

Effect of Xenon Anesthesia Compared to Sevoflurane and Total Intravenous Anesthesia for Coronary Artery Bypass Graft Surgery on Postoperative Cardiac Troponin Release

An International, Multicenter, Phase 3, Single-blinded, Randomized Noninferiority Trial

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ABSTRACT

Background: Ischemic myocardial damage accompanying coronary artery bypass graft surgery remains a clinical challenge. We investigated whether xenon anesthesia could limit myocardial damage in coronary artery bypass graft surgery patients, as has been reported for animal ischemia models.

Methods: In 17 university hospitals in France, Germany, Italy, and The Netherlands, low-risk elective, on-pump coronary artery bypass graft surgery patients were randomized to receive xenon, sevoflurane, or propofol-based total intravenous anesthesia for anesthesia maintenance. The primary outcome was the cardiac troponin I concentration in the blood 24 h post-surgery. The noninferiority margin for the mean difference in cardiac troponin I release between the xenon and sevoflurane groups was less than 0.15 ng/ml. Secondary outcomes were the safety and feasibility of xenon anesthesia.

Results: The first patient included at each center received xenon anesthesia for practical reasons. For all other patients, anesthesia maintenance was randomized (intention-to-treat: $n = 492$; per-protocol/without major protocol deviation: $n = 446$). Median 24-h postoperative cardiac troponin I concentrations (ng/ml [interquartile range]) were 1.14 [0.76 to 2.10] with xenon, 1.30 [0.78 to 2.67] with sevoflurane, and 1.48 [0.94 to 2.78] with total intravenous anesthesia [per-protocol]. The mean difference in cardiac troponin I release between xenon and sevoflurane was -0.09 ng/ml (95% CI, -0.30 to 0.11 ; per-protocol: $P = 0.02$). Postoperative cardiac troponin I release was significantly less with xenon than with total intravenous anesthesia (intention-to-treat: $P = 0.05$; per-protocol: $P = 0.02$). Perioperative variables and postoperative outcomes were comparable across all groups, with no safety concerns.

Conclusions: In postoperative cardiac troponin I release, xenon was noninferior to sevoflurane in low-risk, on-pump coronary artery bypass graft surgery patients. Only with xenon was cardiac troponin I release less than with total intravenous anesthesia. Xenon anesthesia appeared safe and feasible. (**ANESTHESIOLOGY 2017; 127:918-33**)

IN coronary artery bypass graft (CABG) surgery, myocardial ischemia provoked by the aortic clamping and subsequent reperfusion of the heart remains a significant clinical challenge.^{1,2} The extent of the resulting myocardial necrosis, as reflected by elevated postoperative blood concentrations of cardiac troponins I (cTnI) and T (cTnT), is an independent risk factor for long-term cardiac outcomes.³⁻⁵ Patients with high postoperative troponin concentrations are particularly at risk for adverse outcomes, major cardiac events, and death.^{3,4} A recent multivariate regression analysis found that postoperative peak troponin release of more than 0.6 ng/ml was an independent predictor of in-hospital mortality in a concentration-dependent

What We Already Know about This Topic

- Previous studies have suggested that xenon could be administered safely to patients with impaired cardiac function.

What This Article Tells Us That Is New

- This randomized prospective study compared xenon-, sevoflurane-, and propofol-based anesthesia in patients undergoing elective on-pump coronary artery bypass graft surgery.
- With regard to postoperative cardiac troponin I release, xenon was noninferior to sevoflurane in low-risk, on-pump coronary artery bypass graft surgery patients. Only with xenon was cardiac troponin I release less than with total intravenous anesthesia. Xenon anesthesia appeared safe and feasible.

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manner.⁶ A retrospective analysis of randomized clinical trials also found a concentration-dependent relationship between troponin release and mortality after CABG surgery.⁷ Thus, clinicians have sought to minimize cardiac damage and reperfusion injury through various improvements in surgical and anesthetic techniques and frequently use the release of cardiac troponins to assess the extent of myocardial injury.^{1,8–10}

Compared to total intravenous anesthesia (TIVA), volatile anesthetics are thought to be cardioprotective and to result in less ischemia–reperfusion injury during cardiac surgery. In several meta-analyses and clinical trials in cardiac surgery patients, anesthesia with desflurane or sevoflurane resulted in less myocardial damage demonstrated by cardiac troponin release, shorter hospital stay, less morbidity and mortality, and better left ventricular function than anesthesia with propofol-based TIVA.^{11–17}

Xenon anesthesia can be useful when cardiovascular stability is needed.^{18–22} In noncardiac surgery, xenon maintained arterial pressure and autonomic nervous system tone and preserved coronary blood flow and left ventricular function better than sevoflurane or propofol.^{23–28} Several reports have suggested that xenon could be administered safely to patients with impaired cardiac function.^{22,24,29–31} In a recent pilot study in off-pump CABG surgery patients,

intraoperative vasopressor use was significantly less with xenon anesthesia than with sevoflurane anesthesia.³² Xenon anesthesia also enhanced myocardial recovery and limited myocardial infarct size after experimental ischemia in animal models.^{33–35} Given these properties, xenon anesthesia may provide cardioprotective benefits to patients undergoing on-pump CABG surgery.

Before this study, the question of whether xenon anesthesia during cardiac surgery is associated with a cardioprotective effect had not yet been investigated. This study was dedicated to investigate this question. In this first large-scale randomized prospective study, we compared xenon-, sevoflurane-, and propofol-based anesthesia in a three-arm study in patients undergoing elective on-pump CABG surgery. Because xenon and sevoflurane appear to share cardioprotective properties, it was hypothesized that both would similarly and favorably limit postoperative myocardial damage compared to propofol-based TIVA. Myocardial damage assessed by postoperative release of cTnI at 24 h after surgery was the primary evaluation criterion. Secondary objectives were to assess the effects of xenon anesthesia on the release of other factors related to myocardial damage and to assess the safety and feasibility of xenon anesthesia in patients undergoing CABG surgery. Because xenon has previously demonstrated neuroprotective effects in some animal models,^{35–37} and cardiac surgery patients are at risk of postoperative delirium,³⁸ we also assessed whether xenon anesthesia reduced the incidence of postoperative delirium as determined by the Confusion Assessment Method (CAM).³⁹

Materials and Methods

Study Design

This was prospective, randomized, three-arm, single-blinded, international, multicenter, phase 3, noninferiority study to compare the effects of anesthesia maintenance with xenon, sevoflurane, and a propofol-based TIVA on postoperative cTnI concentrations in patients undergoing on-pump CABG surgery with a cardioplegic arrest. The study was registered with ClinicalTrials.gov (NCT01294163) and the European Union Clinical Trials Database (EudraCT 2010-020677-17). The principal investigator is Jan Hofland, M.D., Ph.D. Patients were approached by study staff and enrolled at 17 university hospitals in France (8), Germany (6), Italy (1), and The Netherlands (2; see table in Supplemental Digital Content 1, <http://links.lww.com/ALN/B531>, for numbers of patients enrolled at each study site). The first included patient at each center received xenon anesthesia in the presence of a sponsor medical device expert to confirm the training efficacy of the local study team on the xenon anesthesia equipment. These patients were only evaluated for safety. Subsequent patients were randomized 1:1:1 to receive xenon, sevoflurane, or a propofol-based TIVA for maintenance according to a computer-generated, fixed-block randomization list created before the start of the study and stratified by center. Block size was not specified

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in the protocol nor communicated to investigators to avoid predictability of the next treatment. The identity of the randomization-allocated maintenance anesthesia method was contained in a sealed envelope that was opened by the investigators or the appointed research assistants only after induction of anesthesia. At all centers, the 24-h blood sample used for determination of the primary endpoint was sent to a central laboratory. The study was blinded such that the patients and the central laboratory were unaware of the anesthesia method used, whereas investigators and the sponsor were not. Central laboratory test results were not released to the investigators and sponsor until after the database was locked.

The trial complied with International Conference on Harmonisation Good Clinical Practice guidelines, the Declaration of Helsinki (2008), and European Directive 2001/20/CE regarding the conduct of clinical trials (April 4, 2001). Independent ethics review committees approved the study protocol, amendments, and consent forms. All participants provided written informed consent before participation.

Study Population and Procedures

Patients scheduled for elective on-pump CABG surgery with cardioplegic arrest were eligible. They were excluded if they had a recent myocardial infarction (within 7 days), ongoing unstable angina, or other indications of unstable or severe cardiac disease. Full inclusion and exclusion criteria are provided in the appendix. Patients received randomization-allocated maintenance anesthesia before and after the cardiopulmonary bypass (CPB) period and propofol-based maintenance anesthesia during CPB. Although in a small, single-center feasibility study, an unregistered prototype was used for administering xenon during CPB, this option was not available for this large international study.²² Furthermore, sevoflurane delivery *via* the heart–lung machine was not routinely used in every participating center. Therefore, it was decided to use propofol for anesthesia maintenance in all study groups during CPB. All patients were ventilated with a Felix Dual anesthesia machine (Air Liquide Medical Systems, France), which was suitable for delivering xenon and sevoflurane with the necessary oxygen/air mixtures. Standard intraoperative monitoring included: five-lead electrocardiogram recording, pulse oximetry, four-lead bispectral index (BIS; Covidien, USA), arterial and central venous pressure, and body temperature. Concentrations of inspiratory oxygen, expiratory oxygen, and carbon dioxide and of the inhaled anesthetics were monitored during intraoperative mechanical ventilation.

Anesthesia was induced in all patients by intravenous propofol, etomidate, or midazolam according to the judgment of the attending team. Intraoperative analgesia was obtained by intravenous administration of sufentanil. In the xenon group, the induction agent was discontinued when the inspired concentration of xenon (LENOXe; Air Liquide Santé International, France) was at least 40% and adjusted with oxygen thereafter to a maximum of 65% xenon. In

the sevoflurane group, the induction agent was discontinued when sevoflurane reached an end-tidal concentration of 1.2% and thereafter was adjusted to a maximum end-tidal concentration of 1.8%, which will be near the minimal alveolar concentration of sevoflurane of the study population. In the TIVA group, propofol was administered intravenously at an initial rate of 2 to 4 mg · kg⁻¹ · h⁻¹ and adapted thereafter by the attending team to maintain an adequate depth of anesthesia. For all patients, the inspiratory oxygen concentration was 35 to 50%, and adequate anesthesia maintenance was defined by a BIS index value between 40 and 60. If BIS index values rose above 60 despite administration of the maximum tolerated or protocol-allowed concentrations of xenon or sevoflurane, propofol at an initial dose of 0.5 mg/kg was suggested by protocol to be administered to obtain prompt correction of the BIS level. After surgery, patients were admitted to the intensive care unit (ICU), where they stayed for at least 18 h.

Blood samples were collected and prepared for central laboratory (BIOMNIS Laboratory, France) analysis of blood chemistry and of cTnI, the MB fraction of creatine kinase (CK-MB), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and C-reactive protein (CRP) concentrations according to the study schedule (see table in Supplemental Digital Content 2, <http://links.lww.com/ALN/B532>) and procedures described in the appendix. For cTnI, the 99th percentile values of 0.033 ng/ml for men and 0.013 ng/ml for women were specified by the assay manufacturer. Flowcharts of study treatments, visits (study measurement points), and other study procedures and evaluations are also provided in the Supplemental Digital Content (see table in Supplemental Digital Content 2, <http://links.lww.com/ALN/B532>, and figure in Supplemental Digital Content 3, <http://links.lww.com/ALN/B533>).

Study Endpoints

The primary endpoint was the blood cTnI concentration at 24 h after the end of surgery for all centers measured by one central laboratory. At the design of the study, this time point was the one chosen most frequently to investigate the correlation between troponin levels and clinical outcome.^{3,4} In support of the primary endpoint, we also investigated cTnI concentrations at ICU admission and at 12 and 48 h after the end of surgery. In addition, integrated approaches that include measurements of other cardiac damage or inflammation markers in addition to cardiac troponins can improve the risk assessment of long-term cardiac outcome after cardiac surgery.^{40,41} Thus, secondary endpoints were the peak postoperative blood concentrations of cTnI, CK-MB, NT-proBNP, and CRP analyzed by the central laboratory. The feasibility of xenon anesthesia was assessed by BIS index, perioperative hemodynamic variables, blood oxygen concentration and saturation, need for vasoactive or inotropic support, and the number of patients with perioperative atrial fibrillation. The CAM in the local language was used to

assess postoperative delirium at inclusion (baseline), 24 and 48 h after surgery (in patients extubated), at ICU discharge, and at the hospital discharge visit. Adverse events (AEs) were collected from the selection visit through hospital discharge or until 30 days after general anesthesia. The incidence of all-cause deaths was surveyed for every new cohort of 80 patients included in the study.

Statistical Analysis

The safety population included all treated patients, the intention-to-treat (ITT) population all randomized patients, and the per-protocol (PP) population all randomized and treated patients who had no major protocol deviations.

The primary analysis was a noninferiority comparison of the xenon and sevoflurane groups based on the blood cTnI concentrations determined by the central laboratory at 24 h after the end of surgery, using an analysis of covariance (ANCOVA) model with the baseline cTnI concentrations as the covariate. Before data analysis, it was anticipated that alternative statistical methods would be used if any of the assumptions underlying the planned formal statistical methods were violated during the analysis of the final data. Examination of the residuals from the ANCOVA model revealed a departure from normality, tested by use of a Shapiro–Wilks test, with a skewed, right-tailed distribution, suggesting a log-normal distribution. After transformation of the cTnI concentrations into log values using a previously reported method,⁴² the normality assumption required for the ANCOVA model was satisfied. The difference in means on the raw scale was converted to an approximate difference on the logarithmic scale, by taking x to be the overall arithmetic mean across groups on the raw scale, and using the following equations:

$$dz = dx / \bar{x}$$

$$SE(dz) = SE(dx) / \bar{x}$$

where dx is the difference in raw means, and $SE(dx)$ is the standard error of dx . From the largest single randomized trial and a large meta-analysis reporting a difference between a volatile-based and a TIVA-based anesthetic comparing cTnI concentrations in CPB patients,^{15,43} the difference in cTnI concentrations between two groups was estimated to be 1.73 ng/ml (95% CI, 0.63 to 2.83), thus defining a noninferiority margin of 0.63 ng/ml. The noninferiority margin in the log scale was estimated to be 0.15 ng/ml as follows:

$$\bar{x} = (3.27 + 5) / 2 = 4.135 \Rightarrow dz = -1.73 / 4.135 = -0.418$$

$$SE(dx) = (2.83 - 1.73) / 2 = 0.55 \Rightarrow SE(dz) = 0.55 / 4.135 = 0.133$$

Log-converted difference: sevoflurane – TIVA = –0.418 (95% CI, –0.68 to –0.15)

Thus, the xenon group was considered noninferior to the sevoflurane group if the upper bound of the adjusted two-sided 95% CI for the difference between the two mean cTnI concentrations was less than the noninferiority margin of 0.63 ng/ml and less than 0.15 ng/ml for log-transformed data. As required for noninferiority comparisons, treatment was first assessed in the PP population and then, if noninferiority was found, confirmed in the ITT population. As required for superiority comparisons, the analysis was first performed in the ITT population and then, if appropriate, confirmed in the PP population. Superiority of the xenon group over the sevoflurane group was to be tested only if noninferiority was demonstrated in both populations. Superiority was demonstrated if the upper bound of the adjusted two-sided 95% CI for the difference between the two mean cTnI concentrations was less than 0. To check for assay sensitivity, superiority of xenon and sevoflurane groups over the TIVA group was also assessed. In the conditions of this three-arm study design, no formal adjustment for multiplicity was necessary for the superiority analyses.⁴⁴ In the sensitivity analyses, pairwise comparisons of the cTnI concentrations at 24 h of the xenon, sevoflurane, and TIVA groups (ITT and PP populations) were repeated using the nonparametric Kruskal–Wallis test.

Maximum postoperative cTnI, CK-MB, NT-proBNP, and CRP concentrations were compared in the ITT population. Mean values for the treatment groups were compared using three-armed ANCOVA tests on log-transformed data. For significant global treatment effects, pairwise comparisons of the mean values of the treatment groups were performed using the Tukey test. In the sensitivity analysis, concentrations for the treatment groups were also compared using the Kruskal–Wallis test. For significant global treatment effects, pairwise comparisons between treatment groups were performed using the Dwass, Steel, Critchlow–Fligner multiple comparison analysis. Analyses of other endpoints were descriptive.

For an adequate power of the study, based on the noninferiority margin of 0.63 ng/ml, a necessary sample size of 164 patients/group (492 randomized patients) was calculated under the assumption that cTnI concentrations in the two groups would be similar with a SD of 1.9 ng/ml and under the condition that a maximum of 15% of the patients might be nonevaluable. Type I error was set at $\alpha = 0.05$ (two-sided), and power was set at 80% (nQuery Advisor version 6.01; Statistical Solutions, USA). All statistical analyses were done using SAS version 9.3 (SAS Institute, USA).

Results

Between 2011 and 2014, 542 patients scheduled for elective on-pump CABG surgery were eligible in the 17 participating university hospitals; 509 of these patients were included and received a study treatment (fig. 1; see table in Supplemental Digital Content 1, <http://links.lww.com/ALN/B531>, patients enrolled by study center). The first patient included at each center (17 patients) received xenon anesthesia for practical reasons and was included in the safety

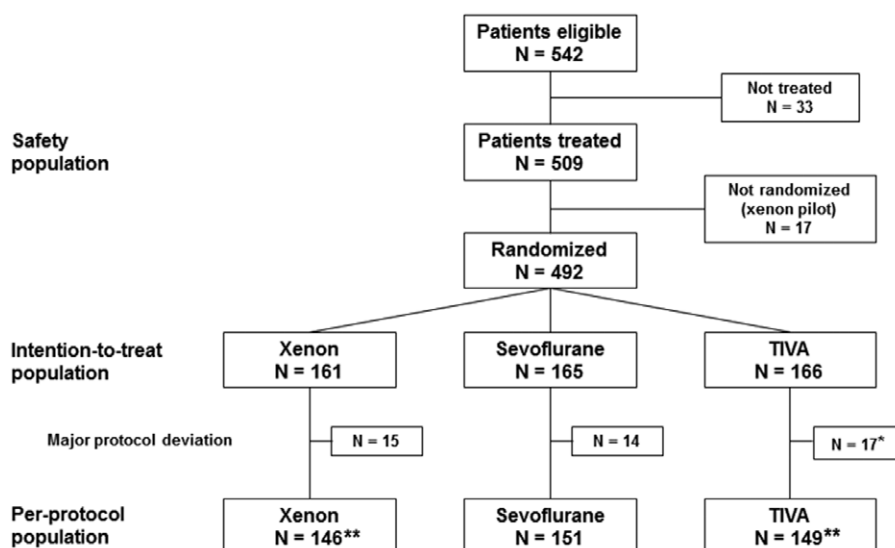


Fig. 1. Patient disposition. Of the 542 patients eligible for the study, 33 were not included or treated because inclusion criteria were not met ($n = 17$); the surgical procedure was not eligible ($n = 14$); or the investigator ($n = 1$) or ventilator ($n = 1$) was not available. The first patient included in the study at each of the 17 study centers was assigned xenon treatment for practical reasons and was included in the safety population. Subsequent patients included at each center were randomized 1:1:1 into the three treatment groups that comprised the intention-to-treat population. A total of 46 patients were excluded from the per-protocol population due to at least one major protocol deviation. *Includes two patients who discontinued the study prematurely. **Includes one patient who discontinued the study prematurely. TIVA = total intravenous anesthesia.

population. The 492 remaining patients (ITT population) were randomized to receive xenon ($n = 161$), sevoflurane ($n = 165$), or propofol-based TIVA ($n = 166$) for anesthesia maintenance. All patients received the study treatment that they were supposed to receive according to randomization. The study was stopped after reaching the recruitment goal. In total, 46 patients had at least one major protocol deviation reported within 24 h after CABG surgery, leaving 446 patients in the PP population: xenon ($n = 146$), sevoflurane ($n = 151$), and TIVA ($n = 149$) (see table in Supplemental Digital Content 4, <http://links.lww.com/ALN/B534>, major protocol deviations).

The three treatment groups were well balanced before surgery (table 1). Most patients were men with New York Heart Association class II cardiac disease and had a low-risk profile. EuroSCORE I medians were 1.7 to 1.9 for the three groups; mean scores were 2.4 to 2.5. Coronary heart disease characteristics and baseline mean serum concentrations of prognostic markers for each group were similar; however, ranges were wide, and some patients had high concentrations of one or more of these markers. Mean concentrations of cTnI in the blood were at most 0.005 ng/ml in all groups. Per the study protocol, patients with high locally determined baseline concentrations of cTnI, cTnT, or CK-MB were excluded from the PP population. The upper limit of the centrally determined baseline cTnI concentration range in the PP population was less than 0.45 ng/ml (table 1).

CABG surgery characteristics, cardioplegia methods (table 1), and mean BIS index values over time were similar across the three study groups (see figure in Supplemental Digital Content 5, <http://links.lww.com/ALN/B535>).

Anesthesia maintenance was achieved with mean inspired concentrations of 52 to 56% xenon or 1.2 to 1.5% sevoflurane or with intravenous propofol at $4.5 \pm 1.9 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. More patients in the xenon group (39; 24%) than in the sevoflurane group (12; 7%) were given rescue medication with a propofol bolus, with the total dose given in table 1. Seven patients (4%) in the xenon group (one permanently) and two patients (1%) in the sevoflurane group discontinued study treatment during surgery due to a high BIS index, high or low arterial pressure, or low oxygen saturation.

Cardioprotective Effects of Xenon and Sevoflurane Anesthesia

Primary Study Endpoint

At 24 h after the end of surgery, mean cTnI concentrations in the blood were 2.12 ng/ml (95% CI, 1.61 to 2.64) in the xenon group, 2.59 ng/ml (95% CI, 1.87 to 3.30) in the sevoflurane group, and 2.90 ng/ml (95% CI, 2.18 to 3.61) in the TIVA group in the PP population (table 2). In the primary analysis of the log-transformed cTnI concentrations at 24 h after surgery, xenon was noninferior to sevoflurane both in the PP population ($P = 0.02$) and in the ITT population ($P = 0.01$). In superiority analysis, xenon was not superior to sevoflurane in either population (ITT: $P = 0.32$; PP: $P = 0.36$) but was superior to TIVA in both populations (ITT: $P = 0.05$; PP: $P = 0.02$). Sevoflurane was not superior to TIVA in either population ($P \geq 0.15$). Similar results were also obtained in a nonparametric Kruskal–Wallis analysis of cTnI concentrations at 24 h after surgery (see table in Supplemental Digital Content 6, <http://links.lww.com/ALN/B536>).

Table 1. Patient Baseline and Perioperative Characteristics

	Anesthesia Method		
	Xenon (N = 161)	Sevoflurane (N = 165)	TIVA (N = 166)
Baseline characteristics			
Patient characteristics			
Men, n (%)	142 (88)	140 (85)	146 (88)
Mean age, yr (SD)	65(9)	64 (9)	64 (9)
Mean body weight, kg (SD)	82 (13)	81 (13)	82 (15)
Mean BMI, kg/m ² (SD)	28 (4)	27 (4)	28 (4)
NYHA classification, n (%)			
Class I	36 (23)	46 (28)	49 (30)
Class II	94 (59)	88 (53)	85 (51)
Class III	29 (18)	30 (18)	32 (19)
Class IV	1 (0.6)	1 (0.6)	0
CHD characteristics, n (%)			
Prior myocardial infarction	44 (27)	55 (33)	56 (34)
Prior unstable angina	23 (14)	25 (15)	22 (13)
Prior PCI	67 (42)	81 (49)	68 (41)
Prior CABG	1 (1)	0	1 (1)
Congestive heart failure	0	0	5 (3)
Number of diseased coronary arteries (by preoperative analysis)			
1	5 (3)	4 (2)	6 (4)
2	32 (20)	42 (26)	31 (19)
3	107 (67)	98 (59)	113 (68)
> 3	17 (11)	21 (13)	16 (10)
Other cardiovascular risk factors			
Median EuroSCORE*, % (IQR)	1.9 (1.4–2.9)	1.8 (1.1–2.8)	1.7 (1.2–3.1)
Current smoker, n (%)	16 (10)	38 (23)	27 (16)
Ex-smoker, n (%)	84 (52)	79 (48)	88 (53)
Occasional alcohol use, n (%)	88 (55)	96 (58)	94 (57)
Regular alcohol use, n (%)	20 (12)	17 (10)	13 (8)
Mean creatinine clearance rate†, ml/min (SD)	99 (30)	104 (29)	105 (39)
Concomitant diseases, n (%)			
Stroke	6 (4)	9 (6)	6 (4)
Peripheral occlusive disease	25 (16)	22 (13)	23 (14)
COPD	11 (7)	10 (6)	17 (10)
Asthma	7 (4)	6 (4)	6 (4)
Diabetes mellitus	51 (32)	49 (30)	49 (30)
Arterial hypertension	130 (81)	126 (76)	124 (75)
Hyperlipidemia	129 (80)	122 (74)	125 (75)
Concomitant medication at inclusion, n (%)			
β-Blockers	99 (62)	100 (61)	101 (61)
Statins	91 (57)	99 (60)	110 (66)
Platelet inhibitors	88 (55)	77 (47)	86 (52)
ACE inhibitors	51 (32)	49 (30)	56 (34)
Angiotensin II antagonists	20 (12)	17 (10)	21 (13)
Calcium-channel blockers	27 (17)	21 (13)	25 (15)
Diuretics	23 (14)	23 (14)	23 (14)
Insulin	10 (6)	16 (10)	17 (10)
Baseline blood concentrations of prognostic markers, median (range)			
cTnI, ng/ml	0.005 (0–5.580)	0.004 (0–1.422)	0.003 (0–0.979)
cTnI, ng/ml (PP population‡)	0.005 (0–0.443)	0.004 (0–0.361)	0.003 (0–0.447)
CK-MB, ng/ml	1.0 (0.3–26)	0.9 (0.3–4)	0.9 (0.2–5)
NT-proBNP, ng/l	146 (25–3,758)	135 (25–1,617)	128 (25–3,159)
CRP, mg/l	1.5 (0.2–99)	1.3 (0.2–70)	1.6 (0.2–49)

(Continued)

Table 1. (Continued)

	Anesthesia Method		
	Xenon (N = 161)	Sevoflurane (N = 165)	TIVA (N = 166)
Perioperative characteristics			
Treatment time, min (SD)			
Pre-CPB anesthesia	110 (33)	109 (30)	122 (36)
Post-CPB anesthesia	53 (17)	52 (19)	56 (18)
Overall	162 (41)	161 (38)	179 (43)
Anesthesia, total	269 (48)	263 (58)	272 (56)
Anesthetic dose			
Postinduction\$, % (SD)	56 (7)	1.2 (0.6)	—
Prebypass\$, % (SD)	56 (8)	1.5 (0.5)	—
Postbypass\$, % (SD)	52 (10)	1.3 (0.6)	—
End of anesthesia\$, % (SD)	53 (10)	1.2 (0.5)	—
Total maintenance dose of propofol, mg/kg per hour (SD)	—	—	4.5 (1.9)
Total dose of propofol administered as rescue medication, mg (SD)	314 (496)	245 (285)	—
Pao ₂ during anesthesia, mmHg (SD)			
Preinduction	133 (112)	139 (109)	142 (112)
Postinduction	162 (75)	202 (99)	215 (118)
Prebypass	145 (48)	193 (70)	193 (71)
Bypass 1	223 (68)	229 (71)	232 (67)
Bypass 2	201 (68)	203 (73)	208 (71)
End of anesthesia	125 (50)	170 (89)	173 (83)
Cardioplegia solution, n (%)			
Blood-based	101 (63)	105 (64)	105 (64)
Crystalloid	59 (37)	59 (36)	60 (36)
Cardioplegia temperature, n (%)			
Cold: < 16°C	111 (69)	118 (72)	117 (71)
Tepid: ≥ 16°C to ≤ 25°C	1 (0.6)	0	0
Warm: > 25°C	48 (30)	46 (28)	48 (29)
Other characteristics			
Duration of CPB, min (SD)	91 (31)	91 (35)	95 (35)
Aortic cross-clamping duration, min (SD)	64 (24)	65 (27)	67 (27)
Median sufentanil dose, µg (IQR)	225 (136–350)	200 (120–302)	200 (125–342)

Values are the means for the intention-to-treat population, unless otherwise indicated. The missing values were excluded from denominators.

*EuroSCORE based on work of Roques *et al.* (EuroSCORE I).² †Calculated using method by Cockcroft and Gault. ‡The PP population included 146 patients in the xenon group, 151 patients in the sevoflurane group, and 149 patients in the TIVA group. §Inspired concentrations.

ACE = angiotensin-converting enzyme; BMI = body mass index; CABG = coronary artery bypass graft; CHD = congestive heart disease; CK-MB = creatine kinase-MB fraction; COPD = chronic obstructive pulmonary disease; CPB = cardiopulmonary bypass; CRP = C-reactive protein; cTnI = cardiac troponin I; IQR = interquartile range; N = total number of patients analyzed; n = number of patients with the characteristic; NT-proBNP = N-terminal probrain natriuretic protein; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PP = per-protocol; TIVA = total intravenous anesthesia.

Secondary Endpoints

Mean cTnI concentrations in all groups increased after surgery, peaking at 3.6 to 3.9 ng/ml after a mean of 12 h and decreasing thereafter to 1.3 to 1.7 ng/ml after 48 h (fig. 2). Median cTnI concentrations in all groups were similar across all time points. Although mean postoperative blood concentrations of cTnI peaked for all groups at a mean of 12 h after surgery, the postoperative times at which the blood concentrations of cTnI and the other markers peaked for individual patients varied. The mean of the peak cTnI concentrations that occurred at any time after surgery were lower in the xenon group than in the sevoflurane or propofol-based TIVA groups (table 3). Although the global treatment effect was not found significant in the ITT population ($P = 0.07$), in the PP population, the effect was significant ($P = 0.04$), with xenon also being superior to TIVA ($P = 0.03$).

A *post hoc* analysis of area under the curve values for cTnI blood concentrations 0 to 48 h after surgery yielded similar mean cTnI release rates (ng/ml per hour) of 4.32 (95% CI, 4.19 to 4.44) for xenon, 4.39 (95% CI, 4.26 to 4.52) for sevoflurane, and 4.50 (95% CI, 4.37 to 4.63) for TIVA.

Mean arterial partial oxygen pressures (Pao₂) before CPB (postinduction, prebypass) and at the end of anesthesia were observed to be approximately 50 mmHg lower in the xenon group than in the sevoflurane and TIVA groups (table 1). To eliminate Pao₂ as a confounder of the effects seen on the cTnI concentrations, a *post hoc* exploratory analysis was done, which confirmed that Pao₂ was not a confounding factor in the difference in 24-h cTnI concentrations between the groups (see table in Supplemental Digital Content 7, <http://links.lww.com/ALN/B537>).

Table 2. Noninferiority and Superiority Analyses of cTnI Concentrations at 24 h after CABG Surgery

Population/treatment group	[cTnI], ng/ml	Analysis	Analysis Results, P Value	Test Criteria	Conclusion
Per-protocol, original data	Median (Q1–Q3)				
Xenon group (N = 146)	1.14 (0.76–2.10)	—	—	—	—
Sevoflurane group (N = 151)	1.30 (0.78–2.67)	—	—	—	—
TIVA group (N = 149)	1.48 (0.94–2.78)	—	—	—	—
Per-protocol, log-transformed data	LS mean (95% CI)				
Xenon group	0.30 (0.15–0.44)	—	—	—	—
Sevoflurane group	0.39 (0.25–0.54)	—	—	—	—
TIVA group	0.55 (0.40–0.69)	—	—	—	—
Treatment difference* (xenon – sevoflurane)	–0.09 (–0.30 to 0.11)	Noninferiority	0.02	CI upper limit < 0.15 ng/ml† and $P < 0.05$	Confirmed
Treatment difference* (xenon – TIVA)	–0.25 (–0.45 to –0.05)	Superiority	0.36	$P < 0.05$	Not confirmed
Treatment difference* (sevoflurane – TIVA)	–0.16 (–0.37 to 0.05)	Superiority	0.02	$P < 0.05$	Confirmed
		Superiority	0.15	$P < 0.05$	Not confirmed
Intention-to-treat, original data	Median (Q1–Q3)				
Xenon group (N = 161)	1.16 (0.76–2.20)	—	—	—	—
Sevoflurane group (N = 165)	1.30 (0.79–2.73)	—	—	—	—
TIVA group (N = 166)	1.44 (0.90–2.80)	—	—	—	—
Intention-to-treat, log-transformed data	LS Mean (95% CI)				
Xenon group	0.32 (0.18–0.47)	—	—	—	—
Sevoflurane group	0.43 (0.29–0.57)	—	—	—	—
TIVA group	0.53 (0.38–0.67)	—	—	—	—
Treatment difference* (xenon – sevoflurane)	–0.10 (–0.30 to 0.10)	Noninferiority	0.01	CI upper limit < 0.15 ng/ml† and $P < 0.05$	Confirmed
Treatment difference* (xenon – TIVA)	–0.21 (–0.41 to –0.01)	Superiority	0.32	$P < 0.05$	Not confirmed
Treatment difference* (sevoflurane – TIVA)	–0.10 (–0.31 to 0.10)	Superiority	0.05	$P < 0.05$	Confirmed
		Superiority	0.33	$P < 0.05$	Not confirmed

*Adjusted treatment difference between the LS mean cTnI concentrations with 95% CI obtained using analysis of covariance analyses. LS means were determined from log-transformed data. †Noninferiority margin reformulated for the log scale as described in the text.

CABG = coronary artery bypass graft; cTnI = cardiac troponin I; LS mean = least squares mean; N = total number of patients analyzed; TIVA = total intravenous anesthesia.

No significant differences among the groups were detected for the highest postoperative concentrations of CK-MB, NT-proBNP, or CRP. The proportion of patients with very high postoperative cTnI concentrations (greater than 100 times the 99th percentile value) was smaller in the xenon group (17%) than in either the sevoflurane (24%) or propofol-based TIVA (26%) groups (see figure in Supplemental Digital Content 8, <http://links.lww.com/ALN/B538>). Overall, only 13 patients (3%) presented with at least one episode of postoperative delirium as assessed by the CAM: 4 patients (3%) in the xenon group, 4 patients (3%) in the sevoflurane group, and 5 patients (3%) in the TIVA group.

Feasibility and Safety of Xenon Anesthesia

Patients in the three groups exhibited similar postoperative characteristics while they recovered in the ICU (table 4). The proportions of patients who received vasodilator, vasopressor, or inotropic treatments after surgery were similar for all groups. Median ICU length of stay (LOS) was in a wide range, with 27 h for the xenon group, 29 h for sevoflurane group, and 42 h for the TIVA group. The median postoperative hospital LOS was 9 days for all groups.

Adverse events were mostly related to the CABG surgery and were generally well balanced across all treatment groups (table 5). Treatment-emergent AEs were reported for 93% of the patients in each group; most of which were cardiac or vascular disorders of mild-to-moderate severity. Serious adverse events were also balanced across all treatment groups, at approximately 16% of the patients in each group, with cardiac disorders being the most frequent in each group. Six serious adverse events in the xenon group, three in sevoflurane group, and five in the TIVA group were considered possibly related to study treatment. Three patients in the TIVA group succumbed to a fatal AE due to surgical complications (air embolism, multiorgan failure, and bowel ischemia), none of which were considered related to study treatment.

Discussion

In this first large randomized clinical trial conducted for xenon anesthesia in patients undergoing low-risk cardiac surgery, we demonstrated that xenon anesthesia was noninferior to sevoflurane anesthesia in preventing cTnI release at 24 h after on-pump CABG surgery. Although xenon was not superior to sevoflurane in this capacity, xenon was superior to propofol-based TIVA, whereas

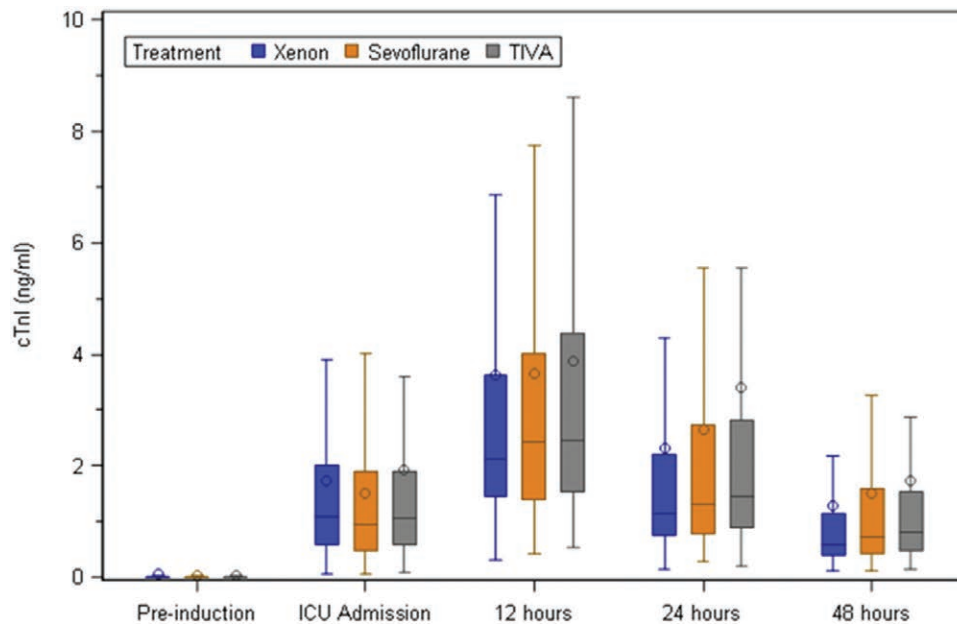


Fig. 2. Box-and-whisker plots of cardiac troponin I (cTnI) concentrations over time. cTnI concentrations in blood samples drawn at the indicated times were measured using the ARCHITECT platform (Abbott Diagnostics, USA). The results presented are for the intention-to-treat population. The *bottom* and *top edges* of each box correspond to the intraquartile range (IQR); the *upper* and *lower whiskers* extending from each box indicate the maximum and minimum cTnI concentrations, respectively, within 1.5 times the IQR. The *horizontal line* inside each box indicates the median cTnI concentration for the group; the *circle* indicates the mean cTnI concentration for the group. ICU = intensive care unit; TIVA = total intravenous anesthesia.

Table 3. Postoperative Peak Concentrations of Cardiac Damage and Prognostic Markers

		Anesthesia Method			P Value of Global Treatment Effect*
	Population Analyzed	Xenon (N = 161)	Sevoflurane (N = 165)	TIVA (N = 166)	
cTnI, ng/ml					
Median (IQR)	ITT	2.23 (1.47–3.68)	2.82 (1.48–4.45)	2.62 (1.74–5.26)	0.11
Mean (SD)	ITT	3.92 (5.27)	4.25 (5.55)	5.09 (9.39)	0.09
cTnI, ng/ml					
Median (IQR)	PP	2.21 (1.48–3.60)	2.77 (1.39–4.30)	2.78 (1.79–5.26)	0.04†
Mean (SD)	PP	3.63 (4.53)	4.14 (5.64)	4.61 (5.27)	0.04†
CK-MB, ng/ml					
Median (IQR)	ITT	18 (10–25)	18 (11–27)	19 (11–30)	0.23
Mean (SD)	ITT	26 (26)	25 (29)	29 (26)	0.22
NT-proBNP, ng/l					
Median (IQR)	ITT	1,614 (1,035–2,599)	1,508 (941–2,209)	1,524 (912–2,225)	0.32
Mean (SD)	ITT	2,303 (2,646)	1,776 (1,072)	2,184 (2,308)	0.32
CRP, mg/l					
Median (IQR)	ITT	181 (137–208)	187 (156–229)	195 (159–231)	0.03‡
Mean (SD)	ITT	183 (65)	191 (68)	199 (61)	0.07

*For the medians, the *P* values correspond to comparisons of treatment groups using a nonparametric Kruskal–Wallis test. To assess significant global treatment effects, pairwise comparisons of the treatment groups were performed using the Dwass, Steel, Critchlow–Fligner multiple comparison analysis. For the means, the *P* values correspond to comparisons of treatment groups using three-armed analysis of covariance tests on log-transformed data. To assess significant global treatment effects, pairwise comparisons of the treatment groups were performed using the Tukey test. †Statistically significant global treatment effect (*P* < 0.05), with xenon superior to TIVA (*P* = 0.03) in a pairwise comparison. ‡Statistically significant global treatment effect (*P* < 0.05), with xenon superior to TIVA (*P* = 0.02) in a pairwise comparison.

CK-MB = creatine kinase-MB fraction; CRP = C-reactive protein; cTnI = cardiac troponin I; IQR = interquartile range; ITT = intention-to-treat; N = total number of patients analyzed; NT-proBNP = N-terminal-probrain natriuretic protein; PP = per-protocol; TIVA = total intravenous anesthesia.

sevoflurane was not. These results are consistent with a cardioprotective effect for xenon anesthesia in humans that is at least similar to that of sevoflurane anesthesia.

Furthermore, xenon-based maintenance anesthesia was feasible with no safety concerns and no clinically meaningful differences in the surgery characteristics or

Table 4. Selected Postoperative Patient Characteristics

	Anesthesia Method		
	Xenon (N = 161)	Sevoflurane (N = 165)	TIVA (N = 166)
Hemodynamic parameters at ICU admission, mean (SD)			
Heart rate, beats/min	81 (14)	78 (13)	76 (13)
Overall systolic arterial pressure, mmHg	111 (21)	114 (22)	107 (20)
Overall mean arterial pressure, mmHg	78 (15)	79 (14)	75 (14)
Overall diastolic arterial pressure, mmHg	61 (12)	61 (11)	59 (12)
Cardiac rhythm at ICU admission, n (%)			
Sinus rhythm	140 (87)	135 (82)	143 (86)
Atrial fibrillation/flutter	1 (1)	3 (2)	0 (0)
Paced cardiac rhythm	15 (9)	25 (15)	13 (8)
Other or missing	5 (3)	2 (1)	10 (6)
Vasoactive, inotropic, and blood product treatments, n (%)			
At least one vasodilator	44 (27)	47 (29)	41 (25)
At least one vasopressor	70 (44)	72 (44)	87 (52)
At least one inotropic medication	19 (12)	14 (9)	15 (9)
At least 1 unit of blood product*	18 (11)	20 (12)	15 (9)
LOS in ICU and hospital			
Median time to fit-for-ICU discharge, hours (IQR)	21 (12–29)	21 (12–36)	21 (12–36)
Median LOS in ICU, hours (IQR)	27 (22–50)	29 (22–53)	42 (21–61)
Median postoperative LOS in hospital, days (IQR)	9 (8–11)	9 (8–11)	9 (8–11)

*Fluids for blood substitution.

ICU = intensive care unit; IQR = interquartile range; LOS = length of stay; N = total number of patients analyzed; n = number of patients with the characteristic; TIVA = total intravenous anesthesia.

in postoperative recovery compared to the other two methods.

Our results for propofol-based TIVA and sevoflurane anesthesia maintenance are consistent with previous studies that found cTnI release at 24 h after coronary surgery to be significantly lower with sevoflurane than with propofol.^{11,43,45,46} In these studies and in ours, the mean cTnI concentrations at 24 h with sevoflurane were similar (~2 ng/ml), but cTnI release with propofol in the previous studies tended to be higher (more than 4 ng/ml) than in our study (2.90 ng/ml). This may explain why the cTnI concentration with sevoflurane in our study was not significantly lower than it was with propofol-based TIVA. The cTnI concentration with xenon, but not sevoflurane, was significantly lower than with TIVA, which suggests that xenon anesthesia may provide a more consistent effect on limiting myocardial damage than sevoflurane anesthesia.

Postoperative release of cTnI measured at 24 h after cardiac surgery has emerged as one of the most reliable predictors of postoperative outcome, morbidity, and mortality.^{3,4} High cTnI concentrations (*i.e.*, more than 13 ng/ml) have been associated with the worst short- and long-term outcomes.⁴ In addition, 2-yr survival in patients with cTnI concentrations of 4.3 to 8.5 ng/ml was measurably lower than in patients with concentrations of less than 2.2 ng/ml.³ This observation, coupled with the studies reported by Mokhtar *et al.*,⁶ Domanski *et al.*,⁷ and others,^{47,48} suggest that even relatively small differences in postoperative cTnI concentrations after cardiac surgery can have long-term implications on patient outcome. Although the clinical benefits of such

differences in low-risk patients might be difficult to measure even in a large trial, it is reassuring that the mean cTnI concentration in our xenon group was the lowest of all three groups, that it was significantly lower than in the propofol-based TIVA group, and that the xenon group had the smallest proportion of patients with very high concentrations of cTnI.

A small significant difference in cTnI release between surgery patients anesthetized with propofol (~3 ng/ml) or sevoflurane (~1.5 ng/ml) was also associated with shorter ICU and hospital stays.⁴⁶ In our study, although we did not test for statistical significance, we observed a similar trend for ICU-LOS.

There were three deaths in the TIVA group, whereas no patient died in either the xenon or sevoflurane group. However, we consider that given the low overall mortality in the study, this result likely occurred by chance. The causes of death were air-embolism, multiorgan failure, and bowel ischemia, none of which can be considered to result from the lack of a cardioprotective effect of propofol.

This study demonstrates that xenon anesthesia is feasible and safe for CABG surgery. Overall, postoperative recoveries and AEs were similar for all three groups. Anesthesiologists were routinely able to maintain target BIS values with xenon; however, more patients in the xenon group than in the sevoflurane group received temporary rescue anesthesia with propofol. This may be due to the average inspired concentrations of xenon (52 to 56%) being near the upper limit of 65%, giving little margin to increase the xenon concentration if needed. No patients in the xenon group died,

Table 5. Peri- and Postoperative Treatment-emergent Adverse Events, SAEs, and Deaths

	Anesthesia Method					
	Xenon (N = 178)		Sevoflurane (N = 165)		TIVA (N = 166)	
	Patients, n (%)	AEs, n	Patients, n (%)	AEs, n	Patients, n (%)	AEs, n
Overall TEAEs						
At least one TEAE	167 (94)	896	154 (93)	793	155 (93)	764
Mild	154 (87)	615	141 (86)	566	143 (86)	525
Moderate	93 (52)	240	86 (52)	194	90 (54)	202
Severe	25 (14)	41	17 (10)	33	19 (11)	37
Most frequent TEAEs						
Cardiac disorders	102 (57)	140	82 (50)	120	83 (50)	115
Atrial fibrillation	55 (31)	55	43 (26)	43	37 (22)	37
Vascular disorders	80 (45)	107	84 (51)	103	80 (48)	104
Hypotension	55 (31)	55	64 (39)	64	55 (33)	55
Hypertension	41 (23)	41	27 (16)	27	37 (22)	37
Most frequent SAEs						
At least one SAE	30 (17)	45	24 (15)	37	26 (16)	44
Cardiac disorders	9 (5)	9	11 (7)	13	7 (4)	7
Myocardial infarction	5 (3)	5	4 (2)	4	3 (2)*	3
Cardiac tamponade	1 (1)	1	3 (2)	3	2 (1)	2
Respiratory, thoracic and mediastinal disorders	7 (4)	8	1 (1)	2	5 (3)	5
Infections and infestations	6 (3)	6	7 (4)	9	7 (4)	8
Injury, poisoning and procedural complications	5 (3)	5	5 (3)	5	7 (4)	7
Post procedural hemorrhage	2 (1)	2	4 (2)	4	3 (2)	3
Post procedural myocardial infarction	0	0	0	0	3 (2)	3
SAEs possibly related to treatment						
At least one SAE	5 (3)	6†	3 (2)	3‡	5 (3)	5§
Deaths						
Fatal adverse events	0	0	0	0	3 (2)	3

*An additional three patients reported postprocedural myocardial infarction. †The six SAEs were severe cases of hyperthermia, renal failure, pneumothorax, pulmonary embolism, hypotension, and hypertension. ‡The three SAEs were severe cases of low cardiac output syndrome, myocardial infarction, and ventricular fibrillation. §The five SAEs were severe cases of pneumonia, postoperative myocardial infarction, increased postoperative troponin I, renal failure, and bronchospasm.

AE = adverse event; N = total number of patients analyzed (safety set); n = number of patients with the indicated adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

and only one patient in this group was discontinued permanently for hypertension, which resolved.

Although the reported incidence of postoperative delirium in patients undergoing cardiac surgery can be as high as 30%, the incidence of postoperative delirium in our study, as solely assessed by the CAM, was only 2.5%, and similarly low in all treatment groups. This may have been partially due to the overall low-risk status of the patients, who had a low median EuroSCORE I of ~1.8. Cardiac surgery patients who develop postoperative delirium tend to have higher EuroSCOREs.^{49,50}

The strengths of the study are that it was a large, international, three-arm trial comparing xenon to two standard anesthetics. The central lab was blinded to patient treatments, and the baseline characteristics of the patients and the characteristics of the performed surgeries were very similar across the study centers, which enabled us to detect significant differences between groups, even in this low-risk cardiac surgery population. Blinding, however, was incomplete because it was not possible to mask the treatments to the attending teams. If this led to any bias, the consistency of

the perioperative characteristics suggests that it was minimal. Randomization was also invoked by opening an envelope just before the time when the anesthesia-induced patient was due to be connected to the study ventilator. We considered this practice more ethical and convenient to do than contacting a central randomization center at that stage of the surgery. Another limitation was that the two inhalatory anesthesia treatments had to be interrupted with propofol-based anesthesia during the CPB period. Despite this methodologic necessity, which may have reduced the differences between groups, we were nevertheless still able to observe significant differences in postoperative cTnI concentrations even in the presence of such a confounder. Finally, the study was not powered to assess clinical outcomes in this low-risk cardiac surgery patient group, so the benefit of a potential cardioprotective effect of xenon anesthesia on the overall outcome of these patients is not known. Furthermore, although reporting on observed AEs is mandatory, as part of safety reporting in clinical studies of any size, our study was not designed to draw detailed conclusions on the aspect of safety. The selection of relatively low-risk cardiac surgery patients for the

study was ethically justified by the fact that, before this trial, no large study investigating xenon for CABG surgery had ever been conducted.

In conclusion, this large, multicenter, international, three-arm, phase 3 noninferiority randomized trial demonstrated for the first time that postoperative cTnI release with xenon anesthesia was noninferior to that of sevoflurane and was measurably and significantly lower than with propofol-based TIVA in low-risk patients undergoing on-pump CABG surgery. Although only xenon anesthesia was associated with significantly lower cTnI concentrations, sevoflurane, a treatment that has reproducibly demonstrated cardioprotective advantages, also appeared have some effect compared to TIVA. The results suggest that xenon anesthesia produced an effect on myocardial damage that was at least similar to that of sevoflurane. Xenon anesthesia was safe and feasible. These results support xenon anesthesia to be further studied to determine whether it can provide additional benefits in higher risk patients undergoing procedures that involve other types of ischemic reperfusion injury and in patients for whom the potential for perioperative cardiac damage is likely to be higher than in the current study.

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Competing Interests

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Reproducible Science

Full protocol available at: jan.hofland@radboudumc.nl. Raw data available at: jan.hofland@radboudumc.nl.

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Appendix

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Supplemental Methods

Selection, Inclusion, and Exclusion Criteria. Selection criteria:

1. Male or female patients aged 18 yr (or having reached majority if the legal age of majority is over 18) or more at the date of selection
2. Coronary heart disease requiring elective isolated coronary artery bypass graft surgery to be performed with cardiopulmonary bypass in mild hypothermia (central temperature between 32 and 34°C) or normothermia with cardiac arrest and cold or warm cardioplegia
3. Normal or moderately impaired left ventricular systolic function (corresponding to a left ventricular ejection fraction above or equal to 35%, if available)
4. Written informed consent signed and dated by the patient after full explanation of the study has been given by the investigator prior to participation

Nonselection criteria:

1. Legal incapacity or limited legal capacity
2. Women who are pregnant or breastfeeding or women of childbearing potential not using adequate contraceptive methods
3. Patient previously randomized in this study
4. Recent acute myocardial infarction (within 7 days)
5. Ongoing unstable angina
6. Active endocarditis
7. Ongoing treatment with nicorandil
8. Ongoing treatment with a sulfonylurea medication if this treatment cannot be replaced 24 h before surgery
9. Participation in a drug or device trial within the previous 30 days
10. Known contraindication to xenon, sevoflurane, propofol, or sufentanil

Inclusion criteria:

1. Confirmation of the surgical procedure planned: elective isolated coronary artery bypass graft surgery to be performed with cardiopulmonary bypass in mild hypothermia (central temperature between 32 and 34°C) or normothermia with cardiac arrest and cold or warm cardioplegia.
2. Patient planned to have his/her intervention scheduled at a date and time when an anesthesia machine dedicated to administer xenon or sevoflurane is available, with an estimated minimum volume of 100 liters of xenon in the xenon cylinder (*i.e.*, a minimal pressure of 10 bars read on the manometer fixed on the xenon cylinder).

Exclusion criteria:

1. Recent or ongoing myocardial damage/infarction with cardiac troponin level assessed within 24 h of surgery above the upper reference limit for the diagnosis of myocardial

infarction (local laboratory) or prolonged thoracic pain and ST-segment deviation at rest

2. Severe renal dysfunction with preoperative value of serum creatinine concentration above 200 $\mu\text{mol/l}$ (local laboratory)
3. Severe hepatic dysfunction with preoperative value of alanine amino-transferase or alkaline phosphatase three times above the upper normal value (local laboratory)
4. Positive pregnancy test in female patients of childbearing potential
5. Severely depressed left ventricular function, corresponding to an ejection fraction below 35%, if available
6. Late discovery of any condition not in compliance with selection/nonselection criteria, including consent withdrawal

Analyses of Cardiac Troponin I and Other Prognostic Markers.

Blood samples for central laboratory analysis of blood chemistry and cardiac troponins I (cTnI), creatine kinase-MB fraction (CK-MB), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and C-reactive protein (CRP) concentrations were collected at preinduction, at intensive care unit (ICU) admission and at 12 h after admission (cTnI and CK-MB only), at 24 and 48 h after admission, and at ICU discharge. Blood samples were prepared for the central laboratory no later than 2 h after collection and were stored at -70 or -20°C until transfer to the central laboratory (BIOMNIS Laboratory, France). The measurements for cTnI were performed on the ARCHITECT platform (Abbott Diagnostics, USA), for NT-proBNP on the COBAS 8000 platform (Roche Diagnostics, USA), for CRP on the BNII platform (Siemens Healthcare Diagnostics, USA), for CK-MB (Abbott Diagnostics), and for creatinine on the COBAS 6000 platform (Roche Diagnostics). For cTnI, the 99th percentile values of 0.033 ng/ml for men and 0.013 ng/ml for women were specified by the assay manufacturer.