ORIGINAL ARTICLE

Volatile Anesthetics versus Total Intravenous Anesthesia for Cardiac Surgery

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ABSTRACT

BACKGROUND

Volatile (inhaled) anesthetic agents have cardioprotective effects, which might improve clinical outcomes in patients undergoing coronary-artery bypass grafting (CABG).

METHODS

We conducted a pragmatic, multicenter, single-blind, controlled trial at 36 centers in 13 countries. Patients scheduled to undergo elective CABG were randomly assigned to an intraoperative anesthetic regimen that included a volatile anesthetic (desflurane, isoflurane, or sevoflurane) or to total intravenous anesthesia. The primary outcome was death from any cause at 1 year.

RESULTS

A total of 5400 patients were randomly assigned: 2709 to the volatile anesthetics group and 2691 to the total intravenous anesthesia group. On-pump CABG was performed in 64% of patients, with a mean duration of cardiopulmonary bypass of 79 minutes. The two groups were similar with respect to demographic and clinical characteristics at baseline, the duration of cardiopulmonary bypass, and the number of grafts. At the time of the second interim analysis, the data and safety monitoring board advised that the trial should be stopped for futility. No significant difference between the groups with respect to deaths from any cause was seen at 1 year (2.8% in the volatile anesthetics group and 3.0% in the total intravenous anesthesia group; relative risk, 0.94; 95% confidence interval [CI], 0.69 to 1.29; P=0.71), with data available for 5353 patients (99.1%), or at 30 days (1.4% and 1.3%, respectively; relative risk, 1.11; 95% CI, 0.70 to 1.76), with data available for 5398 patients (99.9%). There were no significant differences between the groups in any of the secondary outcomes or in the incidence of prespecified adverse events, including myocardial infarction.

CONCLUSIONS

Among patients undergoing elective CABG, anesthesia with a volatile agent did not result in significantly fewer deaths at 1 year than total intravenous anesthesia. (Funded by the Italian Ministry of Health; MYRIAD ClinicalTrials.gov number, NCT02105610.)

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Coronary-artery bypass grafting (CABG) is the most common major surgical procedure performed worldwide.[1,2] More than 300,000 CABG procedures are performed each year in the United States alone,[3] with the incidence of death at 1 year reported to be 2 to 3%.[4,5]

Anesthesia during CABG is typically induced with intravenous drugs only (total intravenous anesthesia) or with a combination of volatile (inhaled) and intravenous agents. When volatile anesthetics are administered before, during, or after periods of organ ischemia, they exert cell-protective effects through multiple mechanisms. These mechanisms include modulation of G-protein–coupled receptors, intracellular signaling pathways, gene expression, potassium channels, and mitochondrial function.[6] Moreover, volatile anesthetics reduce myocardial infarct size in animal models.[7] Several randomized, controlled trials have shown that volatile anesthetics reduce biomarkers of myocardial injury,[7,8] even if the anesthetics are administered for only a short duration before ischemia.[9]

Meta-analyses have shown a reduction in mortality after CABG with volatile anesthetics,[10-12] a finding that is consistent with observations from moderate-sized randomized, controlled trials.[13-15] Two international consensus conferences identified the use of volatile anesthetics as a key nonsurgical intervention to improve survival among patients undergoing major surgery,[16,17] with potential clinical implications for more than 300 million patients each year.[18] Finally, the guidelines from the American College of Cardiology and American Heart Association and the guidelines from the European Association for Cardiothoracic Surgery have suggested that these findings should be applied to the management of anesthesia in patients undergoing cardiac surgery.[19,20] However, other randomized, controlled trials and meta-analyses did not confirm a benefit of volatile anesthetics,[8,21,22] which suggests that this issue is not definitively resolved.

We designed and conducted a large, multicenter, multinational, randomized, controlled trial to test the hypothesis that the use of volatile anesthetics during CABG would result in a lower number of deaths than total intravenous anesthesia.

Methods

Trial Design

The Mortality in Cardiac Surgery Randomized Controlled Trial of Volatile Anesthetics (MYRIAD) trial was a pragmatic, randomized, single-blind trial that was conducted at 36 centers in 13 countries. The ethics committee at each participating center approved the trial protocol, which is available with the full text of this article at NEJM.org. Details of the rationale, design, and statistical plan have been published previously.[23]

The MYRIAD trial was endorsed by the European Association of Cardiothoracic Anesthesiologists and was funded by the Italian Ministry of Health. The funding body had no role in the design of the trial, the collection and analysis of the data, or the writing of the manuscript or in the decision to submit the manuscript for publication. The authors vouch for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol.

Enrollment Criteria and Randomization

All patients scheduled for cardiac surgery were screened for eligibility. Patients were eligible for enrollment if they were 18 years of age or older and if they were scheduled to undergo elective, isolated CABG. Exclusion criteria were planned concomitant valve surgery or aortic surgery; unstable angina; myocardial infarction in the previous 30 days; current use of a sulfonylurea, allopurinol, or theophylline; participation in other randomized, controlled trials in the previous 30 days; general anesthesia in the previous 30 days; nonelective CABG; previous kidney or liver transplantation; cirrhosis; and a previous adverse response to any of the trial anesthetic agents.

Patients who met the enrollment criteria and who provided written informed consent were randomly assigned, in a 1:1 ratio, to an anesthetic regimen that included a volatile anesthetic (desflurane, isoflurane, or sevoflurane) or to total intravenous anesthesia. A randomization list was created with the use of computer-generated, permuted-block sequences, and randomization was stratified according to center. A Web-based central randomization service was used to ensure concealment of the trial-group assignments at 9 centers. The remaining 27 centers used sealed,

opaque, sequentially-numbered envelopes so that randomization could be performed as close as possible to the time of surgery. Patients, personnel who collected data, and personnel who assessed outcomes were unaware of the trial-group assignments. Attending anesthesiologists were aware of the trial-group assignments owing to the nature of the intervention.

TRIAL INTERVENTIONS

Patients in the volatile anesthetics group received an anesthetic regimen that included desflurane, isoflurane, or sevoflurane. Attending anesthesiologists were instructed to administer volatile anesthetics for as long as possible during surgery, but no specific drug-administration protocol was mandated. Several strategies to enhance the cardioprotective effect of volatile anesthetics have been proposed.[8,23,24] We recommended but did not require implementation of the following three specific strategies: maintenance of at least 1.0 minimum alveolar concentration of the volatile anesthetic (which represents an anesthetic maintenance dose with documented clinical and preconditioning effects) for at least 30 minutes; discontinuation of the volatile agent at least 15 minutes before cardiopulmonary bypass; and at least three wash-in and wash-out periods, which were defined by administration of at least 0.5 minimum alveolar concentration of the volatile agent for 10 minutes interspersed by a wash-out period of 10 minutes or more.

Patients in the total intravenous anesthesia group were not allowed to receive any volatile agents. Either target-controlled infusions or manually-controlled infusions of intravenous agents were allowed in accordance with local practice.

With the exception of the trial anesthetic regimen, all aspects of perioperative management were left to the discretion of the attending physicians. Postoperative monitoring, including the measurement of biomarkers of myocardial necrosis, was performed in accordance with local routine practice.

DATA COLLECTION AND FOLLOW-UP

We collected data on baseline characteristics and coexisting conditions, intraoperative care, postoperative duration of stay in an intensive care unit and in the hospital, major outcomes, adverse events, and protocol deviations. An investigator who was unaware of the trial-group assignments contacted patients by telephone at 30 days and at 1 year after randomization to ascertain vital status and to inquire about any new hospital admissions. In cases of loss to telephone follow-up, we assessed vital status by contacting the patient's general practitioner, contacting the city register office, and sending a letter to the home address of the patient.

TRIAL OUTCOMES

The primary outcome of the MYRIAD trial was death from any cause at 1 year. Prespecified secondary outcomes included death from any cause at 30 days, a composite of nonfatal myocardial infarction at 30 days or death at 30 days, death from cardiac causes at 30 days and at 1 year, hospital readmission during follow-up, and duration of stay in an intensive care unit and in the hospital.

We obtained data on several prespecified adverse events, including the following: adverse cerebral outcome (a composite of stroke, delirium, or postoperative cognitive impairment), acute kidney injury, receipt of renal-replacement therapy, surgical revision for bleeding, receipt of high-dose inotropic support, and receipt of mechanical circulatory support. We also obtained data on the following anesthesia-related adverse events: allergic reaction (proven or suspected) to anesthetic agents, the propofol infusion syndrome, and malignant hyperthermia. Definitions of trial outcomes and causes of death classified according to validated criteria[25] are provided in the Supplementary Appendix, available at NEJM.org.

STATISTICAL ANALYSIS

We hypothesized that the 1-year incidence of death from any cause would be 3% in the total intravenous anesthesia group,[26-30] as compared with 2% in the volatile anesthetics group.[15,31] We calculated that with a sample of 5300 patients in each group (total of 10,600 patients), the trial would have 90% power to detect such a difference at a two-sided alpha level of 0.05. Interim analyses were planned after enrollment of 25%, 50%, and 75% of the planned number of patients.[23,32,33]

The planned approach to statistical analysis was published previously.[23] Primary analyses were

performed according to the intention-to-treat principle. No imputation for missing data was planned; however, we performed an unplanned post hoc multiple imputation analysis of the primary outcome (details are provided in the Supplementary Appendix). Per-protocol and as-treated analyses were also performed.

Dichotomous data (including the primary outcome) were compared with the use of two-tailed chi-square tests with the Yates correction or with the use of Fisher's exact test when appropriate. Continuous variables were compared with the use of the Mann–Whitney U test. Two-sided significance tests were used throughout. For dichotomous outcomes, relative risks and 95% confidence intervals were calculated by means of the two-by-two table method with the use of log-normal approximation. Absolute risk differences and 95% confidence intervals were calculated for continuous outcomes. Data are presented as medians and interquartile ranges or as means and standard deviations. Prespecified subgroup analyses were performed as reported previously (see the Supplementary Appendix).[23]

A logistic-regression model with stepwise selection was used to identify predictors of death. Clinical data collected before randomization were entered into the model if they had a univariate P value of less than 0.1. Trial group (volatile anesthetics vs. total intravenous anesthesia) was forced into the multivariate model. Collinearity and overfitting were assessed with the use of a stepwise regression model and a Pearson correlation test. In the multivariate analyses, clinical factors or potential confounding variables were expressed as odds ratios with 95% confidence intervals. A post hoc time-to-event analysis of death from any cause was performed, and the hazard ratio and corresponding 95% confidence interval were calculated.

None of the 95% confidence intervals for secondary or safety outcomes were adjusted for multiplicity; therefore, inferences drawn from these intervals may not be reproducible. Data were stored electronically and were analyzed with the use of Stata software, version 15 (StataCorp).

RESULTS

TRIAL POPULATION AND BASELINE CHARACTERISTICS

From April 2014 through September 2017, we screened 13,642 patients for eligibility. A total of 5504 patients provided written informed consent, of whom 5400 were enrolled; 2709 were randomly assigned to the volatile anesthetics group and 2691 to the total intravenous anesthesia group (Fig. 1).

At the time of the second interim analysis, the data and safety monitoring board advised the management committee to stop the trial because of futility, since there was no possibility of achieving the hypothesized effect (the probability was 0.0% for the 1-percentage-point difference in death from any cause at 30 days and 0.6% for the difference at 1 year). Details are provided in the Supplementary Appendix.

The demographic and clinical characteristics of the two groups were similar at baseline (Table 1). Two patients were lost to follow-up at 30 days; therefore, data from 5398 patients (>99.9%) were included in the analysis of death from any cause at 30 days. A total of 47 patients were lost to follow-up at 1 year; therefore, data from 5353 patients (99.1%) were included in the analysis of death from any cause at 1 year (Fig. 1).

ANESTHETIC AGENTS AND PROCESS OF CARE

A total of 122 patients (2.3%) crossed over from the volatile anesthetics group to the total intravenous anesthesia group or vice versa (Fig. 1). The reasons for crossover are provided in Table S1 in the Supplementary Appendix. In the volatile anesthetics group, the most commonly used volatile agent was sevoflurane (2255 patients [83.2%]), followed by desflurane (248 patients [9.2%]) and isoflurane (157 patients [5.8%]). The most commonly used intravenous hypnotic agent in the total intravenous anesthesia group was propofol (2355 patients [87.7%]), followed by midazolam (863 patients [32.2%]) (Table 2, and Table S2 in the Supplementary Appendix).

Among patients in the volatile anesthetics group with available data, all three of the recommended strategies to enhance the cardioprotective effect of volatile anesthetics were used in 255 of 2581 patients (9.9%). At least one of the three strategies was used in 2522 of 2589 pa-

Figure 1 (facing page). Enrollment, Randomization, and Follow-up.

Because patients could have met more than one exclusion criterion, the number of patients listed for the individual criteria sum to more than 5430. CABG denotes coronary-artery bypass grafting.

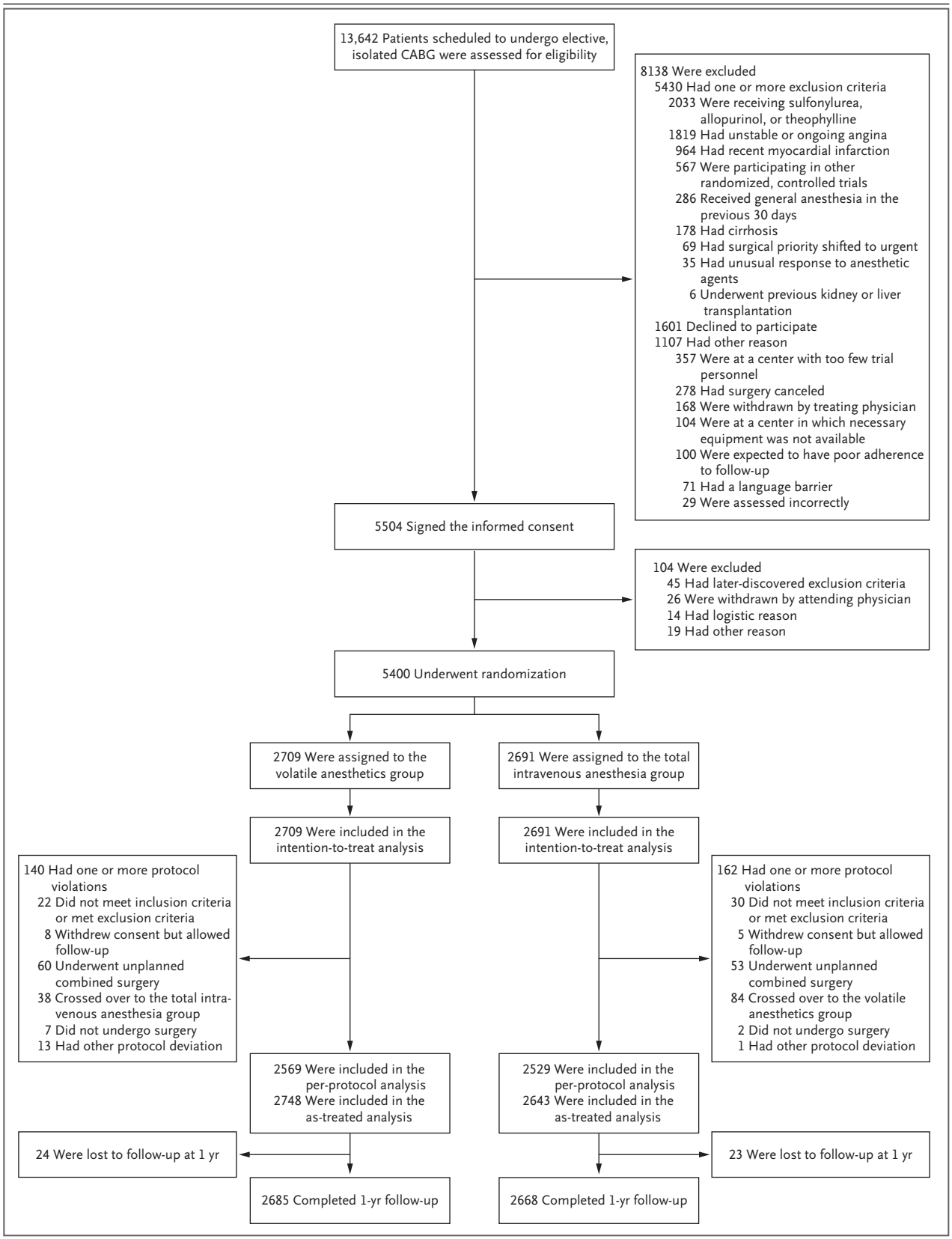


Table 1. Demographic and Clinical Characteristics at Baseline.*

Characteristic	Volatile Anesthetics Group (N=2709)		Total Intravenous Anesthesia Group (N=2691)	
	Value	No. with Missing Data	Value	No. with Missing Data
Mean age (±SD) — yr	62.2±8.37	0	62.3±8.41	1
Female sex — no. (%)	519 (19.2)	0	497 (18.5)	0
Median weight (IQR) — kg	82.0 (71.0–92.0)	48	80.0 (71.0–91.0)	48
Ethnic group — no. (%)				
Asian	77 (2.8)	5	81 (3.0)	4
White	2188 (80.9)	5	2165 (80.6)	4
Other	439 (16.2)	5	441 (16.4)	4
Median left ventricular ejection fraction (IQR) — %	58.0 (50.0–63.0)	13	57.0 (50.0–63.0)	31
Median preoperative serum creatinine (IQR) — mg/dl	1.0 (0.87–1.16)	103	1.0 (0.89–1.15)	103
Previous cardiac surgery — no. (%)	13 (0.5)	8	13 (0.5)	5
Diabetes — no. (%)	736 (27.2)	8	788 (29.4)	9
Hypertension — no. (%)	2326 (86.1)	7	2322 (86.5)	7
Chronic obstructive pulmonary disease — no. (%)	225 (8.3)	10	203 (7.6)	12
Previous vascular surgery — no. (%)	307 (11.4)	9	275 (10.3)	9
Previous myocardial infarction — no. (%)	1416 (52.4)	9	1462 (54.6)	11
Atrial fibrillation — no. (%)	132 (4.9)	5	160 (6.0)	10
Previous stroke or transient ischemic attack — no. (%)	187 (6.9)	6	176 (6.6)	12
Median risk of death at 30 days on the basis of ACEF score (IQR) — %†	1.71 (1.44–2.14)	0	1.73 (1.46–2.17)	0
Preoperative medical therapy — no. (%)				
Beta-blocker	2216 (82.0)	8	2200 (81.9)	4
ARB or ACE inhibitor	1560 (57.8)	12	1559 (58.2)	14
Calcium-channel blocker	827 (30.7)	18	802 (30.0)	17
Diuretic	771 (28.6)	10	762 (28.4)	4
Amiodarone	72 (2.7)	14	73 (2.7)	8
Digoxin	31 (1.2)	17	22 (0.8)	13
Ivabradine	22 (0.8)	13	25 (0.9)	10
Ranolazine	11 (0.4)	13	12 (0.4)	8

* There were no significant differences between the two groups in any of the characteristics listed. To convert the values for serum creatinine to millimoles per liter, multiply by 88.4. Percentages may not total 100 because of rounding. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, and IQR interquartile range.
† Details on the calculation of the age, creatinine, and ejection fraction (ACEF) score are provided in the Supplementary Appendix.

tients in that group (97.4%); maintenance of at least 1.0 minimum alveolar concentration for at least 30 minutes was implemented in 91.8%, discontinuation of volatile anesthetics at least 15 minutes before cardiopulmonary bypass in 42.3%, and at least three wash-in and wash-out periods in 24.0% (Table S3 in the Supplementary Appendix).

PRIMARY AND SECONDARY OUTCOMES

By the time of the 1-year follow-up, 75 of 2685 patients (2.8%) in the volatile anesthetics group and 79 of 2668 patients (3.0%) in the total intravenous anesthesia group had died (relative risk, 0.94; 95% confidence interval [CI], 0.69 to 1.29; P=0.71) (Table 3). The results of the post hoc analyses in which missing data were imputed

Table 2. Intraoperative Characteristics.

Characteristic	Volatile Anesthetics Group (N=2709)		Total Intravenous Anesthesia Group (N=2691)	
	Value	No. with Missing Data	Value	No. with Missing Data
Time from randomization to surgery				
Less than 2 hours				
No. of centers (%)*	25 (69.4)	0	25 (69.4)	0
No. of patients (%)	2191 (80.9)	0	2186 (81.2)	0
1 Day				
No. of centers (%)*	11 (30.6)	0	11 (30.6)	0
No. of patients (%)	518 (19.1)	0	505 (18.8)	0
Surgery				
Cardiopulmonary bypass procedure — no. (%)				
Off-pump	978 (36.4)	22	946 (35.5)	24
On-pump	1709 (63.6)	22	1721 (64.5)	24
Mean duration of on-pump procedure (±SD) — min	78.6±36.62	7	78.9±34.36	5
No. of distal anastomoses — no. (%)		22		16
1	231 (8.6)		221 (8.3)	
2	774 (28.8)		753 (28.1)	
3	1208 (45.0)		1261 (47.1)	
≥4	472 (17.6)		439 (16.4)	
Anesthetic management — no. (%)				
Intravenous opioids†	2701 (100)	8	2688 (100)	3
Volatile anesthetics†	2665 (98.4)	0	84 (3.1)	0
Intravenous hypnotics†	2661 (98.5)	8	2687 (>99.9)	2
Intravenous hypnotics for induction†	2390 (89.1)	26	2683 (99.9)	6
Intravenous hypnotics for maintenance†	1561 (58.8)	56	2655 (99.2)	15
Extubation in operating room	16 (0.6)	20	14 (0.5)	8
Weaning from cardiopulmonary bypass — no. (%)				
High-dose inotropic drugs	113 (4.2)	13	121 (4.5)	6
Intraaortic balloon pump	20 (0.7)	8	23 (0.9)	4
Other mechanical circulatory support	4 (0.1)	12	3 (0.1)	10

* The denominator used to calculate the percentage of centers was 36.
† The specific agents that were used are listed in Table S2 in the Supplementary Appendix.

were similar (Table S4 in the Supplementary Appendix).

At the time of the 30-day follow-up, 38 of 2709 patients (1.4%) in the volatile anesthetics group and 34 of 2689 patients (1.3%) in the total intravenous anesthesia group had died (relative risk, 1.11; 95% CI, 0.70 to 1.76) (Table 3). No significant differences between the two groups in any of the secondary outcomes were observed (Table 3). There was no significant difference in mortality over time (hazard ratio for death at 1 year, 1.07; 95% CI, 0.76 to 1.49) (Fig. 2). The results of the per-protocol and as-treated analyses are shown in Tables S5 and S6 in the Supple-

Table 3. Clinical Outcomes.

Outcome	Volatile Anesthetics Group (N=2709)		Total Intravenous Anesthesia Group (N=2691)		Relative Risk (95% CI)*
	Value	No. with Missing Data	Value	No. with Missing Data	
Primary outcome					
Death from any cause at 1 year — no. (%)	75 (2.8)	24	79 (3.0)	23	0.94 (0.69 to 1.29)†
Secondary outcomes					
Death from any cause at 30 days — no. (%)	38 (1.4)	0	34 (1.3)	2	1.11 (0.70 to 1.76)
Death from cardiac causes — no. (%)					
At 30 days	20 (0.7)	0	24 (0.9)	2	0.83 (0.46 to 1.49)
At 1 year	33 (1.2)	25	43 (1.6)	23	0.76 (0.49 to 1.20)
Composite of nonfatal myocardial infarction or death at 30 days — no. (%)	134 (5.0)	27	127 (4.7)	11	1.05 (0.83 to 1.34)
At least one hospital readmission during follow-up — no.(%)‡					
Within 30 days after discharge from the hospital	56 (2.1)	92	61 (2.4)	99	0.91 (0.64 to 1.30)
Between 30 days and 1 year after discharge from the hospital	222 (8.7)	154	202 (8.0)	154	1.09 (0.91 to 1.31)
Within 1 year after discharge from the hospital	257 (10.1)	153	249 (9.8)	154	1.02 (0.87 to 1.21)
Median duration of stay in intensive care unit (IQR) — nights	1.0 (1.0 to 2.0)	15	1.0 (1.0 to 2.0)	4	−0.04 (−0.18 to 0.11)§
Median duration of stay in hospital (IQR) — nights	8.0 (7.0 to 12.0)	22	8.0 (7.0 to 12.0)	14	−0.12 (−0.52 to 0.29)§

* Data are presented as relative risks for dichotomous outcomes and as absolute risk differences for continuous outcomes. The 95% confidence intervals presented in this table have not been adjusted for multiplicity; therefore, inferences drawn from these intervals may not be reproducible.
† P=0.71.
‡ Patients with missing data included patients who died, patients for whom no information on readmission was available, and patients for whom no information on vital status was available.
§ These data are absolute risk differences.

mentary Appendix, with data on postoperative peak values of myocardial necrosis markers shown in Table S7.

Prespecified subgroup analyses, as well as analyses of subgroups defined according to intraoperative characteristics, showed no treatment-by-subgroup interactions or significant differences between groups with respect to death at 30 days or at 1 year (Figs. S1 through S6 and Tables S8 and S9 in the Supplementary Appendix). Univariate and multivariate analyses of the association of baseline variables and trial intervention with death at 30 days and with death at 1 year did not show a significant effect of trial group for either outcome (Tables S10 through S13 in the Supplementary Appendix, with causes of death shown in Tables S14 and S15).

ADVERSE EFFECTS

No cases of the propofol infusion syndrome or of malignant hyperthermia were reported. Allergic reactions occurred at induction in 9 patients (0.2%; 4 in the volatile anesthetics group and 5 in the total intravenous anesthesia group) and were attributed to antibiotics, muscle relaxants, or hypnotic drugs. A total of 5 patients (4 in the volatile anesthetics group and 1 in the total intravenous anesthesia group) had a severe reaction

to protamine. Three patients died during surgery from cardiogenic shock. Additional prespecified adverse events are reported in Table S16 in the Supplementary Appendix; no significant between-group differences were observed. In particular, we observed no difference in the incidence of myocardial infarction.

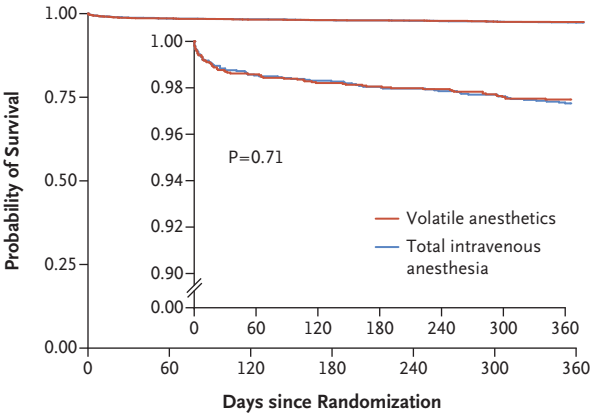
DISCUSSION

In this pragmatic, multicenter, randomized, single-blind trial involving patients undergoing elective, isolated CABG, intraoperative anesthesia with a volatile anesthetic did not result in a significantly lower number of deaths at 1 year than total intravenous anesthesia. Moreover, the outcomes of death at 30 days, a composite of perioperative nonfatal myocardial infarction at 30 days or death at 30 days, and other major secondary outcomes did not differ significantly between the two groups. Finally, the incidence of adverse events also did not differ significantly between the groups.

Previous preclinical studies, observational studies, moderate-sized randomized, controlled trials, meta-analyses of randomized, controlled trials, and consensus opinion had all suggested that the use of volatile anesthetics during cardiac surgery, and especially during CABG, would enhance myocardial protection and reduce the risk of perioperative myocardial infarction, myocardial dysfunction, and death.[11-15,31] Several patterns of administration of volatile anesthetic agents were investigated in previous studies, ranging from a single 5-minute exposure to volatile anesthetics before myocardial ischemia[9] to total inhalational anesthesia.[15] Among various possible strategies for enhancing the cardioprotective effect of volatile anesthetics, the three strategies suggested in our trial were associated with the most promising findings. Possible explanations for our failure to confirm results from previous studies include the known limited reproducibility of preclinical studies in human trials and the risk of type I error in smaller studies.

In our trial, in contrast to most previous studies, approximately one third of the patients enrolled underwent off-pump CABG. Although inclusion of these patients may have influenced our findings, previous randomized, controlled trials reported a lower postoperative troponin level in patients who underwent off-pump CABG with volatile anesthetics than in those who underwent off-pump CABG with total intravenous anesthesia.[34-37] Accordingly, we included such patients.[23] Moreover, a prespecified subgroup analysis that compared the primary outcome in patients who underwent on-pump CABG with those who underwent off-pump CABG in our trial did not suggest a differential treatment effect.

Another factor that may have influenced the results of our trial is the coadministration of propofol during the induction of anesthesia, which has been shown to attenuate the potential beneficial effect of volatile anesthetics.[15,38] However, several studies have shown beneficial effects of volatile anesthetics even with coadministration of propofol,[9,14,39] with some trials even suggesting that myocardial protection may actually be enhanced by the combination therapy.[8] Opioids could have a preconditioning cardioprotective effect that would potentially mask the effect of volatile agents. However, previous trials that showed a beneficial effect of volatile agents did not restrict or specify an intraoperative opioid regimen,[14,15] and cardioprotective doses of opioids are much higher than the doses used for anesthesia in clinical practice.



No. at Risk							
Volatile anesthetics	2677	2639	2629	2625	2622	2613	2610
Total intravenous anesthesia	2660	2621	2615	2608	2603	2597	2590

Figure 2. Kaplan–Meier Survival Estimates of Death from Any Cause.
The inset shows the same data on an enlarged y axis.

Several limitations regarding our trial intervention should be considered in interpreting our findings. First, we did not use a strict protocol for the administration of volatile anesthetics and the management of concomitant anesthetic drugs. However, our trial was pragmatic and was aimed at replicating a real-life environment. For the same reason, we did not compare total intravenous anesthesia with total inhalational anesthesia because the latter strategy is seldom used in adult surgery, and previous trials also allowed for administration of intravenous anesthetics in the volatile anesthetics group.[13-15] Second, we allowed clinicians to use any one of three volatile agents; however, previous meta-analyses had suggested that these agents have equivalent protective effects.[12] Third, implementation of all three strategies of volatile anesthetic administration that we recommended to enhance cardioprotection occurred in relatively few patients, although at least one of the recommended strategies was implemented in more than 95% of the patients in the volatile anesthetics group.

Several other trial limitations should also be noted. First, our trial was stopped early, which increased the risk of type 2 error for the secondary outcomes. However, there was no trend toward a beneficial effect of volatile anesthetics for these outcomes, and the survival plots were almost identical. Second, we did not mandate postoperative measurement of troponin. Thus, our diagnosis of postoperative myocardial infarction had limited sensitivity. Third, the number of deaths at 1 year in our trial was consistent with that in recent literature[26-30] but lower than that in the two largest randomized, controlled trials that favored volatile anesthetics.[14,15] Therefore, the possibility exists that a beneficial effect could have been observed in a population with higher mortality. Fourth, our trial focused on patients who underwent isolated elective CABG. Thus, we cannot comment on whether volatile anesthetics would have a different effect on patients undergoing complex surgery. However, previous trials and meta-analyses showed no benefit in other types of cardiac surgery or in combined procedures.[12,40]

In conclusion, among patients undergoing elective, isolated CABG, an intraoperative anesthetic regimen that included volatile anesthetics did not result in significantly fewer deaths at 30 days or 1 year than a regimen of total intravenous anesthesia.

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APPENDIX

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