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# Volatile compared with total intravenous anaesthesia in patients undergoing high-risk cardiac surgery: a randomized multicentre study

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## Editor's key points

- Considerable preclinical and clinical evidence supports cardioprotection by volatile anaesthetics in cardiac surgery.
- This possibility was tested in high-risk cardiac surgery patients by comparing sevoflurane anaesthesia with propofol total i.v. anaesthesia.
- There was no significant difference between groups in the composite endpoint of intensive care unit stay and death at 30 days or 1 yr.

**Background.** The effect of anaesthesia on postoperative outcome is unclear. Cardioprotective properties of volatile anaesthetics have been demonstrated experimentally and in haemodynamically stable patients undergoing coronary artery bypass grafting. Their effects in patients undergoing high-risk cardiac surgery have not been reported.

**Methods.** We performed a multicentre, randomized, parallel group, controlled study among patients undergoing high-risk cardiac surgery (combined valvular and coronary surgery) in 2008–2011. One hundred subjects assigned to the treatment group received sevoflurane for anaesthesia maintenance, while 100 subjects assigned to the control group received propofol-based total i.v. anaesthesia. The primary outcome was a composite of death, prolonged intensive care unit (ICU) stay, or both. Thirty day and 1 yr follow-up, focused on mortality, was performed.

**Results.** All 200 subjects completed the follow-up and were included in efficacy analyses, conducted according to the intention-to-treat principle. Death, prolonged ICU stay, or both occurred in 36 out of 100 subjects (36%) in the propofol group and in 41 out of 100 subjects (41%) in the sevoflurane group; relative risk 1.14, 95% confidence interval 0.8–1.62; $P=0.5$. No difference was identified in postoperative cardiac troponin release [1.1 (0.7–2) compared with 1.2 (0.6–2.4) ng ml$^{-1}$, $P=0.6$], 1 yr all-cause mortality [11/100 (11%) compared with 11/100 (11%), $P=0.9$], re-hospitalizations [20/89 (22.5%) compared with 11/89 (12.4%), $P=0.075$], and adverse cardiac events [10/89 (11.2%) compared with 9/89 (10.1%), $P=0.8$].

**Conclusions.** There was no observed beneficial effect of sevoflurane on the composite endpoint of prolonged ICU stay, mortality, or both in patients undergoing high-risk cardiac surgery.

**Clinical trial registration.** ClinicalTrials.gov: identifier NCT00821262. Eudra CT (2008-001752-43).

**Keywords:** anaesthetics i.v., propofol; anaesthetics volatile, sevoflurane; cardiovascular anaesthesia; complications, death; heart, myocardial preservation technique

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Cardioprotective properties of volatile anaesthetics have been clearly demonstrated on a laboratory basis,[1–7] and translation of experimental evidence to clinical studies suggests a benefit in postoperative outcomes.[8–17] A recent international consensus conference indicated that volatile anaesthetics are among the few drugs/techniques/strategies that might be associated with mortality reduction.[18] They were recommended by the most recent American College of Cardiology/American Heart Association Guidelines in the setting of coronary artery bypass graft (CABG) surgery,[19] and during non-cardiac surgery to maintain general anaesthesia in patients haemodynamically stable at risk for myocardial ischaemia.[20]

Cardiac surgery has been the main arena for the comparison between volatile and total i.v. anaesthesia (TIVA) with regard to clinically relevant endpoints. Up to now, the main shortcomings of clinical trials were the small number of patients included, the predominance of single-centre studies, the low-risk isolated CABG surgery setting, the use of surrogate endpoints such as cardiac biomarkers, and short-term follow-up.[21 22] In a recent network meta-analysis, we confirmed that

volatile agents might reduce mortality after cardiac surgery when compared with TIVA (mostly propofol-based TIVA) and that sevoflurane is the most studied volatile agent.[17] If we consider that at least 1 million cardiac operations are performed annually, confirmation of the efficacy of this simple and low-cost treatment would have great clinical impact and significant implications for public health, especially for patients undergoing high-risk cardiac surgery.

The objective of this multicentre randomized controlled trial (RCT) was to study the effects of volatile agents in patients undergoing high-risk cardiac surgery with a long-term follow-up. Our *a priori* hypothesis was that sevoflurane reduces the composite endpoint of mortality, prolonged intensive care unit (ICU) stay, or both.

## Methods

### Trial design and participants

We undertook a multicentre, randomized, parallel group, controlled study to determine if sevoflurane has cardioprotective effects compared with propofol-based TIVA in a population of patients planned to undergo high-risk cardiac surgery, defined as combined valvular surgery and CABG. Short-term mortality for this kind of procedures is reported to be 5%.[23–25]

The study was conceived in accordance with the Declaration of Helsinki and its amendments. The study protocol was approved by Ethical Committees of the centres involved and registered with the identifier 2008-001752-43 on Eudra CT (https://www.clinicaltrialsregister.eu/ctr-search/trial/2008-001752-43/IT) and with the identifier NCT00821262 on ClinicalTrials.gov. No change to the methods was made after trial commencement. The study was performed at San Raffaele Scientific Institute and at Azienda Ospedaliero-Universitaria Pisana, in Italy, between September 2008 and June 2011, when the planned number of patients was enrolled. The 1 yr follow-up ended in September 2012. Our report follows the CONSORT 2010 statement guidelines.[26] The methods of the study were previously described.[27]

All patients aged 18 yr or more and undergoing combined valvular and coronary surgery were eligible and, if they provided written informed consent, were enrolled. Exclusion criteria were: ongoing acute myocardial infarction, elevated level of circulating cardiac troponin, previous unusual response to sevoflurane (malignant hyperthermia) or propofol (allergic reaction), thoracotomy, use of sulfonylurea, theophylline, or allopurinol.

### Randomization and masking

Randomization sequence was stratified by site and generated by a computer by permuted block randomization with a 1:1 allocation and block size of 20. An independent epidemiologist prepared the allocation sequence and concealed it with opaque, sequentially numbered, sealed envelopes. After enrolment, subjects were randomly allocated to the placebo or intervention group by assigning them the envelope with the lowest number. Randomization was performed at the last available moment in the operating theatre. Envelopes were closed and sealed again before the end of surgery. No code break was reported.

Subjects and study personnel, including those involved in ICU management, were blinded to treatment for the duration of the study except for the cardiac anaesthesiologists performing the anaesthesia in the surgical theatre, who were not involved in collecting, entering, or analysing data. To reduce bias, data collection was made by trained observers not otherwise involved in patient care and blinded to the anaesthesia regimen.

### Intervention

All subjects were admitted to the cardiac surgery ward before the operation, underwent cardiac surgery with general anaesthesia, and were transferred to the ICU after surgery. All preoperative medications were routinely omitted on the day of surgery. Preoperative β-blockers were continued after operation if permitted by heart rate, arterial pressure, and cardiac index. No other drug was continued routinely or given for cardiac protection.

Premedication was morphine 0.1 mg $kg^{-1}$ subcutaneously and scopolamine 0.25 mg i.m. 1 h before surgery. During anaesthesia induction, subjects received i.v. midazolam (0.15–0.25 mg $kg^{-1}$) or thiopental (3–6 mg $kg^{-1}$), opioid (fentanyl 5–10 μg $kg^{-1}$), and neuromuscular blocking agent (rocuronium 0.6–1.2 mg $kg^{-1}$). Anaesthesia was maintained with opioid (fentanyl 3–5 μg $kg^{-1}$ $h^{-1}$ in repeated boluses), neuromuscular blocking agent (rocuronium 10 μg $kg^{-1}$ $min^{-1}$ continuous infusion), and either sevoflurane or propofol. The study group received sevoflurane (Sevorane, Abbott, Campoverde di Aprilia -LT-, Italy) at 0.5–2 minimum alveolar concentration (MAC), equal to 1–4 vol%, 4–6 h (from induction of anaesthesia to transport to ICU and including cardiopulmonary bypass—CPB). The control group received propofol (Diprivan, Astra Zeneca, Basiglio -MI-, Italy), at an infusion rate of 2–3 mg $kg^{-1}$ $h^{-1}$, for the same 4–6 h period.

All subjects received an infusion of tranexamic acid: 1 g administered in 20 min followed by a 400 mg $h^{-1}$ infusion. Moderate hypothermia (32–34°C) was maintained during CPB and myocardial perfusion during aortic cross-clamping was performed with antegrade, retrograde cold Custodiol or blood cardioplegia, or both. Activated clotting time was maintained >480 s for CPB, heparin (starting dose=3 mg $kg^{-1}$) was reversed with protamine in a 1:1 ratio. Target mean arterial pressure after CPB was 65 mm Hg.

After surgery, subjects were sedated with propofol and transferred to the ICU. After 4 h, weaning from mechanical ventilation began after achievement of haemodynamic stability with no major bleeding, normothermia, adequate level of consciousness and pain control. Postoperative pain relief was provided by morphine and paracetamol.

Transfer from the ICU was performed with the following criteria: peripheral oxygen haemoglobin saturation ($Sp_{O_2}$) ≥94% with an inspired fraction of oxygen ($F_{I_{O_2}}$) ≤0.5 with a facemask, cardiac stability and no haemodynamically significant arrhythmias, chest tube drainage <50 ml $h^{-1}$, urine output >0.5 ml $kg^{-1}$ $h^{-1}$, no i.v. inotropics or vasopressors in

excess of dopamine 5 μg kg$^{-1}$ min$^{-1}$, and no seizures. Hospital discharge was performed with the following criteria: haemodynamic and cardiac rhythm stability, clean and dry incisions, apyrexia, normal bowel movement, and independent ambulation and feeding.

Clinical characteristics were collected together with transoesophageal echocardiography data (collected at least 1 day before surgery). Systolic, mean, and diastolic arterial pressure, heart rate, and central venous pressure, and also data from blood gas analysis, were recorded at seven time points: before induction of anaesthesia, before and after CPB, at ICU arrival, and 4, 8, and 12 h later. Blood was collected at four time points: before surgery and 4 h, 1 and 2 days after ICU arrival. Caregivers were interviewed daily for the occurrence of postoperative adverse events. Myocardial infarction was defined as suggested by the Consensus Conference for the Universal Definition of Myocardial Infarction.[28]

## Outcome measures

The prespecified main outcome measure was the composite endpoint of death, prolonged ICU stay, or both. Death was defined as death during the post-surgery hospital stay, regardless of the number of days after surgery, while prolonged ICU stay was defined as ICU stay >2 days using the above transfer criteria. To overcome bias organizational factors, the times of fitness for criteria of discharge from the ICU were collected and analysed.

Secondary outcome measures were: cardiac troponin release, incidence of perioperative myocardial infarction (cardiac biomarker values >5 times the 99th percentile of the normal reference range during the first postoperative 72 h when associated with new pathological Q-waves or new left bundle branch block or electrocardiogram or occlusion of a new graft or a native coronary artery at angiography with new loss of viable myocardium),[28] time on mechanical ventilation (h), and postoperative hospital stay (days).

Neurological damage was classified as follows: type I neurological damage was defined as fatal or non-fatal stroke, transient ischaemic attack, stupor, or coma at discharge; type II neurological damage was defined as intellectual function worsening, confusion, agitation, disorientation, memory deficit, or seizures.[29] Renal injury was classified according to the RIFLE criteria.[30]

Clinical follow-up was performed before hospital discharge (length of hospital stay, major complications). Thirty day and 1 yr follow-up was performed, focusing on adverse cardiac events and hospital readmissions.

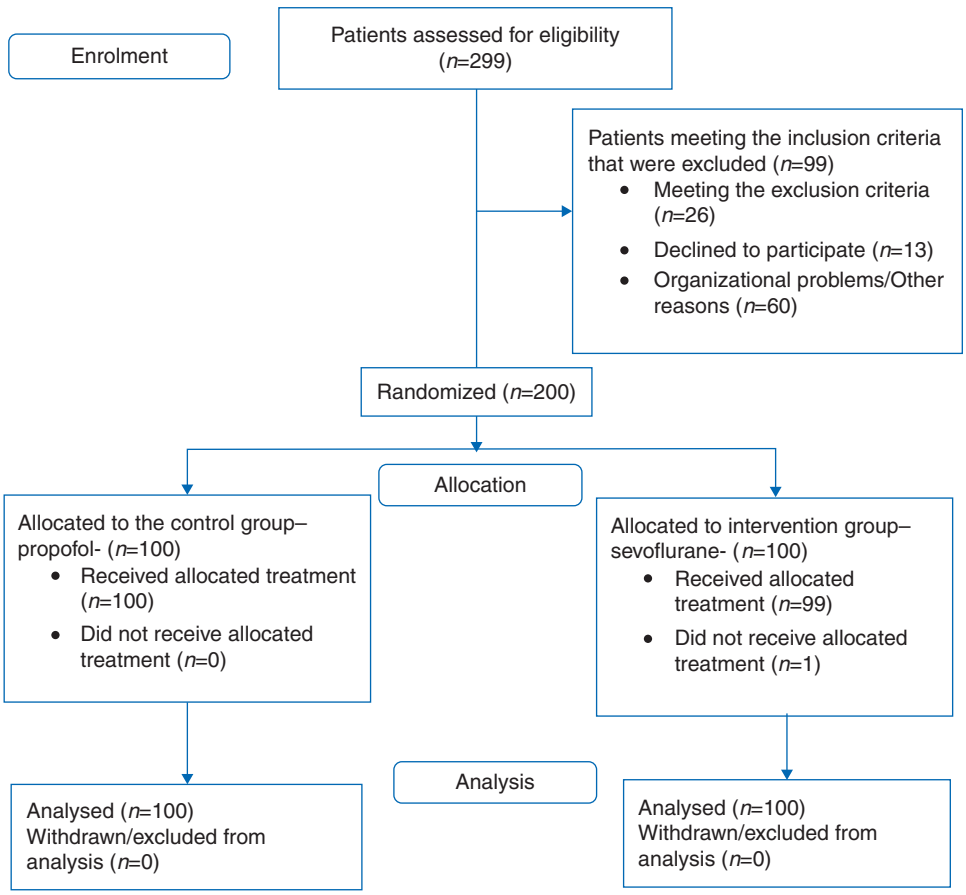


**Fig 1** Trial flow diagram.

## Statistical analysis

Sample size calculation was based on a two-sided $\alpha$-error of 0.05 and a power of 80%. We expected 60% of subjects with a composite endpoint of death, prolonged ICU stay (>2 days), or both in the control group and 40% of patients in the treatment group, with a calculated sample size of 93 subjects per group. Therefore, we planned to enrol 1200 subjects.

Data were stored in an electronic database and analysed using SAS software version 9 (SAS Institute, North Carolina, USA), and are expressed as number (%) or mean (standard deviation) or as medians (25th and 75th percentiles). Data were analysed according to the intention-to-treat principle and following a pre-established analysis plan. Dichotomous data were compared with the two-tailed $\chi^2$ test, using the Yates

**Table 1** Baseline subject characteristics. Dichotomic data are presented as number (%); continuous data are presented as mean (standard deviation) or as median (25–75th percentiles). No significant difference was found between the two groups. EuroSCORE, European System for Cardiac Operative Risk Evaluation; IABP, intra-aortic balloon pump counterpulsation

| | Propofol (control) group ($n=100$) | Sevoflurane (study) group ($n=100$) |
|---|---|---|
| Age (yr) | 70 (extreme range 50–90) | 68 (extreme range 24–84) |
| Female sex | 36 (36%) | 28 (28%) |
| Weight (kg) | 72 (11.6) | 75 (15.2) |
| Height (cm) | 168 (7.9) | 169 (9.0) |
| Co-existing diseases | | |
| Previous cardiac surgery | 8 (8%) | 8 (8%) |
| Hypertension on treatment | 64 (64%) | 67 (67%) |
| Congestive heart failure | 18 (18%) | 12 (12%) |
| New York Heart Association Class | | |
| Class 1 | 10 (10%) | 12 (12%) |
| Class 2 | 47 (47%) | 54 (54%) |
| Class 3 | 29 (29%) | 24 (24%) |
| Class 4 | 3 (3%) | 1 (1%) |
| Chronic obstructive pulmonary disease | 14 (14%) | 12 (12%) |
| Previous history of cerebrovascular accident | 7 (7%) | 7 (7%) |
| Carotid artery disease | 12 (12%) | 8 (8%) |
| Peripheral vascular disease | 9 (9%) | 5 (5%) |
| Drug therapy | | |
| Angiotensin-converting enzyme inhibitors | 43 (43%) | 51 (51%) |
| β-Blockers | 50 (50%) | 53 (53%) |
| Calcium channel antagonists | 15 (15%) | 22 (22%) |
| Diuretics | 50 (50%) | 41 (41%) |
| Statins | 33 (33%) | 38 (38%) |
| Nitrates | 10 (10%) | 11 (11%) |
| Digitalis | 11 (11%) | 4 (4%) |
| Preoperative data | | |
| Additive EuroSCORE | 6 (5–8) | 6 (3–7) |
| Ejection fraction (%) | 51.4 (11.4) | 50.1 (18.2) |
| Rheumatic/degenerative/post-endocarditis mitral regurgitation | 32 (32%) | 31 (31%) |
| Functional (ischaemic/dilated cardiomyopathy) mitral regurgitation | 6 (6%) | 7 (7%) |
| End-diastolic diameter (cm) | 5.2 (4.4–6.0) | 5.4 (4.8–6.0) |
| End-diastolic volume (ml) | 115 (59) | 122 (50) |
| End-systolic diameter (cm) | 3.5 (2.7–4.5) | 3.4 (3.0–3.9) |
| End-systolic volume (ml) | 59 (40.) | 60 (44) |
| Pulmonary artery pressure (mm Hg) | 39 (15) | 40 (15) |
| Interventricular septum (mm) | 13 (3.1) | 13 (3.5) |
| Preoperative positioning of IABP | 3 (3%) | 0 (0%) |
| Type of surgery | | |
| Number of coronary artery bypass graft | 1 (1–2) | 1 (1–2) |
| Mitral valve surgery | 36 (36%) | 46 (46%) |
| Aortic valve surgery | 67 (67%) | 56 (56%) |

correction when appropriate. Continuous measures were compared by analysis of variance or the non-parametric Kruskal–Wallis test, when appropriate. Relative risks with 95% confidence intervals and differences between medians with 95% confidence intervals (using the Hodges–Lehmann estimation) were calculated when appropriate.

Two-sided significance tests were used throughout. No interim analysis was conducted and no change in the analysis plan was made.

## Results

The number of patients screened for enrolment, the number of subjects enrolled, and their fate in the study are summarized in Figure 1. No subject retired or was withdrawn from the study. One subject randomized to the sevoflurane group received propofol during CPB by mistake. All subjects were included in efficacy analyses conducted according to the intention-to-treat principle.

Baseline characteristics are presented in Table 1, and were balanced between the two treatment groups. Intraoperative data, intraoperative and postoperative vital parameters, and other outcome data are listed in Tables 2 and 3. Troponin T, creatinine, and blood natriuretic peptide values before and after surgery are presented in Figure 2.

**Table 2** Intraoperative data. Dichotomic data are presented as number (%); continuous data are presented as mean (standard deviation) or as median (25th–75th percentiles)

| | Propofol (control) group ($n=100$) | Sevoflurane (study) group ($n=100$) | *P*-value |
|---|---|---|---|
| Cardiopulmonary bypass time (min) | 112 (37) | 114 (33) | 0.4 |
| Aortic cross-clamp time (min) | 95 (73) | 92 (29) | 0.4 |
| Surgery time (min) | 288 (75) | 295 (82) | 0.6 |
| Minimum haematocrit during cardiopulmonary bypass (%) | 23 (4.6) | 23 (4.5) | 0.6 |
| Electrical cardioversion after cardiopulmonary bypass | 20 (20%) | 22 (22%) | 0.7 |
| Intraoperative transfusion of packed red blood cells | 29 (29%) | 24 (24%) | 0.4 |
| Intraoperative transfusion of fresh-frozen plasma | 8 (8%) | 12 (12%) | 0.3 |
| Intraoperative transfusion of platelets | 3 (3%) | 4 (4%) | 0.9 |
| Intraoperative inotropes or vasoconstrictors | 41 (41%) | 47 (47%) | 0.5 |

The primary endpoint occurred in 36 patients (36%) in the control group and 41 patients (41%) in the intervention group (relative risk 1.14, 95% confidence interval 0.8–1.62; $P=0.5$). There was no difference between the two groups regarding secondary endpoints (Table 3).

At follow-up, no difference was found between groups in all-cause mortality at 30 days [seven subjects (7%) died in the control group and eight subjects (8%) died in the intervention group, $P=0.8$; relative risk 1.14 (95% confidence interval 0.43–3.03)] and at 1 yr [11 subjects (11%) died in the control group and 11 subjects (11%) died in the intervention group, $P=0.9$; relative risk 1 (95% confidence interval 0.45–2.19)], and in terms of new hospitalizations and adverse cardiac events (Table 3).

## Discussion

This is the first multicentre RCT of volatile anaesthesia compared with TIVA performed in patients undergoing high-risk cardiac surgery with long-term follow-up. There was no difference between groups in the composite primary endpoint of death, prolonged ICU stay, or both; length of hospital stay; and 30 day and 1 yr mortality.

The first important limitation of our study is that the expected incidence of the primary outcome and the expected absolute risk reduction in the study group, on which the power calculation was based, might be considered excessive, rendering the study vulnerable to type II errors. The second limitation of our study is that cardiac anaesthesiologists performing the anaesthesia in the surgical theatre were not blinded to the treatment, but this potential source of bias was minimized by the fact that they were not in charge of post-surgery patient care and monitoring, whereas subjects and all investigators involved in study and data recording, monitoring, and analyses were blinded to treatment allocation. Another limitation of the study is that it was not powered to detect a difference in mortality at 30 days and at the 1 yr follow-up. It is possible that possible beneficial effects of sevoflurane are diluted when valve surgery is included and the study does not exclude the effectiveness of sevoflurane as a cardioprotective agent in a broader cardiac surgical population. The strength of our study in relation to other studies is that, even though it is not sufficiently powered, it is the first multicentre RCT on patients undergoing high-risk cardiac surgery. This multicenter RCT was designed to reduce biases associated with single-centre studies.[31] Secondly, we identified and targeted a group of patients undergoing high-risk cardiac surgery in whom the benefit could, theoretically, have been more relevant. We hypothesized that, in this group of patients, the possible cardioprotective effect of sevoflurane would result not only in a statistically significant, but not relevant to outcome, reduction in cardiac troponin release, but also in a reduction of the composite primary endpoint of death, prolonged ICU stay, or both.

Our present findings do not confirm previous data suggesting that volatile agents might have beneficial effects that translate into a reduction in ICU stay and mortality,[11–15 17] and amelioration of surrogate endpoints including cardiac

**Table 3** Outcome data. Dichotomic data are presented as number of patients (%); continuous data are presented as median (25th–75th percentiles). Relative risks (with 95% confidence interval) for dichotomic data and differences between medians (with 95% confidence intervals) for continuous data are presented when relevant. Neurological damage is defined as: type 1 neurological damage: fatal or non-fatal stroke, transient ischaemic attack, stupor, or coma at discharge; type 2 neurological damage: intellectual function worsening, confusion, agitation, disorientation, memory deficit, and seizures. ICU, intensive care unit; BNP, brain natriuretic peptide; IABP, intra-aortic balloon pump counterpulsation; RR, relative risk; CI, confidence interval.

| | Propofol (control) group ($n=100$) | Sevoflurane (study) group ($n=100$) | *P*-value (RR; 95% CI) or (difference between medians; 95% CI) |
|---|---|---|---|
| Primary endpoint | | | |
| Death during the first hospital stay and/or prolonged ICU stay | 36 (36%) | 41 (41%) | 0.5 (1.14; 0.8–1.62) |
| Secondary endpoints and biomarkers | | | |
| Perioperative myocardial infarction | 6 (6%) | 4 (4%) | 0.8 (0.67; 0.19–2.29) |
| Time on mechanical ventilation (h) | 15 (10.7–24) | 12 (9–23) | 0.2 (1.5; −1 to 4) |
| Length of hospitalization (days) | 10 (7–13) | 10 (7–14) | 0.8 (−0.5; −2 to 1) |
| Troponin T peak during ICU stay (ng $ml^{-1}$) | 1.1 (0.7–2) | 1.2 (0.6–2.4) | 0.6 (−0.09; −0.38 to 0.20) |
| Creatinine peak during ICU stay (mg $dl^{-1}$) | 1.25 (0.95–1.73) | 1.27 (0.96–2.06 | 0.3 (−0.09; −0.27 to 0.10) |
| BNP peak during ICU stay (ng $litre^{-1}$) | 1850 (1280–5900) | 1730 (968–4140) | 0.4 (297; −511 to 1105) |
| Other outcome data | | | |
| ICU inotropes or vasoconstrictors | 41 (41%) | 47 (47%) | 0.4 |
| ICU transfusion | 33 (33%) | 24 (24%) | 0.2 |
| Bleeding in the first 12 h (ml) | 340 (237–480) | 320 (240–600) | 0.9 |
| Postoperative positioning of IABP | 7 (7%) | 8 (8%) | 0.8 |
| Low cardiac output syndrome | 13 (13%) | 20 (20%) | 0.2 |
| Multiple organ failure | 2 (2%) | 4 (4%) | 0.7 |
| Type 1 neurological damage | 2 (2%) | 1 (1%) | 0.9 |
| Type 2 neurological damage | 7 (7%) | 3 (3%) | 0.2 |
| Reintubation | 6 (6%) | 7 (7%) | 0.8 |
| Tracheostomy | 5 (5%) | 4 (4%) | 0.9 |
| Pneumonia | 0 (0%) | 4 (4%) | 0.12 |
| Septic shock | 3 (3%) | 4 (4%) | 0.9 |
| Postoperative atrial fibrillation in the ICU | 16 (16%) | 15 (15%) | 0.8 |
| Acute renal failure (at least R stage of the RIFLE classification) | 21 (21%) | 24 (24%) | 0.6 |
| Continuous veno-venous haemofiltration | 3 (3%) | 7 (7%) | 0.3 |
| ICU stay (h) | 42 (22–83) | 48 (24–92) | 0.6 |
| Fit for ICU discharge (h) | 24 (13–48) | 29 (14–51) | 0.8 |
| Prolonged hospitalization ($\geq$7 days) | 59 (59%) | 65 (65%) | 0.4 |
| Prolonged ICU stay (>2 days) | 35 (35%) | 40 (40%) | 0.5 (1.14; 0.8–1.64) |
| Death during ICU stay | 4 (4%) | 7 (7%) | 0.4 (1.75; 0.53–5.79) |
| Death during the first hospital stay | 5 (5%) | 8 (8%) | 0.4 (1.6; 0.54–4.72) |
| 30 day mortality and/or myocardial infarction, type 1 neurological damage, or reintubation during ICU stay | 15 (15%) | 15 (15%) | 0.9 (1.00; 0.52–1.93) |
| 30 day mortality and/or myocardial infarction during ICU stay | 11 (11%) | 11 (11%) | 0.9 (1.00; 0.45–2.20) |
| 30 day and 1 yr follow up | | | |
| All-cause mortality at 30 days | 7/100 (7%) | 8/100 (8%) | 0.8 (1.14; 0.43–3.03) |
| All-cause mortality at 1 yr | 11/100 (11%) | 11/100 (11%) | 0.9 (1; 0.45–2.19) |
| New hospitalization among survivors at 30 days | 16/93 (17.2%) | 8/92 (8.7%) | 0.08 (0.51; 0.23–1.22) |
| New hospitalization among survivors at 1 yr | 20/89 (22.5%) | 11/89 (12.4%) | 0.075 (0.54; 0.23–1.28) |
| Adverse cardiac events among survivals at 30 days | 7/93 (7.5%) | 5/92 (5.4%) | 0.6 (0.73; 0.24–2.22) |
| Adverse cardiac events among survivals at 1 yr | 10/89 (11.2%) | 9/89 (10.1%) | 0.8 (0.67; 0.20–2.31) |

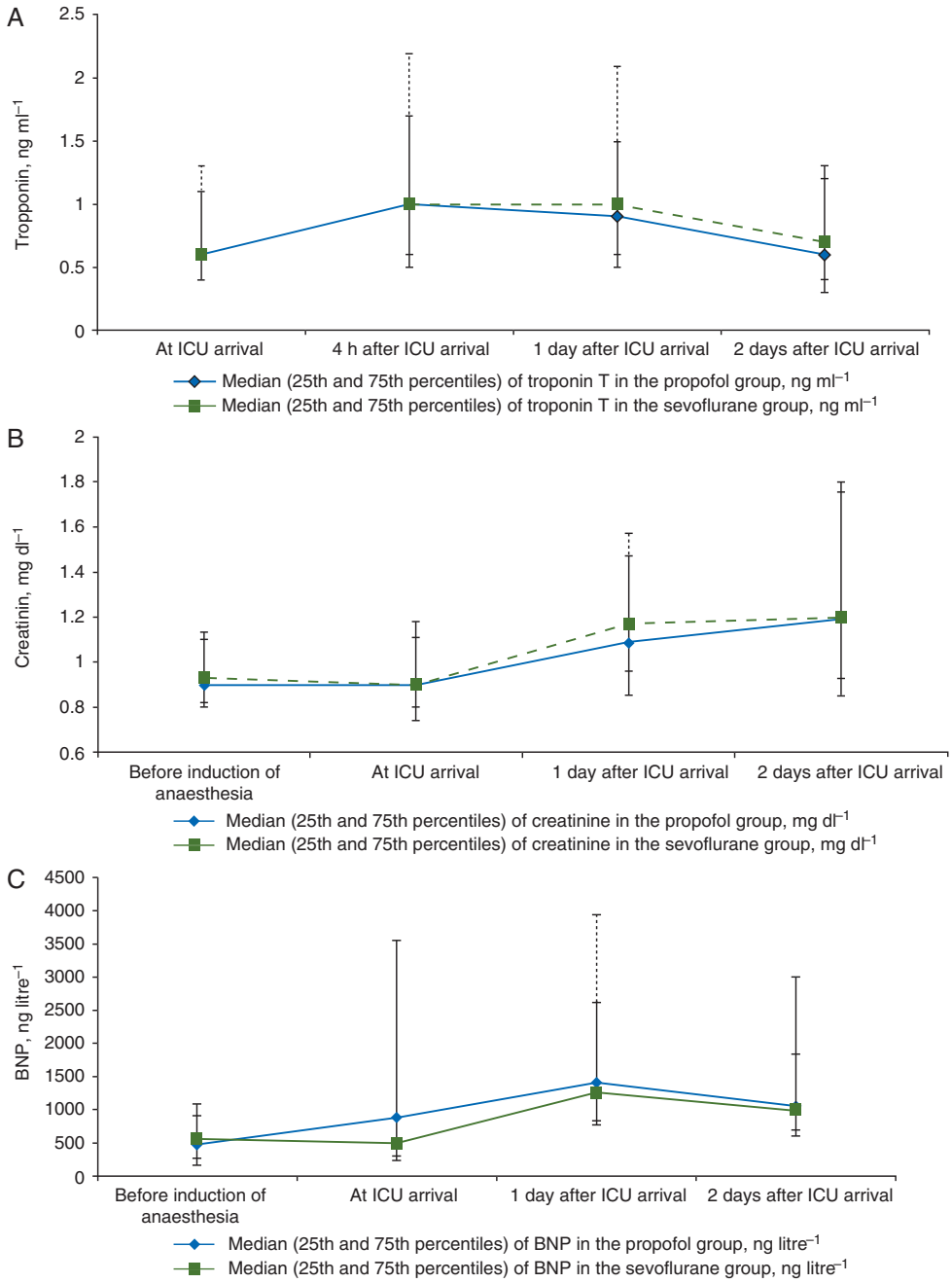


**Fig 2** Troponin T (A), creatinine (B), and brain natriuretic peptide (C) values before and after surgery. Data are presented as median (25th–75th percentiles). ICU, intensive care unit; BNP, brain natriuretic peptide.

biomarker release.[11] The first paper to suggest a survival difference was a meta-analysis of RCTs performed in cardiac surgery comparing desflurane or sevoflurane with TIVA.[11] Similar results were suggested by a meta-analysis of RCTs comparing isoflurane with TIVA when only high-quality studies performed in cardiac surgery were considered.[13] An RCT reported large 1 yr mortality differences between sevoflurane, desflurane, and TIVA in CABG surgery patients, even if the high mortality rates observed in the TIVA group could be attributed, at least in part, to chance effects.[15] A retrospective study suggested a beneficial survival effect with the use of sevoflurane in low-risk CABG surgery.[32] A meta-regression on more than 34 000 CABG procedures showed that the 30 day mortality was lower in patients receiving volatile anaesthetics.[32] Finally, we recently performed an updated network meta-analysis comparing desflurane, isoflurane, sevoflurane, and TIVA,[17] and, including 38 RCTs with survival data in this setting, found that halogenated anaesthetics were associated with a mortality reduction when compared with TIVA at the longest follow-up available [25/1994 (1.3%) in the volatile anaesthetic group compared with 43/1648 (2.6%)

in the TIVA group, $P=0.004$]. This Bayesian network meta-analysis showed that sevoflurane (odds ratio=0.31, 95% credible interval 0.14–0.64) and desflurane (odds ratio=0.43, 95% credible interval 0.21–0.82) were associated individually with mortality reduction compared with TIVA (>60% of the time propofol-based TIVA). Notably, most studies performed so far on this topic were single-centre, include low-risk CABG surgery and have a short-term follow-up.

Our study does not confirm our hypothesis that in high-risk cardiac surgery, volatile anaesthetics are superior to propofol-based TIVA using significant postoperative outcomes such as prolonged ICU stay, mortality, or both. Therefore, the promising beneficial effects of volatile anaesthetics, if any, might be limited to the isolated low-risk CABG surgery setting, and do not apply to high-risk cardiac surgery. Notably, patients undergoing high-risk cardiac surgery are those who would benefit more from improvement in cardioprotective strategies. Since the cardiac protective properties of volatile agents are well established in cellular and preclinical studies, our negative findings could be attributed to the absence of these cardiac protective properties in patients undergoing high-risk cardiac surgery, since in these patients, the mechanisms of cardiac damage might only in part be due to ischaemia/reperfusion injury.

## Conclusions

This multicentre RCT study did not demonstrate any difference between sevoflurane anaesthesia and propofol TIVA on the composite endpoint of prolonged ICU stay, mortality, or both in patients undergoing high cardiac surgery.

## Authors' contributions

All authors took part in all stages of the study, from design to writing and editing the manuscript. All authors had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

## Declaration of interest

None declared.

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