.edu.pl
*A list of the PERI-CRIT Investigators (Perioperative and Critical Care Research Group) is given in the Appendix in the Supplemental Material.
This work was presented as an abstract at the European Society of Cardiology Congress, Madrid, Spain, August 29–September 1, 2025.
Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.125.076704.
Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.
For Sources of Funding and Disclosures, see page 1135.

Circulation is available at www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- In large multicenter randomized trials, ivabradine did not reduce the risk of myocardial injury after noncardiac surgery.
- Ivabradine modestly lowered heart rate without causing hypotension but was associated with a higher risk of clinically important bradycardia.
- Patients with coronary artery disease receiving ivabradine appeared to have a higher incidence of myocardial injury after noncardiac surgery and adverse cardiovascular outcomes compared with placebo.

What Are the Clinical Implications?

- Ivabradine should not be used for the prevention of myocardial injury after noncardiac surgery in patients undergoing noncardiac surgery.
- Alternative strategies are needed to safely control perioperative sympathetic stress without increasing complications.

Nonstandard Abbreviations and Acronyms

CAD	coronary artery disease
hsTn	high-sensitivity troponin
hsTnI	high-sensitivity troponin I
hsTnT	high-sensitivity troponin T
MINS	myocardial injury after noncardiac surgery
PREVENT-MINS	Ivabradine for Prevention of Myocardial Injury After Noncardiac Surgery
RR	relative risk

A large randomized controlled trial,[5] and subsequent meta-analyses,[6] demonstrated that β blockers reduced heart rate and lowered the risk of perioperative myocardial infarction; however, this benefit was offset by an increased risk of clinically important hypotension, stroke, and mortality. Epidemiological data demonstrated that clinically important hypotension was associated with the increased risk of stroke and death.[5] Ivabradine selectively inhibits the *I* f (pacemaker) current in the sinoatrial node, thereby reducing heart rate without affecting blood pressure or ventricular contractility, a key distinction from beta-blockers. Preliminary perioperative data suggests ivabradine may prevent MINS.[7,8]

We conducted the PREVENT-MINS trial (Ivabradine for Prevention of Myocardial Injury After Noncardiac Surgery) to test the hypothesis that ivabradine, compared with placebo, reduces the risk of 30-day MINS in patients with, or at risk of, atherosclerotic disease undergoing noncardiac surgery.

METHODS

Trial Design

The PREVENT-MINS trial was an investigator-initiated, double-blind, randomized, placebo- controlled superiority trial conducted between June 2022 and April 2025 at 26 hospitals in Poland.[9] The trial protocol was developed by the investigators.[10] No patients or members of the public were involved in the design, conduct, reporting, or dissemination of the trial results. The trial was reported according to the CONSORT checklist (Supplemental Material).

Trial Oversight

The trial was conducted in accordance with the protocol, the Declaration of Helsinki, and Good Clinical Practice guidelines. Approval was obtained from the institutional review board, the Polish Medicines Regulatory Agency, and the European Clinical Trials Information System (CTIS; EU CT No. 2024-515226-81-00).

Jagiellonian University Medical College, the coordinating center, was responsible for the randomization scheme, drug procurement and distribution, trial site coordination, and database validation according to the data management plan. A contract research organization was responsible for trial monitoring, including on-site source document verification. A summary of any changes to the study protocol is available in the Supplemental Material. An independent statistical agency was engaged to monitor data quality and completeness and to identify potential protocol noncompliance. A statistical analysis plan was finalized before any data analysis was initiated and is available in the Supplemental Material. The study database will be made available upon reasonable request after publication of the main results. Interested researchers must submit a scientific proposal to the trial steering committee for review and approval. All shared data will be fully anonymized to protect participant confidentiality. The first author drafted the initial version of the article, and all authors made revisions and made the decision to submit the article for publication.

Patients

Eligible patients were ≥45 years of age, undergoing inpatient noncardiac surgery, and had either established atherosclerotic disease (ie, coronary artery disease [CAD], peripheral artery disease, or previous stroke) or substantial risk factors for atherosclerotic disease. Key exclusion criteria included cardiac conduction abnormalities, recent use of ivabradine, and failure to meet the hemodynamic requirements for study drug administration. A complete list of eligibility criteria is provided in the Supplemental Material.

Procedures

Before surgery, all eligible patients who provided written informed consent and fulfilled hemodynamic criteria (heart rate ≥65 beats per minute and systolic blood pressure ≥90 mm Hg) were randomly assigned in a 1:1 ratio to receive ivabradine or

placebo. Randomization was conducted using an interactive web-based system using random permuted blocks, with stratification by center. Study personnel were unaware of block sizes. Patients, health care providers, data collectors, and outcome adjudicators were blinded to trial group assignments. Chronic β-blocker therapy was maintained throughout the study, with doses neither adjusted nor withheld except for clinically justified reasons.

The first dose of the study drug (ivabradine 5 mg or placebo) was administered on the day of surgery, at least 1 hour before surgery. Subsequent postoperative doses were administered if patients met the required hemodynamic criteria. The first postoperative dose was given either on the evening of surgery or the next morning, at least 12 hours after the preoperative dose. Starting on the day after surgery, patients received ivabradine 5 mg or placebo twice daily until postoperative day 7 or until hospital discharge, whichever occurred first.

Blood samples for measurement of the hsTn (high-sensitivity troponin) level were collected before surgery and daily for the first 3 days after surgery. ECG was performed if the troponin level was elevated. The majority of sites (20 of 26), accounting for 85% of all troponin measurements, used hsTnT (high-sensitivity troponin T) assays (Roche Diagnostics). Details of the troponin assays used at each site are provided in Table S2. Research personnel at participating centers followed patients until 30 days after randomization, collected data, and submitted the case report forms and supporting event documentation directly to the electronic data management system.

Trial Outcomes

The primary outcome was MINS that occurred during or within 30 days after noncardiac surgery.[11] MINS was defined as any elevated postoperative cardiac troponin (including myocardial infarction) judged as resulting from myocardial ischemia and fulfilling the enzymatic criteria:

- For Roche's fifth-generation Elecsys hsTnT, cutoff of 20 ng/L with an absolute change of ≥5 ng/L[11]
- For the Siemens ADVIA Centaur hsTnI (high-sensitivity troponin I), cutoff of 75 ng/L with a change of at least 20%[12]
- For Abbott's hsTnI, cutoff of 60 ng/L with a change of at least 20%[13]
- For other troponin assays, absolute change of at least the upper norm limit was used[14]

In rare cases when only 1 postoperative troponin concentration was available, MINS was diagnosed with higher, previously specified postoperative troponin levels (Supplemental Material).

The secondary, tertiary, and safety outcomes along with all outcome definitions are reported in the Supplemental Material. Two independent adjudicators evaluated all potential cases of MINS to determine if MINS diagnostic criteria were met. The adjudicators' final decision was used for all statistical analyses.

Statistical Analyses

We determined that enrolling 2500 patients would provide 86.4% power to detect a 25% relative risk (RR) reduction with the ivabradine group, at a 2-sided α level of 0.05, on the assumption that the risk of the primary outcome in the placebo group would be 18%, using the Lan-DeMets (O'Brien-Fleming) α spending function that accounts for 2 planned interim analyses conducted when 50% and 75% of the primary outcomes were collected (Table S1).

An independent data and safety monitoring committee reviewed the data and performed prespecified interim analyses after reaching approximately 50% and 75% of the planned number of primary outcomes according to the data and safety monitoring committee charter (Supplemental Material).

The conditional power, based on the method of stochastic curtailment, was used for the early stopping for futility. This procedure evaluates the conditional probability that a particular statistical comparison has the chance to be significant at the end of the trial at the α level used in the design, given the hypothesized treatment difference and the end point data accumulated during the trial. The trigger point to consider termination of the trial was set at conditional power <0.2.

Analyses were based on the intention-to-treat principle, whereby all patients who underwent randomization were evaluated in the group to which they were randomized. For the primary outcome, we used a chi-square test and determined the RR with 95% CIs. We used the same analytic method for all other dichotomous secondary and tertiary outcomes.

Continuous secondary outcomes (ie, days alive and at home, health-related quality-of-life scores, intraoperative mean arterial pressure, intraoperative heart rate, nights in hospital), were analyzed with linear regression models to estimate the mean difference between treatment arms, with corresponding 95% CIs. For the outcomes days in the intensive care unit, peak troponin levels, and area under the curve troponin, we report the analytic approaches in the Supplemental Material.

For the primary outcome, we conducted 4 prespecified subgroup analyses to explore whether the effect of the intervention differed across clinically relevant patient subgroups. These 4 subgroups, along with our hypothesized direction of effect modification in parentheses, were presence versus absence of CAD (greater efficacy expected in patients with coronary disease); baseline heart rate ≥75 versus <75 beats per minute (greater efficacy expected with heart rate ≥75); preoperative troponin level >99th percentile versus ≤99th percentile of the upper reference limit (greater efficacy expected with troponin level >99th percentile); and nonthoracic versus thoracic surgery (greater efficacy expected in nonthoracic surgery). We used a generalized linear model with log-link function to test for an interaction between the treatment assignment and the subgrouping variable. We report the RRs and 95% CIs within each subgroup.

All *P* values are 2-sided, with a *P* value <0.05 considered to indicate statistical significance. Analyses were performed with the use of R software version 4.4 (R Foundation for Statistical Computing).

RESULTS

After its second planned meeting on March 7, 2025, the independent data monitoring committee recommended early termination of the trial for futility, based on the prespecified interim analysis. Among 2043 participants evaluated, the observed event rates were 16.9% (173 of 1025) in the ivabradine arm and 15.4% (157 of 1018)

in the placebo arm. Assuming that the remaining 457 participants experience events at the originally hypothesized rates, 18.0% in the placebo arm and 13.5% in the ivabradine arm, corresponding to a 25% RR reduction, the projected final event rates would be 15.9% for the placebo group and 16.3% for the ivabradine group. Under these assumptions, the conditional power to detect a statistically significant difference at the final analysis (2-sided α=0.044) was estimated to be 5.2%, below the predefined futility threshold of 20%. This

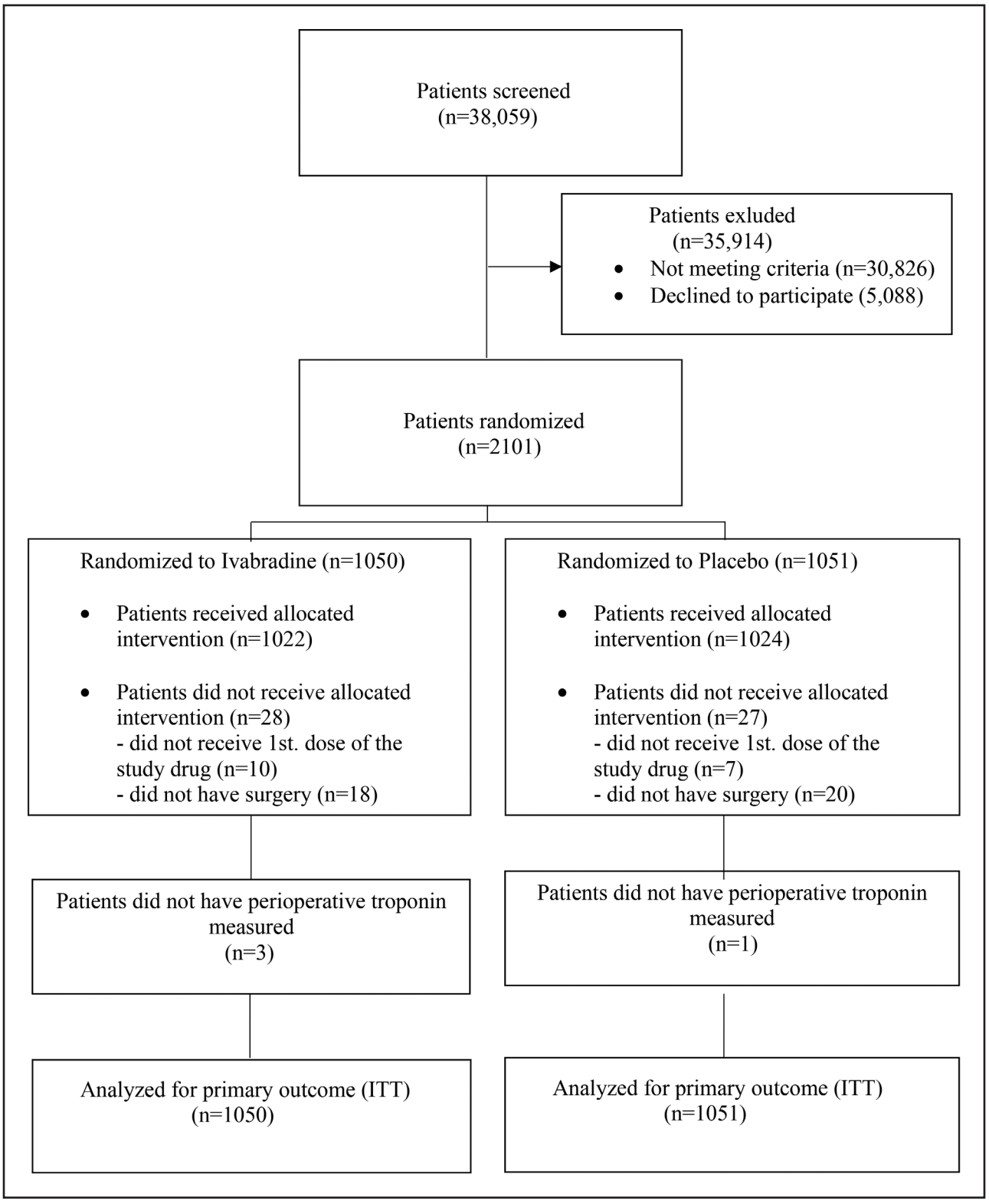

Figure 1. Study flow diagram.

Table 1. Baseline Characteristics, Type of Surgery, Anesthesia, and Perioperative Medications

Characteristic	Ivabradine (N=1050)	Placebo (N=1051)
Age, y	70 (65–74)	70 (65–75)
Male sex, No. (%)	547 (52.1)	515 (49.0)
Eligibility criteria met, No. (%)		
History of coronary artery disease	276 (26.3)	232 (22.1)
History of peripheral artery disease	196 (18.7)	194 (18.5)
History of stroke	82 (7.8)	82 (7.8)
Undergoing major vascular surgery	113 (10.8)	106 (10.1)
Risk criteria*		
Undergoing major surgery†	822 (78.3)	825 (78.5)
History of congestive heart failure	27 (2.6)	21 (2.0)
History of a transient ischemic attack	21 (2.0)	30 (2.9)
Diabetes requiring medication	464 (44.2)	442 (42.1)
Age ≥70 y	587 (55.9)	594 (56.5)
History of hypertension	959 (91.3)	981 (93.3)
Serum creatinine >175 μmol/L (>2.0 mg/dL)	9 (0.9)	10 (1.0)
History of smoking within 2 y of surgery	419 (39.9)	424 (40.3)
Undergoing emergent/urgent surgery	18 (1.7)	21 (2.0)
Median preoperative hemoglobin (IQR), g/L	13.3 (12.0–14.5)	13.4 (12.1–14.5)
Median preoperative systolic blood pressure (IQR), mm Hg	140 (130–151)	140 (129–151)
Median preoperative heart rate (IQR), beats per min	75 (70–80)	76 (70–82)
Median preoperative troponin (IQR) ng/L‡	10.0 (6.5–14.6)	9.6 (6.3–15.0)
Surgery, No. (%)		
Orthopedic	248 (23.6)	249 (23.7)
Urology	183 (17.4)	181 (17.2)
Thoracic	168 (16.0)	177 (16.8)
Vascular	175 (16.7)	168 (16.0)
General	149 (14.2)	132 (12.6)
Gynecological	70 (6.7)	85 (8.1)
Other	52 (4.9)	51 (4.9)
Neurological/spinal	6 (0.6)	7 (0.7)
Anesthesia type, No. (%)		
General	592 (56.4)	600 (57.1)
Regional (spinal or epidural)	303 (28.9)	297 (28.3)
General and regional (spinal/epidural)	98 (9.3)	93 (8.8)
Other	32 (3.0)	39 (3.7)
Procedure duration (min)	130 (90–182)	130 (95–177)
ASA Physical Status Classification System, No./total No. (%)		
I	0 (0.0)	1 (0.1)
II	455 (43.3)	496 (47.2)
III	575 (54.8)	536 (51.0)
IV	19 (1.8)	18 (1.7)
V	1 (0.1)	0 (0.0)
Medications taken within 24 h before surgery, No./total No. (%)		
Beta-blocker	609 (58.0)	590 (56.1)
ACE inhibitor/ARB	534 (50.9)	520 (49.5)
Dihydropyridine calcium channel blocker	293 (27.9)	333 (31.7)

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASA, American Society of Anesthesiologists; and IQR, interquartile range.

*Meeting this eligibility criterion involved meeting ≥3 of the 9 risk criteria listed here.

†Major surgery was defined as undergoing an intraperitoneal, intrathoracic, retroperitoneal, or major orthopedic procedure.

‡Values represent the median pool troponin concentration across all assays.

recommendation was accepted by the steering committee and agreed to by the sponsor.

Patients, Adherence, and Follow-Up

We randomized 2101 patients to receive ivabradine (n=1050) or placebo (n=1051) (Figure 1). Baseline characteristics, type of noncardiac surgeries and anesthesia, and preoperative medications were well balanced between the groups (Table 1). The median age of the patients was 70.0 years (interquartile range, 65–74), and 49.4% were women. The median preoperative heart rate was 75 (interquartile range, 70–81).

The median length of hospital stay was 5 days (interquartile range, 4–8 days). Overall, 898 of 1050 (85.5%) patients in the ivabradine group and 911 of 1051 (86.7%) patients in the placebo group took at least 90% of the doses of the study drug while they were in the hospital. In 2097 of 2101 patients (99.8%), at least one postoperative troponin measurement was obtained, and in 1340 patients (63.8%), at least 3 postoperative measurements were performed. The 30-day follow-up was completed in 2089 of 2101 (99.4%) participants.

Outcomes

The primary outcome MINS occurred in 178 of 1050 patients (17.0%) receiving ivabradine and in 159 of 1051 patients (15.1%) receiving placebo (RR, 1.12 [95% CI, 0.92–1.37]; P=0.25). Among patients with MINS, 7 of 178 in the ivabradine group and 10 of 159 in the placebo group fulfilled the criteria for myocardial infarction (Table 2). A total of 325 (96.5%) MINS events occurred

Table 2. Effects of Ivabradine on the Primary, Secondary, and Safety Outcomes at 30 Days

Outcome	Ivabradine (N=1050)	Placebo (N=1051)	Relative risk (95% CI)
Primary outcome			
MINS	178 (17.0)	159 (15.1)	1.12 (0.92 to 1.37) *P*=0.25
Secondary outcomes			
Vascular death or nonfatal MINS, stroke, or cardiac arrest	192 (18.3)	166 (15.8)	1.16 (0.96 to 1.4)
Myocardial infarction	7 (0.7)	10 (1.0)	0.7 (0.27 to 1.84)
Perioperative myocardial infarction/injury*	115 (11.0)	106 (10.1)	1.09 (0.85 to 1.4)
Vascular death	8 (0.8)	3 (0.3)	2.67 (0.71 to 10.05)
Stroke	6 (0.6)	4 (0.4)	1.50 (0.42 to 5.31)
All-cause mortality	15 (1.3)	14 (1.4)	1.07 (0.52 to 2.21)
New clinically important atrial fibrillation	6 (0.6)	13 (1.2)	0.46 (0.18 to 1.21)
Cancellation/postponement of surgery because of HR concerns	0 (0)	0 (0)	…
Cancellation/postponement of surgery because of troponin elevation concerns	0 (0)	1 (0)	…
Days alive and at home, days, median (IQR)	26 (24 to 28)	26 (24 to 28)	0.03 (−0.43 to 0.50)‡
Health-related quality of life,† median (IQR)	0.94 (0.89 to 0.98)	0.94 (0.89 to 0.98)	−0.00 (−0.02 to 0.01)‡
Intraoperative mean arterial pressure, mm Hg, median (IQR)	82 (75 to 89)	83 (75 to 90)	−0.61 (−1.56 to 0.34)‡
Intraoperative heart rate, bpm, median (IQR)	65 (60 to 70)	68 (62 to 75)	−3.22 (−4.07 to −2.36)‡
Safety outcomes			
Clinically significant bradycardia	236 (22.5)	200 (19.0)	1.18 (1.00 to 1.40)
Clinically significant hypotension	399 (38.0)	366 (34.8)	1.09 (0.97 to 1.22)
Phosphenes	1 (0.1)	0 (0.0)	…

bpm indicates beats per minute; HR, heart rate; IQR, interquartile range; and MINS, myocardial injury after noncardiac surgery.
*PMI defined by the 2022 European Society of Cardiology guidelines on cardiovascular assessment and management of patients undergoing noncardiac surgery.
†Health-related quality of life calculated as an index of EuroQoL 5 Dimension tool.
‡Presented as the mean difference (95% CI).

up to 3 days after surgery (during protocolized troponin screening), and the remaining 12 events occurred after this period. The composite outcome of vascular death or nonfatal MINS, stroke, or cardiac arrest occurred in 192 patients (18.3%) in the ivabradine group and 166 patients (15.8%) in the placebo group (RR, 1.16 [95% CI, 0.96–1.40]).

The median time from drug or placebo administration to induction of anesthesia was 120 minutes (interquartile range, 70–240 minutes). The intraoperative mean heart rate was lower in the ivabradine group by −3.22 beat per minute than in the placebo group (95% CI, −4.07 to −2.36), with no difference in the intraoperative mean arterial pressure. Similar differences were recorded postoperatively ≥12 hours after the primary dose (Figure 2). Clinically important bradycardia was more common in the ivabradine group (RR, 1.18 [95% CI, 1.00 to 1.40]). There was no interaction between β-blocker use and the study intervention (Table S3). Only 1 participant in the ivabradine group experienced phosphenes. Primary, secondary, and safety outcomes are reported in Table 2 and tertiary outcomes in Table 3. Patients in the ivabradine group had fewer episodes of intraoperative tachycardia >100 beats per minute compared with the placebo group (59 of 1050 [5.6%] versus 95 of 1051 [9.0%]).

Ivabradine or placebo was withheld in total in 167 patients—109 in the ivabradine group and 58 in the placebo group. In 109 patients (74 in the ivabradine group and 35 in the placebo group), the drug or placebo was withheld at the evening dose on the day of surgery. The study drug was reintroduced in 131 of the 167 patients (78%); of these, 85 were in the ivabradine group and 46 in the placebo group.

Prespecified Subgroup Analyses

The 4 prespecified groups subgroup analyses are presented in Figure 3. Among patients with a history of CAD, ivabradine was associated with a RR of MINS of 1.49 (RR, 1.49 [95% CI, 1.03–2.16]) compared with placebo; however, the interaction *P* value was not significant (*P*=0.059). In the same subgroup, the RR of the composite vascular outcome in a post hoc, exploratory analysis was 1.55 (95% CI, 1.09–2.21).

DISCUSSION

In this trial, ivabradine did not reduce the incidence of MINS compared with placebo in patients undergoing noncardiac surgery. Ivabradine lowered the intraoperative

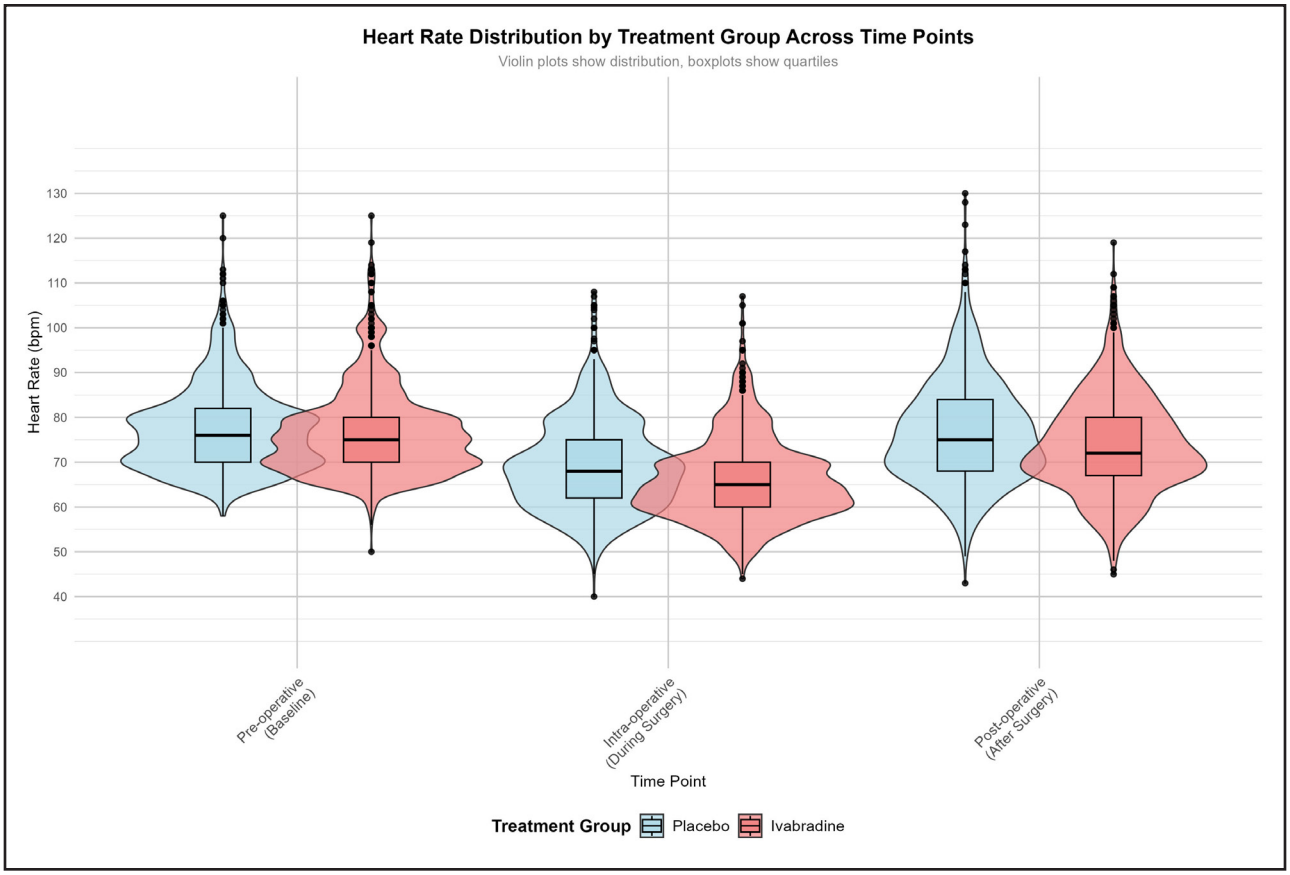

Figure 2. Heart rate distribution by treatment group allocation across time points.
Postsurgery troponin measurement ≥12 hours after the preoperative dose of ivabradine (typically on the evening of surgery or the next morning).

mean heart rate but only by 3 beats per minute compared with placebo and increased the risk of clinically important bradycardia. Ivabradine did not affect intraoperative mean arterial pressure and was not associated with a higher incidence of hypotension.

The majority of MINS events (96.5%) occurred within the first 3 postoperative days during protocolized troponin surveillance. This aligns with the VISION study data, which established the definition and prognostic importance of MINS, in which only 0.6% of events were detected beyond the third postoperative day.[11,16] The MINS definition encompasses both myocardial injury and myocardial infarction in the perioperative period. Of the 337 MINS events, 17 met the criteria for myocardial infarction.

PREVENT-MINS was based on the hypothesis that ivabradine, by lowering heart rate without inducing hypotension, would reduce myocardial oxygen consumption and thereby prevent MINS. This rationale was supported by previous studies investigating perioperative use of beta-blockers.[5] Ivabradine did, in fact, lower heart rate compared with placebo without causing hypotension; however, the reduction in heart rate was modest and notably smaller than the effect typically observed with β blockade.[5] Considering clinically important bradycardia as a surrogate for heart rate control, ivabradine demonstrated an increase in risk relative to placebo (RR, 1.18 [95% CI, 1.00–1.40]); however, metoprolol controlled release in POISE-1 (Perioperative Ischemic Evaluation Study 1) demonstrated a much larger increase compared with placebo (hazard ratio, 2.74 [95% CI, 2.19–3.43]).

Ivabradine reaches peak plasma concentration approximately 1 hour after oral administration, with a distribution half-life of about 2 hours and an effective half-life of roughly 6 hours.[17] Given the mean 2-hour interval from ivabradine/placebo administration to the induction of anesthesia (not <1 hour) and the intraoperative observation of more frequent bradycardia and less frequent tachycardia in the ivabradine group compared with placebo, along with modest but consistent heart rate differences between groups, we believe the study drug was active.

During the study period, 2 other, smaller studies evaluated the effects of perioperative ivabradine. A 2-center Australian trial conducted in 199 patients undergoing urgent orthopedic surgery showed that ivabradine reduced heart rate by an average of 5 to 11 beats per minute compared with placebo.[7] There was no significant difference in the incidence of perioperative

Table 3. Effects of Ivabradine on the Tertiary Outcomes at 30 Days

Tertiary outcome	Ivabradine (N=1050)	Placebo (N=1051)	Relative risk (95% CI)
Cardiac revascularization	0 (0.0)	2 (0.2)	…
Rehospitalization for vascular reasons	5 (0.5)	6 (0.6)	0.83 (0.26 to 2.72)
Nonfatal cardiac arrest	3 (0.3)	1 (0.1)	3.00 (0.31 to 28.82)
Acute congestive heart failure	3 (0.3)	1 (0.1)	3.00 (0.31 to 28.82)
Deep vein thrombosis/pulmonary embolism	3 (0.3)	1 (0.1)	3.00 (0.31 to 28.82)
Bleeding independently associated with mortality after noncardiac surgery*	88 (8.4)	82 (7.8)	1.08 (0.81 to 1.44)
Bleeding according to the ISTH criteria	28 (2.7)	44 (4.2)	0.64 (0.40 to 1.02)
Infection	78 (7.4)	76 (7.2)	1.03 (0.76 to 1.39)
Sepsis	14 (1.3)	13 (1.2)	1.08 (0.51 to 2.28)
Acute kidney injury	139 (13.2)	123 (11.7)	1.13 (0.90 to 1.42)
Amputation	7 (0.7)	7 (0.7)	1.00 (0.35 to 2.84)
Peak troponin concentration (ng/L)			
Roche's fifth generation Elecsys hsTnT	15.0 (9.9 to 23.2)	14.3 (10.0 to 21.1)	1.00 (0.94 to 1.06)†
Siemens ADVIA Centaur hsTnI	9.5 (5.6 to 16.6)	9.8 (5.6 to 26.2)	0.81 (0.69 to 0.95)†
Abbott's hsTnI	9.6 (5.3 to 26.6)	6.7 (5.0 to 12.3)	1.51 (1.12 to 2.02)†
Other troponin assays	5.4 (2.9 to 19.0)	13.0 (4.7 to 14.5)	1.10 (0.75 to 1.60)†
Area under the curve troponin (ng/L × day)			
Roche's fifth generation Elecsys hsTnT	27.2 (17.9 to 41.1)	26.0 (18.3 to 37.5)	1.01 (0.95 to 1.06)†
Siemens ADVIA Centaur hsTnI	16.3 (10.0 to 27.1)	17.5 (9.9 to 38.3)	0.86 (0.74 to 0.99)†
Abbott's hsTnI	14.8 (10.0 to 35.9)	10.8 (10.0 to 24.0)	1.33 (1.01 to 1.74)†
Other troponin assays	9.4 (4.8 to 31.0)	21.7 (7.9 to 26.3)	1.1 (0.78 to 1.55)†
Length of hospital stay, days	5 (4 to 7)	5 (3 to 8)	−0.15 (−0.56 to 0.27)†
Days outside the intensive care unit, days	5 (4 to 8)	5 (4 to 7)	0.95 (0.54 to 1.69)‡

hsTnI indicates high-sensitivity troponin I; hsTnT, high-sensitivity troponin T; ISTH, International Society on Thrombosis and Haemostasis; and MINS, myocardial injury after noncardiac surgery.

*Based on the bleeding independently associated with mortality after noncardiac surgery (BIMS) criteria.[15]

†Presented as ratio of geometric means (95% CI).

‡Presented as the rate ratio (95% CI).

myocardial injury between the ivabradine and placebo groups (28.6% versus 31.6%); however, among those who sustained myocardial injury, the ivabradine group had a lower average peak troponin concentration than the placebo group.

The second trial was a single-center pilot study in patients 45 to 75 years of age with cardiovascular risk factors undergoing intermediate- or high-risk noncardiac surgery.[8] Seventy-nine patients were randomized to receive a tailored dose of ivabradine (2.5 to 7.5 mg) based on preoperative heart rate, administered up to 2 days postoperatively. Both studies concluded that larger trials are warranted.

In contrast with the mentioned studies, in PREVENT-MINS, we chose to use a fixed dose of 5 mg BID. Dose titration, as applied in the management of chronic heart failure, requires weeks to months of follow-up to achieve the target heart rate. In the perioperative setting, such an approach is not feasible because most patients are seen only shortly before surgery, randomization occurred on the day of surgery, and the majority of MINS events occur within the first 48 hours postoperatively. Therefore, we selected a pragmatic, fixed starting dose of 5 mg BID, which is commonly used as an initial dose and was considered safe in the context of potential perioperative hemodynamic instability.

Contrary to the initial hypothesis that participants with a history of CAD would have a greater benefit from the intervention, in our sample, ivabradine was observed to have an almost 50% greater risk of MINS compared with placebo. In a post hoc analysis, the composite vascular outcome also appeared more frequent among patients with CAD receiving ivabradine compared with those receiving placebo. A similar effect was observed in the large SIGNIFY trial (Study Assessing the Morbidity–Mortality Benefits of the I_f Inhibitor Ivabradine in Patients With Coronary Artery Disease) that evaluated the long-term effects of ivabradine in patients with CAD and without heart failure.[18] In that trial, ivabradine was associated with an increased incidence of the primary

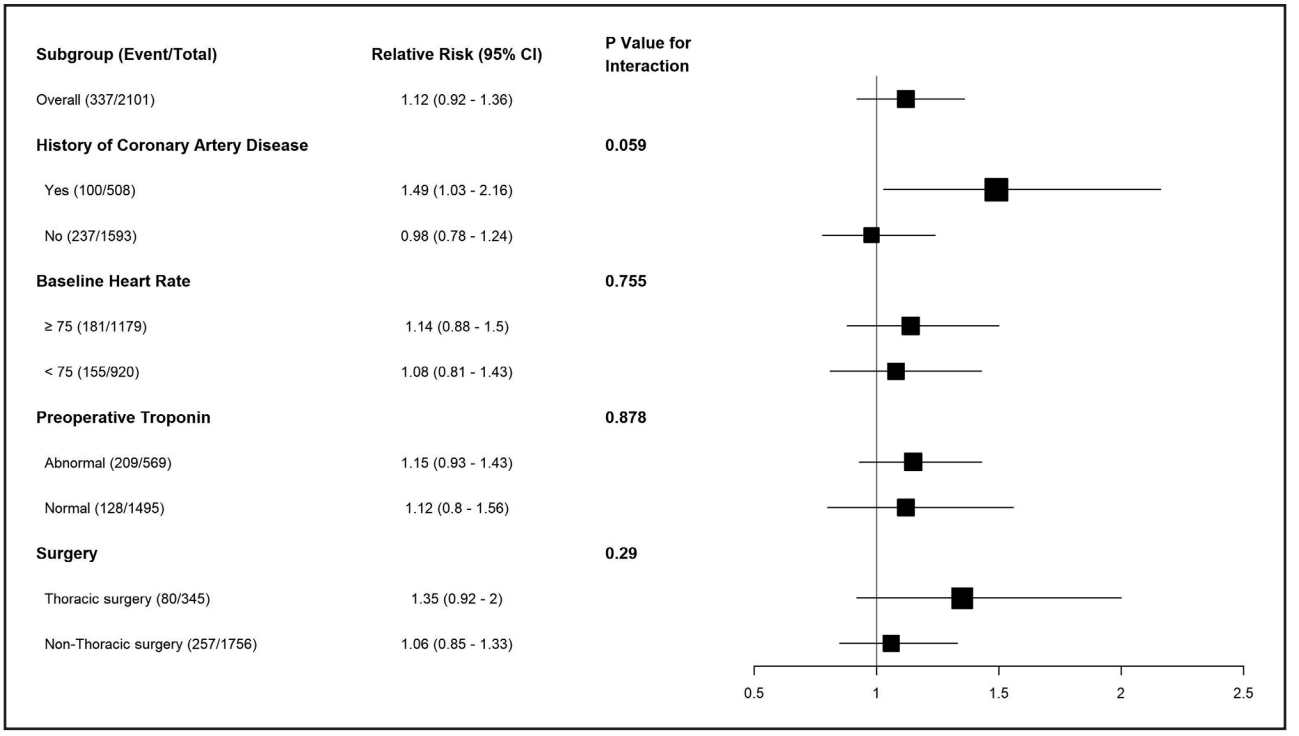

Figure 3. Subgroup analyses.
The size of the square indicates the effect size (relative risk).

composite end point of cardiovascular death or nonfatal myocardial infarction in patients with activity-limiting angina (hazard ratio, 1.18 [95% CI, 1.03–1.35]). In contrast, no such increase was observed in patients without activity-limiting angina (hazard ratio, 0.89 [95% CI, 0.74–1.08]). It is possible that the PREVENT-MINS and SIGNIFY subgroup effects represent chance findings; however, it is also possible that ivabradine causes negative physiological effects that increase the risk of major cardiovascular complications in patients with CAD with activity-limiting angina or undergoing noncardiac surgery.

Strengths of the trial include a large sample size and good protocol adherence. Limitations of the study include its conduct in a single country, which may limit generalizability despite involvement of many sites. Like other multicenter cardiovascular trials, we allowed for the use of different troponin assays depending on local standards. That said, the majority of sites used hsTnT, which comprised 85% of all troponin measurements. The study was not large enough to rule out all safety concerns (eg, mortality, stroke) as demonstrated in POISE trial. The study was also stopped prematurely after reaching 84% of the planned sample size because of meeting futility criteria. Furthermore, we evaluated a fixed dose of ivabradine, and a dose titrated according to heart rate might have produced different results.

In this trial, ivabradine did not reduce the risk of MINS in patients undergoing noncardiac surgery. Further research is needed to establish a method to safely control the sympathetic stress associated with noncardiac surgery.

ARTICLE INFORMATION

Received July 29, 2025; accepted August 15, 2025.

Affiliations

Centre for Intensive Care and Perioperative Medicine (W.S., J.F., Z.P., A. Władarczyk, J.G., B.S.), Jagiellonian Center for Clinical Trials (D.G., A. Widawska), Department of Anesthesiology and Intensive Care (M.Z.), Department of Urology (M.P.), Jagiellonian University Medical College, Krakow, Poland. Department of Anesthesiology and Intensive Care, Faculty of Medical Sciences in Zabrze (S.B., P.P.), Department of Anesthesiology and Intensive Care, School of Medicine in Katowice (A.S.), Medical University of Silesia, Katowice, Poland. Faculty of Medicine, Institute of Medical Sciences, John Paul II Catholic University of Lublin, Poland (M.B., P.K.). Department of Anesthesiology and Intensive Care, Institute of Medical Sciences, University of Opole, Poland (T.C.). Department of Anesthesiology and Intensive Care, Military Institute of Medicine-National Research Institute, Warsaw, Poland (M. Możański). Department of Anesthesiology and Intensive Care, School of Medicine, Collegium Medicum, University of Warmia and Mazury, Olsztyn, Poland (M. Mieszkowski). Department of Anesthesiology, Intensive Care and Pain Management (K.K.), Department of Anesthesiology and Intensive Therapy (J.S.-P.), Pomeranian Medical University in Szczecin, Poland. 1st Department of Anesthesiology and Intensive Care (J.T.), 2nd Department of Anesthesiology and Intensive Care (A.M.), Medical University of Warsaw, Poland. Department of Anesthesiology and Intensive Therapy, Central Teaching Hospital of the Medical University of Lodz, Poland (Ł.S.). Department of Anesthesiology and Intensive Therapy, Specialized Hospital of E. Szczeklik in Tarnów, Poland (P.G.). Department of Anesthesiology and Intensive Therapy, Ludwik Rydygier Memorial Specialist Hospital in Krakow, Poland (W.M.). Department of Anesthesiology and Intensive Therapy, Silesian Hospital in Cieszyn, Poland (A.M.-K.). Department of Anesthesiology and Intensive Therapy, Faculty of Medicine, Medical University of Gdansk, Poland (R.O.). Department of Anesthesiology, Intensive Care and Emergency Medicine, Collegium Medicum, University of Zielona Gora, Poland (B.K.). Faculty of Medical Sciences, Academy of Silesia, Katowice, Poland (D.S.). Faculty of Medicine and Health Sciences, Andrzej Frycz Modrzewski Krakow University, Poland (J.P.). 2nd Department of Anesthesiology and Intensive Care, Saint John Paul

II Hospital in Krakow, Poland (M.Z.). Clinical Department of Anesthesiology and Intensive Therapy, Wroclaw Medical University, Poland (W. Goździk). The Institute of Health Sciences, Department of Nursing, Midwifery and Emergency Medicine, Collegium Medicum, Jan Kochanowski University in Kielce, Poland (W. Gola). Department of Anesthesiology and Intensive Care, Nicolaus Copernicus University Ludwik Rydygier Collegium Medicum in Bydgoszcz, Poland (P.J.). Department of Biostatistics and Center for Quantitative Sciences (Z.Z., Y.S.), Vanderbilt University, Nashville, TN. Departments of Health Evidence and Impact and Medicine and Population Health Research Institute, McMaster University, and the World Health Research, Hamilton, Canada (P.J.D.).

Acknowledgments

The authors would like to thank the patients and their families for participating in this trial; all the bedside clinicians who supported this work; the collaborating research teams and investigators in the trial centers; interim analysis statistician Huang Shi; members of the management committee and trial steering committee; members of the Polish Perioperative Research Group (PERI-CRIT); and members of the Data Monitoring Committee (Christian S. Meyhoff, Fei Ye, and Pierre Foex).

Sources of Funding

This research has been financed by Medical Research Agency, Poland (Agencja Badań Medycznych, Polska), grant No. 2019/ABM/01/00019.

Disclosures

None.

Supplemental Material

CONSORT (Consolidated Standards of Reporting Trials) Checklist
Protocol Changes Summary
Study Inclusion Criteria
Study Exclusion Criteria
Outcome Definitions
Supplemental Methodological Information
Tables S1–S3
PREVENT-MINS Investigators and Committees
Statistical Analysis Plan
Data Monitoring Committee Charter

REFERENCES

1. Spence J, LeManach Y, Chan MTV, Wang CY, Sigamani A, Xavier D, Pearse R, Alonso-Coello P, Garutti I, Srinathan SK, et al; Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators. Association between complications and death within 30 days after noncardiac surgery. *CMAJ*. 2019;191:E830–E837. doi: 10.1503/cmaj.190221
2. Devereaux PJ, Xavier D, Pogue J, Guyatt G, Sigamani A, Garutti I, Leslie K, Rao-Melacini P, Chrolavicius S, Yang H, et al; POISE (Perioperative Ischemic Evaluation) Investigators. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. *Ann Intern Med*. 2011;154:523–528. doi: 10.7326/0003-4819-154-8-201104190-00003
3. Abbott TEF, Pearse RM, Archbold RA, Ahmad T, Niebrzegowska E, Wragg A, Rodseth RN, Devereaux PJ, Ackland GL. A prospective international multicentre cohort study of intraoperative heart rate and systolic blood pressure and myocardial injury after noncardiac surgery: results of the VISION study. *Anesth Analg*. 2018;126:1936–1945. doi: 10.1213/ANE.0000000000002560
4. Ladha KS, Beattie WS, Tait G, Wijeysundera DN. Association between preoperative ambulatory heart rate and postoperative myocardial injury: a retrospective cohort study. *Br J Anaesth*. 2018;121:722–729. doi: 10.1016/j.bja.2018.06.016
5. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, et al; POISE Study Group. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet*. 2008;371:1839–1847. doi: 10.1016/S0140-6736(08)60601-7
6. Wijeysundera DN, Duncan D, Nkonde-Price C, Virani SS, Washam JB, Fleischmann KE, Fleisher LA; ACC/AHA Task Force Members. Perioperative beta blockade in noncardiac surgery: a systematic review for the 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130:2246–2264. doi: 10.1161/CIR.0000000000000104
7. Rafiudeen R, Barlis P, Hau R, Vasanthakumar S, Ng R, Wu P, Tacey M, Banning A, van Gaal W. Ivabradine in the prevention, and reduction in size, of perioperative myocardial injury in patients undergoing orthopedic surgery for acute fracture. *J Am Heart Assoc*. 2023;12:e028760. doi: 10.1161/JAHA.122.028760
8. White MJ, Zaccaria I, Ennahdi-Elidrissi F, Putzu A, Dimassi S, Luise S, Diaper J, Mulin S, Baudat AD, Gil-Wey B, et al. Personalised perioperative dosing of ivabradine in noncardiac surgery: a single-centre, randomised, placebo-controlled, double-blind feasibility pilot trial. *Br J Anaesth*. 2024;133:738–747. doi: 10.1016/j.bja.2024.05.020
9. Szczeklik W. The formation of a collaborative network in Poland: the Perioperative and Critical Care Research Group (PERI-CRIT). *Anaesthesiol Intensive Ther*. 2025;57:1–3. doi: 10.5114/ait.2025.147587
10. Szczeklik W, Fronczek J, Putowski Z, Władarczyk A, Górka J, Seczyńska B, Gryszówka D, Widawska A, Białka S, Palaczyński P, et al. Ivabradine for prevention of myocardial injury after noncardiac surgery (PREVENT-MINS trial): study protocol for a randomized controlled trial [In press]. Trials. doi: 10.1186/s13063-025-09087-z
11. Devereaux PJ, Biccard BM, Sigamani A, Xavier D, Chan MTV, Srinathan SK, Walsh M, Abraham V, Pearse R, Wang CY, et al; Writing Committee for the VISION Study Investigatorsfor the VSI. Association of postoperative high-sensitivity troponin levels with myocardial injury and 30-day mortality among patients undergoing noncardiac surgery. *JAMA*. 2017;317:1642–1651. doi: 10.1001/jama.2017.4360
12. Borges FK, Duceppe E, Heels-Ansdell D, Patel A, Sessler DI, Tandon V, Chan M, Pearse R, Srinathan S, Garg AX, et al. High-sensitivity troponin I predicts major cardiovascular events after non-cardiac surgery: a Vascular Events in Non-Cardiac Surgery Patients Cohort Evaluation (VISION) substudy. *Clin Chem*. 2023;69:492–499. doi: 10.1093/clinchem/hvad005
13. Duceppe E, Borges FK, Tiboni M, Pearse R, Chan MTV, Srinathan S, Kavsak PA, Garg AX, Sessler DI, Sapsford R, et al. High-sensitivity cardiac troponin I thresholds to identify myocardial injury after noncardiac surgery: a cohort study. *Can J Cardiol*. 2023;39:311–318. doi: 10.1016/j.cjca.2023.01.008
14. Halvorsen S, Mehilli J, Cassese S, Hall TS, Abdelhamid M, Barbato E, De Hert S, de Laval I, Geisler T, Hinterbuchner L, et al; ESC Scientific Document Group. 2022 ESC guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery. *Eur Heart J*. 2022;43:3826–3924. doi: 10.1093/eurheartj/ehac270
15. Roshanov PS, Eikelboom JW, Sessler DI, Kearon C, Guyatt GH, Crowther M, Tandon V, Borges FK, Lamy A, Whitlock R, et al. Bleeding independently associated with mortality after noncardiac surgery (BIMS): an international prospective cohort study establishing diagnostic criteria and prognostic importance. *Br J Anaesth*. 2021;126:163–171. doi: 10.1016/j.bja.2020.06.051
16. Ruetzler K, Smilowitz NR, Berger JS, Devereaux PJ, Maron BA, Newby LK, de Jesus Perez V, Sessler DI, Wijeysundera DN. Diagnosis and management of patients with myocardial injury after noncardiac surgery: a scientific statement from the American Heart Association. *Circulation*. 2021;144:e287–e305. doi: 10.1161/CIR.0000000000001024
17. Cada DJ, Bindler R, Baker DE. Ivadradine. *Hosp Pharm*. 2015;50:806–817. doi: 10.1310/hpj5009-806
18. Fox K, Ford I, Steg PG, Tardif JC, Tendera M, Ferrari R; SIGNIFY Investigators. Ivabradine in stable coronary artery disease without clinical heart failure. *N Engl J Med*. 2014;371:1091–1099. doi: 10.1056/NEJMoa1406430