Randomized Comparison of Sevoflurane vs. Propofol to Reduce Perioperative Myocardial Ischemia in Patients Undergoing Noncardiac Surgery

Running title: Lurati Buse et al.; Sevoflurane to reduce myocardial ischemia

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Abstract:

Background—Volatile anesthetics provide myocardial preconditioning in coronary surgery patients. We hypothesized that sevoflurane compared to propofol reduces the incidence of myocardial ischemia in patients undergoing major noncardiac surgery.

Methods and Results—We enrolled 385 patients at cardiovascular risk in 3 centers. Patients were randomized to maintenance of anesthesia with sevoflurane or propofol. We recorded continuous ECG (cECG) for 48 hours perioperatively, measured troponin T and NT-proBNP on postoperative days (POD) 1 and 2, and evaluated postoperative delirium by the Confusion Assessment Method. At 6 and 12 months, we contacted patients by phone to assess major adverse cardiac events (MACE). The primary endpoint was a composite of myocardial ischemia detected by cECG and/or troponin elevation. Additional endpoints were postoperative NT-proBNP concentrations, MACE, and delirium. Patients and outcome assessors were blinded. We tested dichotomous endpoints by chi-squared and NT-proBNP by Mann-Whitney test on an intention-to-treat basis. Myocardial ischemia occurred in 75 patients (40.8%) in the sevoflurane and 81 (40.3%) in the propofol group (relative risk [RR], 1.01; 95% confidence interval [CI], 0.78-1.30). NT-proBNP release did not differ across allocation on POD 1 or 2. Within 12 months, 14 patients (7.6%) suffered a MACE after sevoflurane and 17 (8.5%) after propofol (RR, 0.90; 95% CI, 0.43-1.87). The incidence of delirium did not differ (11.4% vs. 14.4%, P=0.760)

Conclusions  Compared to propofol, sevoflurane did not reduce the incidence of myocardial ischemia in high-risk patients undergoing major noncardiac surgery. The sevoflurane and propofol groups did not differ in postoperative NT-proBNP release, MACE at 1 year, or delirium.

Clinical Trial Registration Information—http://www.clinicaltrials.gov/; Identifier: NCT00286585

Key words: acute coronary syndrome; cardiovascular events; preconditioning; volatile anesthetics
Introduction

Cardiac complications after noncardiac surgery represent a major population health problem. In a large study in noncardiac surgical patients aged ≥45 years with atherosclerosis or at risk for it, myocardial infarction was found in 5% and troponin release in 8% of patients. In a noncardiac surgical population with documented coronary artery disease (CAD) or at high risk for it, we have previously found troponin elevation in 16% and myocardial ischemia in continuous electrocardiography (cECG) in 46% of patients. Multiple studies have reported an independent association between postoperative myocardial ischemia and major adverse cardiac events (MACE) and mortality, both short- and long-term. The estimated global volume of surgical procedures amounts to 200 million per year. As such, every year millions of patients may suffer a perioperative myocardial ischemia after noncardiac surgery, and even more patients are at risk for future cardiac events.

There is extensive evidence from animal studies supporting a protective preconditioning effect of volatile anesthetics on ischemic myocardial injury. In patients undergoing coronary artery bypass graft (CABG) surgery, there is some preliminary but inconsistent evidence suggesting clinically relevant preconditioning by volatile anesthetics. Volatile anesthetics significantly reduced troponin release in a meta-analysis of 32 randomized controlled trials (RCT); however, the results showed relevant heterogeneity. Further, the results were not conclusive regarding mortality. A systematic review and meta-analysis that included studies comparing sevoflurane vs. total intravenous anesthesia (TIVA) during CABG surgery found similar results for on-pump CABG but did not detect a preconditioning effect of sevoflurane in off-pump CABG patients. In contrast, Landoni and coworkers found a significant reduction of inhospital mortality and inhospital myocardial infarction without heterogeneity in their meta-

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analysis in studies addressing either sevoflurane or desflurane vs. TIVA during cardiac surgery.

Based on this preliminary but promising evidence in patients undergoing on-pump CABG surgery, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend the use of volatile anesthetics as beneficial in hemodynamically stable patients at cardiovascular risk undergoing noncardiac surgery (Class IIa recommendation).

However, data on myocardial preconditioning by volatile anesthetics during noncardiac surgery are scarce. A systematic review failed to retrieve studies with data on perioperative myocardial ischemia in patients undergoing noncardiac surgery, and a small RCT published in the meantime did not detect any protective effect of volatile anesthetics on cardiovascular endpoints in noncardiac surgical patients.

The objective of the Trial on the Effect of Anesthetics on Morbidity and Mortality (TEAM) (NCT00286585) was to evaluate the hypothesis that anesthesia maintenance with sevoflurane compared to propofol reduces the incidence of myocardial ischemia in patients at cardiovascular risk who undergo major noncardiac surgery.

**Methods**

**Study Design**

After approval from the local ethics committee (Ethikkommission beider Basel), we conducted a parallel RCT with fixed 1:1 allocation at a tertiary care center, the University Hospital Basel, Switzerland (February 2006 to October 2010) and at 2 secondary care centers, the Bürgerspital Solothurn, Switzerland (August 2006 to October 2010) and the Kantonsspital Liestal (May 2007 to November 2007), Switzerland. We used a computer-generated random allocation sequence stratified by site and by β-blocker intake without randomization blocks (see Limitations).
Allocation concealment occurred by numbered, sealed, opaque envelops. Research personnel enrolled the patients after the preoperative visit by the anesthetist to ensure that general anesthesia was the planned technique. Randomization took place shortly before surgery. Patients, laboratory personnel, outcome adjudicators, and data analyzers were blinded to allocation. Anesthesiologists were not blinded, because they could easily guess allocation even when using a double dummy.

**Eligibility Criteria**

Patients scheduled for surgery under general anesthesia were eligible if they either 1) had proven CAD and were scheduled for major surgery or 2) had two or more risk factors for CAD and were scheduled for major *vascular* surgery.

Proof of CAD was predefined as a history of myocardial infarction or coronary revascularization, or a >50% stenosis in coronary angiography, or myocardial ischemia induced by radionuclide or echocardiographic stress testing. Major surgery was defined as high or intermediate risk according to the AHA/ACC guidelines.11,14 We considered head and neck surgery to result in intermediate risk11,14 in presence of an expected duration >120 minutes and potential blood loss ≥1000 mL.15 Eligible procedures included thoracotomies; laparotomies; orthopedic surgeries of spine, hip, pelvis or lower limb; open urologic surgeries of prostate, kidney, or bladder; and extensive neck and throat surgery (eg, neck dissection).

The predefined risk factors for CAD were age >70 years, diabetes mellitus requiring treatment (oral antidiabetics or insulin), arterial hypertension, history of stroke, functional capacity <4 MET, absence of sinus rhythm, and abnormal ECG (signs of left ventricular hypertrophy, left bundle branch block abnormalities of the ST-segment or T-wave). Major vascular surgery was defined as open surgery of the abdominal aorta or lower limb arteries.
We excluded patients in case of: 1) current medication with sulfonylurea derivatives\textsuperscript{16} or theophylline\textsuperscript{17} unless stopped $\geq 2$ days before surgery, as these drugs reportedly inhibit anesthetic preconditioning; 2) current congestive heart failure; 3) current unstable angina pectoris; 4) preoperative hemodynamic instability, defined as the use of vasopressors; 5) hepatic disease, defined as ALAT and/or ASAT values $>100$ U/L; 6) renal insufficiency, defined as creatinine clearance $<30$ mL/min; 7) emergent surgery; 8) severe chronic obstructive pulmonary disease, defined as FEV1 $<1$ L; 9) prior enrollment in the study; 10) concurrent enrollment in another RCT; 11) pregnancy; or 12) absence of written informed consent.

**Intervention**

The study protocol mandated anesthesia induction with etomidate in all patients and anesthesia maintenance with the allocated drug (sevoflurane or propofol). The agent was started immediately after anesthesia induction and confirmation of the correct tube position. In accordance to the pragmatic purpose of the study, the protocol did not regulate dosage for the induction or maintenance of anesthesia, or any other aspects of the intraoperative management. Thus, the anesthesiologist in charge was not limited in the decision of choice and dosage of opioids, muscle relaxants, fluids or transfusion of blood products, and choice of vasopressor, if any. Also, extent of perioperative monitoring, type of postoperative analgesia, and specifics of postoperative care were at the discretion of the attending physicians.

**Outcomes**

The predefined primary endpoint was a composite of any ischemic episode, as detected by 3-lead cECG and/or by troponin T elevation on postoperative days 1 and 2. The definition of ischemia by cECG followed the guidelines for cECG interpretation and required a ST-segment deviation of $\geq 1$ minute duration.\textsuperscript{18}
Secondary endpoints were the single components of the primary composite endpoints (myocardial ischemia detected by cECG, or troponin elevation) and a composite of myocardial ischemia by the cECG, troponin elevation, and postoperative Q-wave development (Minnesota codes I.1.a-g, I.2.a-i, I.3.a-c). Minnesota code I.2. and I.3. represent the more sensitive but less specific Q and QS patterns than those applied in clinical routine to define Q-waves infarctions (Minnesota codes I.1). Additional secondary endpoints were postoperative NT-proBNP release, MACE, and all-cause mortality after discharge up to 12 months. MACE were defined as a composite of cardiac death, acute coronary events, and congestive heart failure or arrhythmia requiring hospitalization. Acute coronary events included unstable angina, non-ST-elevation myocardial infarction, or ST-elevation MI. Congestive heart failure requiring hospitalization was defined as hospitalization in consequence of clinical (respiratory rales, S3, jugular venous distension) and radiological signs (vascular redistribution, interstitial pulmonary edema, and alveolar edema) of heart failure.

Tertiary endpoints were postoperative delirium (according to the Confusion Assessment Method [CAM]), postoperative nausea and vomiting (PONV), and patient satisfaction. Patient reports of nausea or vomiting, or postoperative therapeutic use of antiemetics were defined as evidence of PONV.

**Monitoring and Methods of Follow-up and Outcome Adjudication**

Three-lead cECG monitoring (Schiller MT 100 or Schiller MT 101, Schiller Reomed AG, Baar, Switzerland) was applied shortly before anesthesia induction and recorded for 48 hours. The leads were an inferior lead, V5, and an inverse Nehb J lead. Troponin T and NT-proBNP were measured before induction of anesthesia and on postoperative days 1 and 2. A 12-lead ECG was recorded preoperatively and on postoperative day 7 or on the day of hospital discharge,
whichever occurred first. Research personnel visited the patients shortly after surgery and on postoperative days 1, 2, and 7 to ensure compliance with the cECG and troponin monitoring and to assess CAM, PONV, and overall patient satisfaction. Patient satisfaction was assessed using a numeric rating score (NRS) with a range from 0 to 10, the latter indicating highest satisfaction. Blinded research personnel contacted the patients by phone 6 and 12 months after randomization. If patients reported an event after discharge, the research personnel contacted their treating physicians to obtain appropriate documentation.

Two trained, blinded investigators independently analyzed the cECG and adjudicated on myocardial ischemia as defined by the ACC/AHA guidelines for interpretability of cECG from computer analyzer-processed cECG recordings (Schiller MT 200 Schiller Reomed AG, Baar, Switzerland). Inconsistencies were resolved by discussion. The ACC/AHA guidelines for the interpretability of cECG recommend that the cECG recordings fulfill a set of 12-lead ECG- and medication-based criteria and of cECG-based criteria to be considered suitable for ST-monitoring. As adherence to the cECG-based interpretability criteria has been shown to not improve the association between cECG-based ischemia and outcome at 12 months, we analyzed all cECG for ST-monitoring that fulfilled the 12-lead ECG and medication-based criteria. Blinded research personnel entered all cECG data in the database in duplicate.

All blood samples were analyzed centrally at the laboratory of the University Hospital Basel. Laboratory personnel were blinded to allocation and were unaware of the study question. From February 2006 to January 2010 the central laboratory measured 4th generation troponin T (Elecsys, Roche Diagnostics, Rotkreuz, Switzerland). The 99th percentile of 4th generation troponin T is 0.03 ug/L. Thereafter, the hospital laboratory switched to the measurement of 5th generation troponin T (Roche Diagnostics, Rotkreuz, Switzerland). Given that quality controls
applied thereafter to the 5th generation assay, we measured 5th generation troponin T after January 2010. The upper limit of the norm for 5th generation troponin T is <0.014 ug/L. Blinded research personnel entered all the measured troponin concentrations into the database in duplicate. NT-proBNP was measured by Elecsys proBNP (Roche Diagnostics, Rotkreuz, Switzerland), which has an upper limit of the norm of 127 pg/mL.

Two trained, blinded investigators evaluated the 12-lead ECG for the development of Q-waves (codes I.1.a-g, I.2.a-I, I.3.a-c) according to the Minnesota criteria. Inconsistencies were resolved by discussion. Blinded research personnel entered all the 12-lead ECG data in the database in duplicate.

Two blinded investigators independently adjudicated all cardiac events during follow-up 12 months after surgery. Blinded research personnel entered all the events in the database in duplicate.

Research staff previously trained by a neuropsychologist assessed the occurrence of delirium by the CAM at baseline, on postoperative day 1, 2, and 7 or on the day of hospital discharge, whichever occurred first. Postoperative delirium on postoperative day 1, 2, or 7 was defined as a CAM suggestive of delirium according to the interpretation algorithm published by Inouye and coworkers.

Statistical Analysis

The sample size estimation (n=187 per arm) was based on an event rate of 46% for myocardial ischemia in cECG in the control group, a relative risk reduction of 30%, a 2-sided alpha 0.05, and power of 80% in the chi-squared test.

The statistical analysis followed a prespecified analysis plan and was conducted blindly. We applied a 2-sided alpha=0.05 for statistical significance. All calculations were performed
using IBM SPSS Statistics 20 (IBM Corporation, Somers, NY, USA). All analyses were based on the intention-to-treat principle.

Continuous data are reported as mean (standard deviation [SD]) or as median (interquartile range [Q1-Q3]), as appropriate. Agreement in the adjudication of myocardial ischemia in cECG was assessed by kappa statistics.

As primary efficacy analysis, we conducted an intention-to-treat analysis of the incidence of the composite of myocardial ischemia, as detected in the cECG and/or by troponin elevation in each group by chi-squared test. Supportive efficacy analyses included the comparison of the secondary endpoints by chi-squared test, of time to MACE by log-rank test, and of differences in the distribution of postoperative NT-proBNP by Mann-Whitney U-test.

Further, we compared the incidence of delirium on days 1, 2, or 7 and of PONV on days 1 and 2 by chi-squared test (tertiary endpoint). We tested for differences in the NRS score distribution by Mann-Whitney U test (tertiary endpoint).

Finally, post-hoc, we assessed the impact of the troponin assay (4th and 5th generation troponin) on the primary endpoint by chi-squared test for heterogeneity. We did not model missing data but assumed that missing cECG, troponin T, and 12-lead ECG did not demonstrate ischemia.

**Results**

We enrolled 385 patients between February 2006 and October 2010 (Figure 1). Seventeen patients (4.4%) were erroneously randomized. In 2 patients (both in the sevoflurane group), sulfonyl urea intake was recognized after randomization, and 15 other patients (7 [3.9%] in the sevoflurane and 8 [4.0%] in the propofol group) were randomized in spite of a calculated
creatine clearance of <30 mL/min. Three patients (0.8%) underwent minor surgery instead of the planned major procedure. The data of all of these patients were included in the intention-to-treat analysis. One patient (0.5%) allocated to propofol received both propofol and sevoflurane. Cross-over did not occur. The unequal number of patients allocated to sevoflurane and propofol was a consequence of the use of an allocation sequence without randomization blocks (see Limitations).

Table 1 reports the baseline characteristics of the patients by allocation. All patients were Caucasians. Patients in the sevoflurane group were more frequently administered phenylephrine (71.6% vs. 61%, p=0.029). Continuous vasopressor requirements did not differ between groups.

cECG was missing in 10 patients (2.6%), 4 (2.2%) in the sevoflurane group and 6 (3%) in the propofol group. Agreement in the cECG adjudication was high, (κ=0.85; observed agreement, 0.92, 95% CI, 0.89-0.95). Troponin data on both postoperative day 1 and 2 were missing in 7 patients (1.8%), 3 (1.6%) in the sevoflurane and 4 (2%) in the propofol group. In none of the patients were both troponin values and the cECG recording missing. Twelve-month follow-up could be obtained for all patients.

Cardiovascular Endpoints

The primary composite endpoint occurred in 75 patients (40.8%) after sevoflurane and 81 (40.3%) after propofol (Table 2). There was no evidence of heterogeneity in either the results of the primary composite endpoint (test for heterogeneity, p=0.407) or of troponin T elevation (test for heterogeneity, p=0.291) based on the troponin T assay. There were no sex-based differences (test for heterogeneity, p=0.560). None of the cardiovascular secondary endpoints differed between treatments (Table 2).

Fourteen patients (7.6%) allocated to sevoflurane and 17 patients (8.5%) allocated to
propofol suffered the composite endpoint of MACE at 12 months (log-rank test, \( p=0.772 \)) (Table 2, Figure 2). All-cause mortality at 12 months was 12.5% and did not differ between the two groups (Table 2). The cause of death could not be clarified in 3 patients (6%). Death of unknown cause was considered to be noncardiac as prespecified. Ten patients (2.6%) suffered a cardiac death (Table 2).

We performed a per-protocol analysis excluding the 17 erroneously included patients and 3 patients that underwent minor surgery instead of the planned major procedure. Seventy patients (40.2%) in the sevoflurane and 76 patients (39.8%) in the propofol group suffered the primary endpoint (\( p=0.932 \)). In the per-protocol analysis, MACE at 12 months occurred in 6.3% (11/174) and 6.8% (13/191) patients in the sevoflurane and propofol group, respectively (\( p=0.772 \)). In an analysis excluding the patients with preoperatively elevated troponin the relative risk (RR) for the primary endpoint was 1.07 (95% CI, 0.80-1.43).

Other Endpoints

The incidence of delirium did not differ between groups (Table 3). PONV was more frequent after sevoflurane anesthesia on postoperative day 1. However, this difference in PONV did not persist on day 2 after surgery (Table 3).

Patient satisfaction was systematically assessed in 2 of the 3 study centers (\( n=284 \)). The NRS distribution did not differ across the two groups at any time-point (Table 3).

Discussion

In the present trial, anesthesia maintenance with sevoflurane compared to propofol did not reduce the incidence of perioperative myocardial ischemia in high-risk patients undergoing major noncardiac surgery. In addition, our study did not suggest any effect of sevoflurane on
postoperative NT-proBNP release or on MACE at 12 months.

Perioperative myocardial ischemia occurs frequently after noncardiac surgery.1-3 The present trial confirms these findings with the observation of a 40% incidence of perioperative ischemia, defined as ischemia detection by cECG or postoperative troponin elevation, in patients at cardiovascular risk undergoing major noncardiac surgery. The high incidence of myocardial ischemia occurred despite a perioperatively continued state-of-the-art medication with β-blockers, statins, and aspirin in a large proportion of patients. It is not established what represents a perioperative ischemic event; the authors applied various definitions.1, 2, 26-29 Perioperative troponin elevation is of prognostic importance, because it is associated with postoperative morbidity and mortality.1-3 A metaanalysis of cohorts30 reported an OR 6.7 (95% CI, 5.1-10.9) for <12-month mortality and 1.8 (95% CI, 1.4-2.3) for >12-month mortality. The independent association of postoperative troponin elevations independent of ischemic symptoms was reported for 30-day mortality,1 and the population-attributable risk of postoperative elevated troponin for 30-day mortality was quantified at 42% in over 15,000 patients. Presence or absence of ischemic symptoms was not considered in this last analysis.31 In the present trial of patients at high cardiovascular risk, the incidence of troponin elevations within the first two days after noncardiac surgery was 26.7%. This estimate was consistent with reported incidences in patients at cardiovascular risk undergoing noncardiac surgery.15,32,33

In spite of the incidence of perioperative myocardial ischemia, little progress has been made in its prevention over the last decade, and there is still no established efficacious and safe prophylaxis for perioperative myocardial ischemia. Animal models of myocardial ischemia5-7 suggest pharmacological preconditioning by volatile anesthetics as a potential approach for prevention of perioperative myocardial ischemia. Further, the administration of volatile
anesthetics resulted in a significant reduction of troponin release in patients undergoing CABG surgery.8-10 These promising results prompted the recommendation by the AHA/ACC guidelines11 in 2007 to use volatile anesthetics in patients at cardiovascular risk undergoing noncardiac surgery.

However, data on the effect of volatile anesthetics on perioperative risk in noncardiac surgical patients were not available at that time and still are scarce. A secondary, retrospective analysis of data obtained in a phase II study in 784 vascular surgical patients at cardiac risk failed to detect an effect of volatile anesthetics on troponin release and incidence of postoperative cardiac events when compared to propofol.34 A recent small prospective and randomized study of sevoflurane vs. propofol also did not detect any difference in the incidence of troponin elevation in 88 patients with CAD undergoing thoracic or vascular surgery.13 The results of our adequately sized randomized controlled trial did not detect an effect of volatile anesthetics on perioperative ischemia in noncardiac surgical patients with CAD or at risk for it. It was, thus, in agreement with the preliminary results of the two previous studies.

In patients undergoing valvular cardiac surgery, data are scarce and do not support a protective effect by sevoflurane.35 The results of studies investigating the effects of volatile anesthetics on perioperative ischemia and postoperative cardiac events in patients undergoing CABG surgery are inconsistent. The largest multicenter RCT in patients undergoing on-pump CABG surgery allocated a total of 414 patients to sevoflurane vs. desflurane vs. TIVA, but did not detect any difference in postoperative troponin release36 between the groups. In contrast, a previous systematic review and meta-analysis that focused on studies comparing sevoflurane vs. TIVA during CABG surgery suggested reduced troponin release and improved cardiac index in the sevoflurane group. These results, however, showed significant heterogeneity.9 Another meta-
analysis including any volatile anesthetics during CABG surgery also found reduced troponin release after administration of a volatile anesthetic in the pooled results. However, significant heterogeneity affects the validity of these results as well.\textsuperscript{10} Data suggesting an effect of volatile preconditioning on the incidence of postoperative cardiac complications rely on a very limited number of events in CABG patients and are inconsistent. One metaanalysis assessing sevoflurane or desflurane vs. TIVA during cardiac surgery of mostly CABG patients reported a reduced incidence of inhospital fatalities and inhospital myocardial infarction.\textsuperscript{9} In contrast, two other metaanalyses\textsuperscript{9, 10} and a large multicenter RCT\textsuperscript{36} published more recently failed to reproduce these findings.

Overall, there are some data suggesting a clinically relevant preconditioning effect of volatile anesthetics in patients undergoing on-pump CABG surgery, although these results are conflicting and open to diverging interpretations.\textsuperscript{37, 38} In contrast, there are no data suggesting a clinically relevant preconditioning effect of volatile anesthetics outside the CABG surgery setting. The present, adequately sized RCT as well as a previous small study\textsuperscript{13} failed to detect a clinically relevant effect of volatile anesthetics on the incidence of perioperative myocardial ischemia in noncardiac surgical patients at coronary risk. This growing evidence questions the recommendation to preferentially use volatile anesthetics in noncardiac surgical patients at cardiac risk,\textsuperscript{11} because volatile anesthetics are also associated with specific adverse effects.\textsuperscript{39} Several potential explanations have been proposed for the divergence of animal and clinical data. Researchers hypothetized that the non-transferability of the promising animal results to the clinical setting may depend on co-medications, age, and comorbidities that attenuate the preconditioning response.\textsuperscript{38} The inconsistent results during on-pump CABG surgery may arise from varying protocols particularly in terms of continuous vs. intermittent aortic cross-clamping,
which in itself may induce preconditioning secondary to repeated ischemia and reperfusion stimuli (ischemic preconditioning). 36, 40, 41

Our finding of similar NT-proBNP release in both groups is consistent with the similar incidence of ischemia, because ischemia and volume overload causing wall stress are triggers of natriuretic peptide release. 42, 43

Delirium is an unsolved problem after major surgery. The pathophysiological mechanisms of delirium have not been elucidated. Animal data have demonstrated neuroprotection to ischemia by exposure to volatile anesthetics. 44, 45 Preliminary human data suggest that inhalational anesthetics may be associated with better short-term cognitive performance after on-pump CABG surgery. 46, 47 In contrast, the incidence of delirium did not differ between the desflurane and propofol groups. 46 In the present trial, we also did not detect an influence of the volatile anesthetic sevoflurane on the incidence of delirium.

Major cardiovascular complications and deaths did not differ in larger trials, which randomized patients to combined anesthesia techniques. 48-50 The results of this trial may, thus, be viewed in the broader evidence-context suggesting that the applied anesthetic technique may not play a major role on the occurrence of major cardiovascular complication and death after noncardiac surgery.

**Strengths and Limitations**

The validity of our results is supported by a randomized design and a blinded cECG analysis with high inter-reader agreement. We achieved complete follow-up at 12 months, and all events were adjudicated independently by two blinded investigators. Further, prognostic balance at the end of the trial was maintained by an intention-to-treat analysis. In addition, the statistical analysis followed a predefined analysis plan and was performed by a blinded data analyst.
Extensive consistency checks and duplicate entry of all endpoint data supported high data quality. We are aware of the following limitations: first, we renounced using a double-dummy approach, because it was not clinically feasible to reliably blind the anesthesiologists. However, outcome assessment and adjudication (cECG, troponin T, NT-proBNP measurement, 12-lead ECG analysis, and long-term follow-up) occurred blindly. A second limitation is the switch from 4th to 5th generation troponin T assays during the study period. However, we did not detect any interaction by troponin assay. A third limitation resulted from the erroneous enrollment of a small number of patients with a creatinine clearance <30 mL/min. We included the data of these patients in the analysis, as per intention-to-treat. The number of patients with reduced creatinine clearance did not differ between groups. Therefore, we do not expect that the inclusion of these patients might have biased our findings. Further, none of the endpoints differed in the per-protocol analysis excluding erroneously randomized patients. Forth, the sample size of the study was powered to compare the incidence of perioperative ischemia (ie, the primary endpoint and not for comparing postoperative cardiac events). Therefore, the interpretation of MACE results warrants caution. If current findings are used as pilot data for calculating the sample size to compare the incidence of MACE, more than 14,000 patients are needed to achieve a power of 80%. As our data do not suggest any relevant anesthetic preconditioning effect at the myocardial damage level (ie, at the level of the assumed pathophysiological link between preconditioning and outcome), we consider realization of such a large trial as not justified. A final limitation is that we did not use randomization blocks, which resulted in a larger number of patients allocated to propofol than sevoflurane.

**Conclusions**
This randomized controlled trial found that sevoflurane compared to propofol anesthesia does not reduce the incidence of myocardial ischemia in patients at high risk for cardiac complications undergoing major noncardiac surgery. Our study also did not detect an effect of sevoflurane on NT-proBNP release, MACE, or delirium.

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Conflict of Interest Disclosures: Roche Diagnostics Switzerland provided in-kind support (assay kits). Abbot AG Switzerland provided some financial support for the conduction of the study. No other potential conflicts of interest are to be disclosed for any of the authors.

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Table 1. Baseline characteristic by treatment.

<table>
<thead>
<tr>
<th></th>
<th>Sevoflurane (n=184)</th>
<th>Propofol (n=201)</th>
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<tbody>
<tr>
<td><strong>Mean age (SD), years</strong></td>
<td>72 (8)</td>
<td>73 (8)</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>138 (75.0)</td>
<td>156 (77.6)</td>
</tr>
<tr>
<td><strong>ASA physical status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>21 (11.4)</td>
<td>32 (15.9)</td>
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<tr>
<td>III</td>
<td>155 (84.2)</td>
<td>160 (79.6)</td>
</tr>
<tr>
<td>IV</td>
<td>8 (4.3)</td>
<td>9 (4.5)</td>
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<tr>
<td><strong>History of CAD</strong></td>
<td>128 (69.6)</td>
<td>156 (77.6)</td>
</tr>
<tr>
<td><strong>History of TIA/stroke</strong></td>
<td>21 (11.4)</td>
<td>24 (12.0)</td>
</tr>
<tr>
<td><strong>History of CHF</strong></td>
<td>4 (2.2)</td>
<td>9 (4.5)</td>
</tr>
<tr>
<td><strong>History of diabetes</strong></td>
<td>42 (22.8)</td>
<td>41 (20.4)</td>
</tr>
<tr>
<td><strong>Creatinin &gt;170 mmol/L</strong></td>
<td>5 (2.8)</td>
<td>7 (3.5)</td>
</tr>
<tr>
<td><strong>Medication</strong></td>
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</tr>
<tr>
<td>Aspirin</td>
<td>136 (73.9)</td>
<td>145 (72.1)</td>
</tr>
<tr>
<td>Aspirin discontinued ≥7d before surgery*</td>
<td>33 (24.3)</td>
<td>32 (22.1)</td>
</tr>
<tr>
<td>Chronic β-blocker</td>
<td>130 (70.7)</td>
<td>139 (69.2)</td>
</tr>
<tr>
<td>New β-blocker</td>
<td>1 (0.6)</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>ACE-inhibitor/angiotension</td>
<td>122 (66.3)</td>
<td>119 (59.2)</td>
</tr>
<tr>
<td>II receptor blocker</td>
<td>121 (65.8)</td>
<td>131 (65.2)</td>
</tr>
<tr>
<td>Statins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin (with or without oral antidiabetics)</td>
<td>21 (11.4)</td>
<td>17 (8.4)</td>
</tr>
<tr>
<td>Oral antidiabetics only</td>
<td>16 (8.7)</td>
<td>19 (9.4)</td>
</tr>
<tr>
<td><strong>Type of surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major general</td>
<td>24 (13.0)</td>
<td>31 (15.4)</td>
</tr>
<tr>
<td>Major orthopedic</td>
<td>46 (25.0)</td>
<td>55 (27.4)</td>
</tr>
<tr>
<td>Major vascular</td>
<td>111 (60.3)</td>
<td>114 (56.7)</td>
</tr>
<tr>
<td><strong>Surgery duration (min)</strong></td>
<td>187 (86)</td>
<td>193 (90)</td>
</tr>
<tr>
<td><strong>Preoperative troponin elevation</strong></td>
<td>13 (7.1)</td>
<td>15 (7.5)</td>
</tr>
</tbody>
</table>

Data are number of patients (%) or mean (standard deviation), as appropriate. *Percentage refers to patients with preoperative aspirin therapy.

ACE, angiotensin converting enzyme; ASA, American Society of Anesthesiologists; CAD, coronary artery disease; CHF, congestive heart failure; RR, relative risk; TIA, transient ischemic attack.
Table 2. Study endpoints and 12-month outcome by treatment.

<table>
<thead>
<tr>
<th></th>
<th>Sevoflurane (n=184)</th>
<th>Propofol (n=201)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial ischemia (cECG and</td>
<td>75 (40.8)</td>
<td>81 (40.3)</td>
<td>1.01 (0.78-1.30)</td>
</tr>
<tr>
<td>troponin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial ischemia in cECG*</td>
<td>41 (36.3)</td>
<td>36 (28.1)</td>
<td>1.29 (0.87-1.91)</td>
</tr>
<tr>
<td>Troponin T elevation</td>
<td>46 (25.0)</td>
<td>57 (28.4)</td>
<td>0.88 (0.62-1.25)</td>
</tr>
<tr>
<td>Myocardial ischemia or any Q-</td>
<td>85 (46.2)</td>
<td>94 (46.8)</td>
<td>0.99 (0.79-1.24)</td>
</tr>
<tr>
<td>wave development</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Q-wave development</td>
<td>17 (9.2)</td>
<td>18 (9.0)</td>
<td>1.03 (0.52-2.0)</td>
</tr>
<tr>
<td>(Minnesota codes I1-3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q-wave infarction</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
<td>1.09 (0.03-39.8)</td>
</tr>
<tr>
<td>NT-proBNP d1, median (Q1-Q3)</td>
<td>526</td>
<td>559</td>
<td>p=0.709</td>
</tr>
<tr>
<td>pg/mL</td>
<td>(257-1031.5)</td>
<td>(238-1234.5)</td>
<td></td>
</tr>
<tr>
<td>NT-proBNP d2, median (Q1-Q3)</td>
<td>932.5</td>
<td>928.5</td>
<td>p=0.766</td>
</tr>
<tr>
<td>pg/mL</td>
<td>(450.5-1670.5)</td>
<td>(417.75-2068.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Twelve-month outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MACE</td>
<td>14 (7.6)</td>
<td>17 (8.5)</td>
<td>0.90 (0.44-1.83)</td>
</tr>
<tr>
<td>Cardiac mortality</td>
<td>5 (2.7)</td>
<td>5 (2.5)</td>
<td>1.09 (0.32-3.77)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>25 (13.6)</td>
<td>23 (11.4)</td>
<td>1.19 (0.67-2.09)</td>
</tr>
</tbody>
</table>

Data are number of patients (%) or median (interquartile range), as appropriate. * Percentage refers to number of patients with cECG suitable for ischemia analysis according to the AHA/ACC guidelines for cECG interpretability; any Q-wave development was defined as the development of Minnesota codes I.1.a-g, I.2.a-i, I.3.a-c, Q-infarction as the development of Minnesota codes I.1.a-g, cECG, continuous electrocardiography; HR, hazard ratio; RR, relative risk; CI, confidence interval; MACE, major adverse cardiac event, defined as a composite of cardiac death, acute coronary events, congestive heart failure, or arrhythmia requiring hospitalization.

Table 3. Patient satisfaction and incidence of delirium and PONV

<table>
<thead>
<tr>
<th></th>
<th>Sevoflurane (n=184)</th>
<th>Propofol (n=201)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative delirium</td>
<td>21 (11.4)</td>
<td>29 (14.4)</td>
<td>0.379</td>
</tr>
<tr>
<td>PONV day 1</td>
<td>29 (15.8)</td>
<td>18 (8.9)</td>
<td>0.042</td>
</tr>
<tr>
<td>PONV day 2</td>
<td>17 (9.2)</td>
<td>15 (7.5)</td>
<td>0.544</td>
</tr>
<tr>
<td>Median NRS (Q1-Q3) day 1</td>
<td>7 (5-8)</td>
<td>7 (5-8)</td>
<td>0.173</td>
</tr>
<tr>
<td>Median NRS (Q1-Q3) day 2</td>
<td>7 (5-8)</td>
<td>7 (5-8)</td>
<td>0.734</td>
</tr>
<tr>
<td>Median NRS (Q1-Q3) day 3</td>
<td>8 (6-9)</td>
<td>7 (5-9)</td>
<td>0.122</td>
</tr>
</tbody>
</table>

Data are number of patients (%) or median (interquartile range), as appropriate. Q1-Q3: interquartile range; NRS: numerical rating scale for satisfaction; PONV: postoperative nausea and vomiting.
Figure Legends:

**Figure 1.** Trial flow diagram.

**Figure 2.** MACE-free survival by treatment after discharge.
Assessed for eligibility n= 649

- Not meeting the inclusion criteria n= 103
- Declined participation n= 158
- Anesthetist declined participation n= 3

Enrolled n= 385

- Allocated to Sevoflurane n= 184
  - received Sevoflurane n= 184

  Loss of follow-up n= 0

  Analysis n= 184

- Allocated to Propofol n= 201
  - received Propofol and Sevoflurane n= 1

  Loss of follow-up n= 0

  Analysis n= 201