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Anaesthetic drugs and survival: a Bayesian network meta-analysis of randomized trials in cardiac surgery

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Editor's key points

- Numerous studies have suggested that volatile agents provide myocardial protection in cardiac surgery.
- No adequately powered clinical trials have been conducted to evaluate the effect of volatile agents on mortality after cardiac surgery.
- Bayesian network meta-analysis allows indirect comparisons of drugs not otherwise compared in head-to-head trials.
- Volatile-based anaesthesia seems to reduce mortality after cardiac surgery when compared with TIVA.

Background. Many studies have compared desflurane, isoflurane, sevoflurane, total i.v. anaesthesia (TIVA), or all in cardiac surgery to assess their effects on patient survival.

Methods. We performed standard pairwise and Bayesian network meta-analyses; the latter allows indirect assessments if any of the anaesthetic agents were not compared in head-to-head trials. Pertinent studies were identified using BioMedCentral, MEDLINE/PubMed, Embase, and the Cochrane Library (last updated in June 2012).

Results. We identified 38 randomized trials with survival data published between 1991 and 2012, with most studies (63%) done in coronary artery bypass grafting (CABG) patients with standard cardiopulmonary bypass. Standard meta-analysis showed that the use of a volatile agent was associated with a reduction in mortality when compared with TIVA at the longest follow-up available [25/1994 (1.3%) in the volatile group *vs* 43/1648 (2.6%) in the TIVA arm, odds ratio (OR)=0.51, 95% confidence interval (CI) 0.33–0.81, *P*-value for effect=0.004, number needed to treat 74, I^2=0%] with results confirmed in trials with low risk of bias, in large trials, and when including only CABG studies. Bayesian network meta-analysis showed that sevoflurane (OR=0.31, 95% credible interval 0.14–0.64) and desflurane (OR=0.43, 95% credible interval 0.21–0.82) were individually associated with a reduction in mortality when compared with TIVA.

Conclusions. Anaesthesia with volatile agents appears to reduce mortality after cardiac surgery when compared with TIVA, especially when sevoflurane or desflurane is used. A large, multicentre trial is warranted to confirm that long-term survival is significantly affected by the choice of anaesthetic.

Keywords: anaesthesia; anaesthesia inhalation; cardiovascular surgical procedures

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Every year more than 200 million patients worldwide undergo major surgery and are exposed to significant morbidity and mortality. A recent international consensus conference identified only 12 drugs, techniques, or strategies associated with a reduction in perioperative mortality, and the only anaesthetic drugs included in this short list were volatile agents.[1]

Volatile agents have documented pharmacological but non-anaesthetic properties conferring cardiac protection and influencing perioperative[2–4] and long-term clinically relevant outcomes,[5 6] probably because of favourable transcriptional changes in protective and anti-protective proteins.[5] The mechanism of action is related, but not limited, to the modulation of cytosolic calcium concentration through the potassium mitochondrial channels.[7]

Five studies suggested that the beneficial effect of volatile agents (desflurane, isoflurane, and sevoflurane) might translate into reduced mortality rate when compared with total i.v. anaesthesia (TIVA) in cardiac surgery.[2–4 6 8] Even if no randomized study or meta-analysis of randomized studies in favour of TIVA exists, it should be acknowledged that several meta-analysis performed in cardiac surgery[9 10] and one large randomized trial performed in non-cardiac surgery[11] did not confirm the beneficial effects of volatile anaesthetics on clinically relevant outcomes. Perhaps this is why TIVA is still commonly used in cardiac surgery.

A network meta-analysis is a statistical technique for comparison of different treatments that were never directly compared in head-to-head trials. On the basis of statistical

inference, it is possible to establish which treatment is superior, reaching, through indirect comparison, reliable conclusions otherwise impossible to achieve. The primary objective of this study was therefore to determine whether anaesthetic techniques (TIVA *vs* volatile-based anaesthesia) confer a survival advantage for patients undergoing cardiac surgery. A secondary aim was to explore whether a particular volatile (desflurane, isoflurane, or sevoflurane) or TIVA (propofol) agent is associated with improved survival.

Methods

To address the question whether the choice of the anaesthetic might influence patients' survival after cardiac surgery, we carried out standard meta-analyses and Bayesian network meta-analyses to compare the effect on mortality of desflurane, isoflurane, sevoflurane, and TIVA.

When head-to-head treatment comparisons are not available or conclusive, network meta-analyses can provide estimates of treatment efficacy of multiple treatment regimens. Different treatments are analysed by statistical inference, rather than simply summing up trials that evaluated the same drug management compared with control, so that the results come from combining both direct and indirect estimates. To model the binomial data, we applied the Bayesian hierarchical model using Markov Chain Monte Carlo (MCMC) approaches.

Search strategy and study selection

Pertinent studies were independently searched in BioMedCentral, MEDLINE/PubMed, Embase, and the Cochrane Central Register of clinical trials by two expert investigators. Literature searches were last updated on June 1, 2012. The full PubMed search strategy was developed according to Biondi-Zoccai and colleagues[12] and is available in the Appendix. Further hand or computerized searches involved the recent (2010–2012) conference proceedings from the International Anaesthesia Research Society, American Heart Association, American College of Cardiology, American Society of Anesthesiologists, and European Society of Cardiology congresses.

Study selection

References obtained from database, literature searches with cross-check of references, experts, and manufacturers were first independently examined at a title/abstract level by two investigators and then, if potentially pertinent, retrieved as complete articles. No language restriction was imposed and non-English articles were translated and included in the analyses. The following inclusion criteria were used for potentially relevant studies: random allocation to treatment and comparison between a TIVA and an anaesthesia plan including administration of isoflurane, desflurane, or sevoflurane or a comparison between volatile agents, performed in cardiac surgical patients with no restriction in dose and time of administration. The exclusion criteria were duplicate publications (in this case, the article reporting the longest follow-up was abstracted), non-human experimental studies, and lack of outcome data. Studies in which epidural analgesia/anaesthesia was given to all patients were included.[13 14] Studies in which ischaemic pre-conditioning or remote ischaemic pre-conditioning were performed in all patients were excluded because ischaemic pre-conditioning has pathways of cardiac protection that are similar to those of volatile anaesthetics[15 16] even if the cardiac protective properties of volatile agents are not limited to pre-conditioning. Two investigators independently assessed compliance to selection criteria and selected studies for the final analysis, with divergences finally resolved by consensus.

Data abstraction and study characteristics

Year of publication, setting, number of patients, volatile agent, anaesthetic comparator, and length of follow-up were collected (Table 1) together with baseline (age, diabetes, ejection fraction, chronic obstructive pulmonary disease, use of beta-blockers, and management of sulfonylurea, theophylline, or allopurinol) (Supplementary Table S1) and procedural (cardioplegia, time of cross-clamping, and number of coronary artery grafts) (Supplementary Table S2) data. Furthermore, we extracted and pooled data on mechanical ventilation, intensive care unit (ICU) stay, hospital stay, troponin I (ng ml^{-1}), myocardial infarction (as per author definition), and use of inotropic agent.

'Total Intravenous Anaesthesia' was defined as a group not receiving volatile agents. 'Propofol' was defined as a TIVA group receiving propofol as main hypnotic agent and not receiving volatile agents. 'Volatile' (desflurane, isoflurane, or desflurane) was defined as a group receiving a volatile agent (even if added on top of a TIVA regimen and irrespectively on time of administration).

The endpoint of the present systematic review and meta-analysis of randomized trials was to identify differences in mortality at the longest follow-up available between volatile agents and TIVA and to identify whether one or more anaesthetics were superior or inferior in terms of survival, using standard meta-analyses and Bayesian network meta-analyses. If we found that the study had missing or incomplete data on survival, we contacted all authors by letter, e-mail, or both.

The methodological details[17–21] for the internal validity and risk of bias assessment, for the statistical analyses and for the details on the conduction of the Bayesian network meta-analyses are reported as Supplementary data. In summary, the internal validity was evaluated according to the Cochrane Collaboration methods; the overall risk of bias was expressed as low, moderate, or high; the evidence of publication bias was assessed by analytic appraisal based on both Peters' and Begg's test; the heterogeneity assumption among studies within direct contrast was evaluated by means of Cochran *Q*-test and by I^2 by Higgins and Thompson;[17] the validity and the symmetry of the entire Bayesian network meta-analysis was investigated visually by a graph of the network configuration. The presence of effect-modifiers attributable to heterogeneity was considered acceptable if the χ^2 *P*-value was >0.10. Mortality data from individual studies

Table 1 Description of the 38 studies included in the meta-analysis. *Study published as abstract only. †Supplementary material references. TIVA, total i.v. anaesthesia; CPB, cardiopulmonary bypass; CABG, coronary artery bypass graft; OPCABG, off-pump coronary artery bypass grafting; ICU, intensive care unit

First author	Year	Setting	Volatile anaesthetic patients	TIVA patients	Volatile anaesthetic	Comparator	Follow-up
Amr[15]	2010	CPB-CABG	15	15	Isoflurane	Oxygen on sufentanil and midazolam based TIVA	Hospital stay
Ballester (75†)	2011	OPCABG	21	19	Sevoflurane	Propofol	1 yr
Bein (76†)	2005	Minimally invasive OPCABG	26	26	Sevoflurane	Propofol	Hospital stay
Belhomme (77†)	1999	CPB-CABG	10	10	Isoflurane	Oxygen and air in a fentanyl and flunitrazepam-based TIVA	3 days
Bignami (78†)	2011	Mitral surgery	50	50	Sevoflurane	Propofol	1 yr
Cavalca (79†)	2008	Cardiac surgery with CPB	22	22	Sevoflurane	Propofol	24 h
Conzen (80†)	2003	OPCABG	12	11	Sevoflurane	Propofol	Hospital stay
Cromheecke (81†)	2006	Aortic valve replacement	15	15	Sevoflurane	Propofol	Hospital stay
De Hert[23]	2003	CPB-CABG	15 and 15	15	Desflurane, sevoflurane	Propofol	36 h
De Hert[24]	2004	CPB-CABG	80 and 80	80	Desflurane, sevoflurane	Propofol, midazolam	Hospital stay
De Hert (82†)	2004	CPB-CABG	150	50	Sevoflurane	Propofol	30 days
De Hert[6]	2009	CPB-CABG	132 and 137	145	Desflurane, sevoflurane	TIVA	1 yr
Flier (83†)	2010	CPB-CABG	51	49	Isoflurane	Propofol	1 yr
Garcia[5]	2005	CPB-CABG	37	35	Sevoflurane	Oxygen in air in a propofol-based TIVA	1 yr
Goździk (84†)*	2012	CPB-CABG	40	20	Sevoflurane	Propofol	24 h
Guarracino (85†)	2006	OPCABG	57	55	Desflurane	Propofol	30 days
Hellström (86†)	2012	CPB-CABG	50	50	Sevoflurane	Propofol	30 days
Helman (87†)	1992	CPB-CABG	100	100	Desflurane	Sufentanyl on a midazolam based TIVA	3 days
Hemmerling[13]	2008	OPCABG	20	20	Isoflurane, sevoflurane	Volatile *vs* volatile study	Hospital stay
Howie (88†)	1996	Mitral surgery	27	23	Isoflurane	Fentanyl	4 h
Huang[25]	2011	CPB-CABG	30	30	Isoflurane	Propofol, midazolam	Hospital stay
Jovic (89†)	2004	Aortic valve replacement	11	11	Sevoflurane	Propofol	Hospital stay
Kendall[14]	2004	OPCABG	10	10	Isoflurane	Propofol	48 h
Kottenber[16]	2012	CPB-CABG	19	19	Isoflurane	Propofol	3 days
Landoni (90†)	2007	Mitral surgery	59	61	Desflurane	Propofol	30 days
Lee (91†)	2006	CPB-CABG	20	20	Isoflurane	Propofol	Hospital stay
Leung (92†)	1991	CPB-CABG	62	124	Isoflurane	Sufentanyl	Surgery
Meco (93†)	2007	CPB-CABG	14	14	Desflurane	Propofol	3 days
Musialowicz (94†)	2007	CPB-CABG	12	12	Isoflurane	Propofol	Surgery
Royse (95†)	2011	CPB-CABG	91	91	Desflurane	Propofol	1 yr
Schoen (96†)	2011	Cardiac surgery with CPB	62	62	Sevoflurane	Propofol	Hospital stay
Searle (97†)	1996	CPB-CABG	140 and 133		Isoflurane, sevoflurane	Volatile *vs* volatile study	Hospital stay
Story[26]	2001	CPB-CABG	120	120	Isoflurane, sevoflurane	Propofol	3 days

Continued

Table 1 *Continued*

First author	Year	Setting	Volatile anaesthetic patients	TIVA patients	Volatile anaesthetic	Comparator	Follow-up
Tempe (98†)	2011	OPCABG	23	22	Isoflurane	Propofol	Hospital stay
Thomson (99†)	1991	CPB-CABG	21	20	Isoflurane, desflurane	Volatile *vs* volatile study	Hospital stay
Tritapepe (100†)*	2003	CPB-CABG	52	55	Desflurane	Propofol	30 days
Tritapepe (101†)	2007	CPB-CABG	75	75	Desflurane	Propofol	ICU stay
Yildirim[27]	2009	CPB-CABG	20 and 20	20	Isoflurane, sevoflurane	Propofol	30 days

were analysed in order to compute pooled odds ratio (OR) with pertinent 95% confidence intervals (CIs), by means of the inverse variance method with the fixed effect model or the DerSimonian–Laird method with random effect model; the pairwise association between each treatment was delineated by a graphical representation of the network; the network analysis was carried out modelling the binary outcome mortality with the Bayesian hierarchical model (binomial model with logit link function) using the MCMC approach; the indirect estimate was calculated as the difference from the appropriate direct estimates and the corresponding 95% credibility intervals (CrI) was obtained by normal approximation; we selected the fixed or random effect model calculating the posterior mean of residual deviance (D_{res}) and the deviance information criterion (DIC) statistics.

To explore the association between log-risk of mortality and both the length of study follow-up and the year of publication, we performed meta-regression analyses using the Bayesian approach. Other sub-analyses on mortality outcome were performed analysing the three volatile agents (isoflurane, desflurane, and sevoflurane) separately, in studies using propofol as TIVA, in studies with >100 patients and stratifying by setting, such as overall coronary artery bypass graft (CABG) patients, off-pump or on-pump with cardiopulmonary bypass (CPB), and non-CABG surgery.

Sensitivity meta-analyses were performed by analysing data from studies with low risk of bias and by sequentially removing each study from the overall dataset. The statistical analysis was performed by STATA (release 11, College Station, TX, USA), winBUGS (release 1.4, freeware available by BUGS project), and SAS 2002–2008 program (release 9.2 by SAS Institute, Inc., Cary, NC, USA). Statistical significance was set at the two-tailed 0.05 level for hypothesis testing. Unadjusted *P*-values are reported throughout. This study was performed in compliance with the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[20 22]

Results

Description of included trials

Figure 1 shows the flow chart for the selection of randomized trials. Database searches, snowballing, and contacts with experts yielded a total of 2630 citations. Excluding 2518 non-pertinent titles or abstracts, we retrieved in complete form and assessed according to the selection criteria 112 studies. A total of 74 studies were further excluded because of their non-experimental design, including the use of historical controls, or because of duplicate publication. Specifically, we excluded 48 studies[1–48] because there were no outcome data and further details could not be obtained by the authors, 16 studies because of overlapping populations,[49–64] 7 observational studies,[65–71] 3 studies performed in non-cardiac surgery settings.[72–74] We finally identified 38 eligible randomized clinical trials,[5 6 13–16 23–27 75–101] which were included in the final analysis (Table 1, Supplementary Tables S1 and S2).

Study characteristics

The 38 included trials enrolled 3996 patients, including 1648 (41%) receiving TIVA and 2348 (59%) receiving volatile agents. Specifically, 1086 (27%) patients received propofol, 622 (16%) received isoflurane, 701 (17%) received desflurane, and 1025 (26%) received sevoflurane. The trials had a median sample size of 60 (range 20–414) and were published between 1991 and 2012. Clinical heterogeneity was mostly because of control treatment and the follow-up duration. Most studies [24/38 (63%)] were performed on CABG patients with CPB[5 6 15 16 23–27 77 82 83 84 86 87 91–95 97 98–101] and only five studies were performed in valve surgery patients (two aortic valve replacement and three mitral surgery). Baseline and procedural features were largely similar across the included studies.

The most common pairwise comparison was sevoflurane *vs* propofol (11 studies) followed by isoflurane *vs* propofol (six studies) and desflurane *vs* propofol (six studies). Three- and four-arm studies represented altogether 16% of the trials. Studies appeared to be of medium quality. Particularly, 19 (50%) of the randomized controlled trials (RCTs) were regarded to have low risk of bias, while the other studies lacked important details on the method used for random sequence generation and allocation (Supplementary Table S3). Many studies did not have blinding of the anaesthesiologists but of the staff collecting the outcome data.

Quantitative data synthesis

The overall standard meta-analysis (Fig. 2) showed that the use of volatile agents (isoflurane, desflurane, or sevoflurane) was

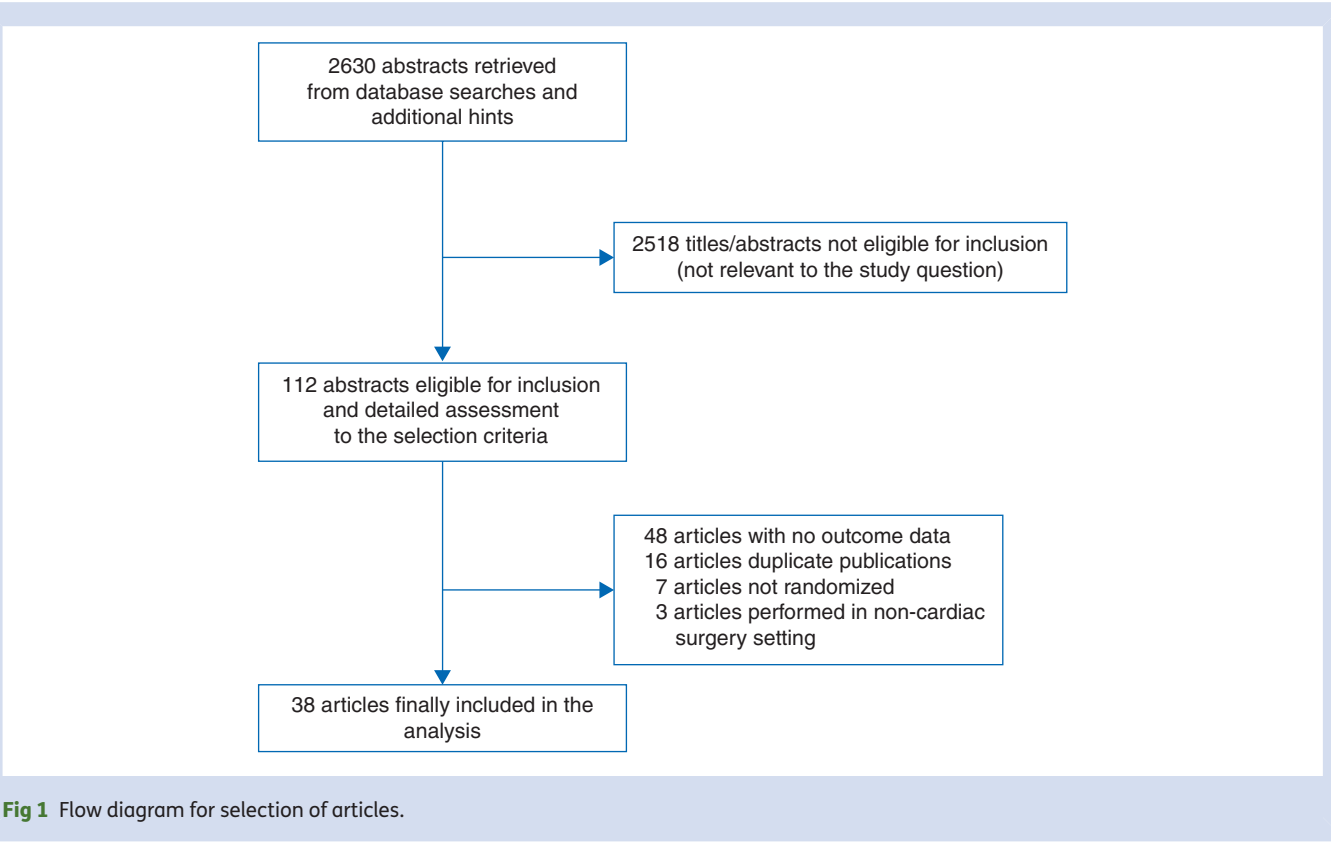

Fig 1 Flow diagram for selection of articles.

associated with a reduction in mortality when compared with TIVA at the longest follow-up available [25/1994 (1.3%) in the volatile group *vs* 43/1648 (2.6%) in the TIVA arm, OR=0.51, 95% CI 0.33–0.81, *P*-value for effect=0.004, number need to treat=74, *P*-value for heterogeneity=0.9, I^2=0% with 35 studies included and the three studies comparing a volatile agent *vs* another volatile agent excluded].

Visual inspection of the funnel plot did not identify an important skewed or asymmetrical shape (Supplementary Fig. S1). Nonetheless, as quantitative evaluation suggested a possible presence of publication bias, as measured by Peters' test (*P*=0.02) and Begg's test (*P*=0.18), we used the trim-and-fill approach (adding the missing studies as suggested by the computer) to confirm the results of our meta-analysis after adjusting for the theoretical presence of unpublished studies (OR=0.43, 95% CI 0.28–0.64, *P*-value for effect <0.001, *P*-value for heterogeneity=0.9, I^2=0%, with 13 studies added).

The results of secondary and sensitivity analysis are reported in Table 2. Volatile agents were associated with a reduced time of mechanical ventilation, and duration of ICU and hospital stay. Furthermore, of 17 studies with troponin I analysis, 7 significantly favoured the volatile regimen, in 6 we observe a trend in favour of volatile agents and in 4 a trend in favour of TIVA.

When comparing TIVA, isoflurane, desflurane, and sevoflurane through direct comparisons, we found non-significant differences in mortality: (i) isoflurane [3/449 (0.7%)] *vs* TIVA [10/504 (2.0%)], OR=0.71, 95% CI 0.29–1.75, *P*-value for effect=0.5, I^2=0% with 13 studies included; (ii) desflurane [12/680 (1.8%)] *vs* TIVA [31/771 (4.0%)], OR=0.64, 95% CI 0.35–1.18, *P*-value for effect=0.15, I^2=0% with 10 studies included; (iii) sevoflurane [10/865 (1.2%)] *vs* TIVA [25/833 (3.0%)], OR=0.80, 95% CI 0.45–1.41, *P*-value for effect=0.4, I^2=0% with 17 studies included; (iv) sevoflurane [2/300 (0.7%)] *vs* isoflurane [4/293 (1.4%)], OR=0.71, 95% CI 0.14–3.74, *P*-value for effect=0.7, I^2=0% with 4 studies included; and (v) sevoflurane [4/227 (1.8%)] *vs* desflurane [9/232 (3.9%)], OR=0.70, 95% CI 0.34–1.44, *P*-value for effect=0.3, I^2=0% with 3 studies included.

The similarity assumption, within each contrast, was confirmed by I^2<25%. The network configuration of each contrast analysed by a Bayesian network meta-analysis is reported in Figure 3. As the fixed (D_{res}=127.5 and DIC=149.4 at the longest follow-up available; D_{res}=111.5 and DIC=131.4 at short-time mortality) and random (D_{res}=126.5 and DIC=150.1 at the longest follow-up available; D_{res}=110.8 and DIC=132.0 at short-time mortality) effects models were indistinguishable in terms of model fit, we selected the first that estimated the effect by slightly increasing the precision. The final results are reported in Table 3. We calculated the indirect estimate as difference from the appropriate direct estimates (probability in favour of inconsistency model equal to 0.03 and to 0.05 at the longest follow-up available and at short-time mortality, respectively) and calculated the indirect 95% CrI by normal approximation.

The Bayesian network meta-analysis (Table 3) found that the use of sevoflurane (posterior mean of OR=0.31, 95% CrI

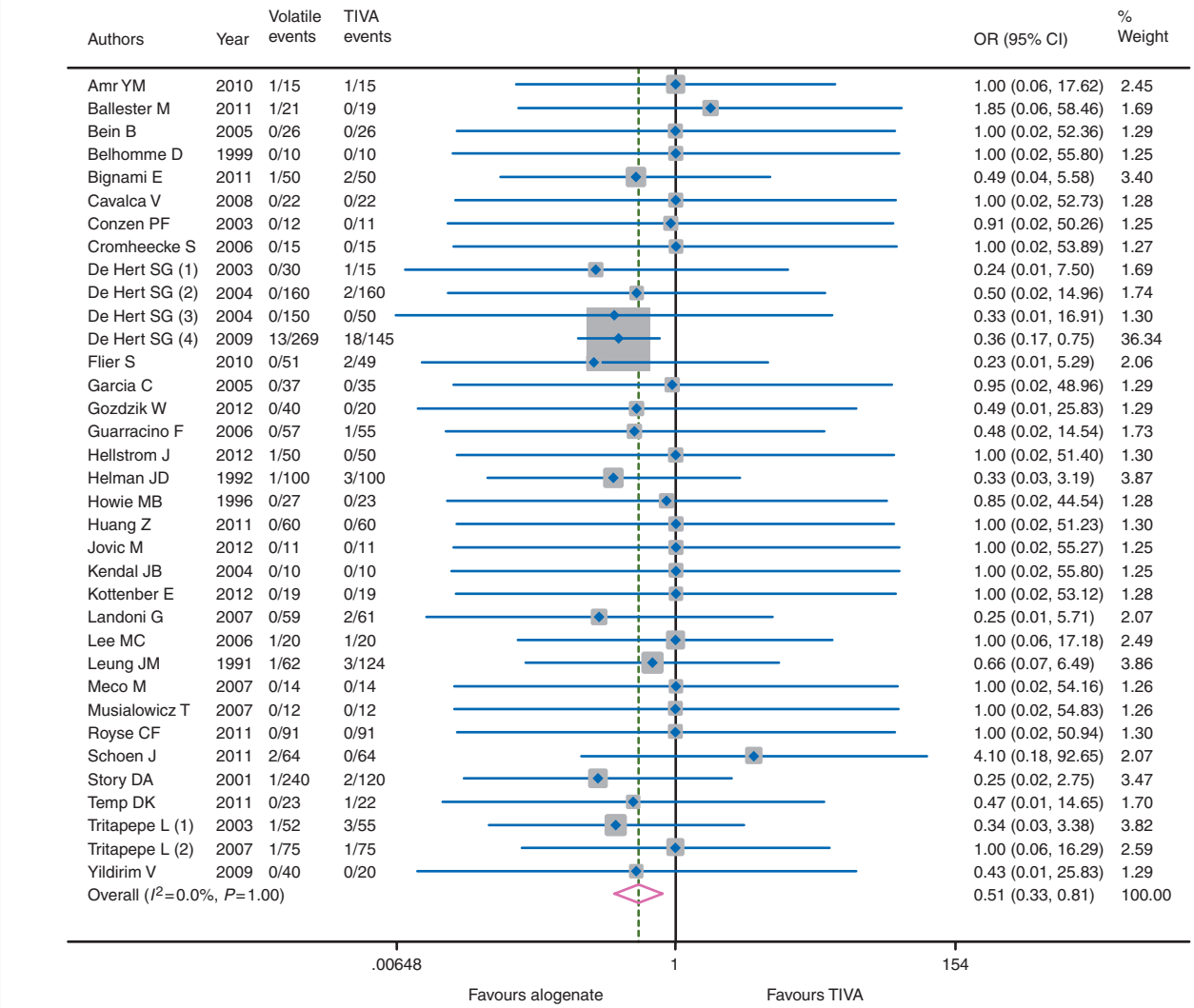

Fig 2 Forest plot of volatile agents (isoflurane, desflurane, or sevoflurane) *vs* TIVA for the risk of mortality at the longest follow-up available. CI, confidence interval; OR, odds ratio.

0.14–0.64) and desflurane (posterior mean of OR=0.43, 95% CrI 0.21–0.82) were associated with a reduction in mortality when compared with TIVA at the longest follow-up available. When the De Hert study[18] was removed, we found that only the use of desflurane was associated with a significant reduction in mortality with respect to TIVA (posterior mean of OR=0.30, 95% CrI 0.09–0.88).

When the Bayesian network meta-analysis was repeated, including all studies using propofol, we found a significant treatment difference effect between sevoflurane and propofol (posterior mean of OR=0.37, 95% CrI 0.13–0.98). Furthermore, Bayesian meta-regressions of the average follow-up against log-risk of mortality showed no significant effect for time on mortality (regression coefficient=−0.0008, CrI −0.004 to 0.002 and regression coefficient=−0.019, CrI −0.060 to 0.003, including all studies using TIVA or propofol, respectively). The Bayesian meta-regressions of average of the year of publication against mortality log-risk showed no significant effect when including all studies using TIVA (regression coefficient=−0.058, CrI −0.048 to 0.185) and a significant association when analysing only those studies using propofol (regression coefficient=0.259, CrI 0.007–0.545): adjusting for the effect of year of publication, we observed a more intense difference effect between sevoflurane and propofol (posterior mean of OR=0.30, 95% CrI 0.10–0.86).

When repeating all the Bayesian network meta-analyses using short-term mortality (≤30 days after surgery) as an endpoint, we found only a trend towards a reduction in mortality when comparing desflurane *vs* TIVA (posterior mean of OR=0.41, 95% CrI 0.15–1.04).

Supplementary Table S4 reports, for each anaesthetic agent, the posterior distribution of the probability to be the best and the worst, showing a trend of both TIVA and propofol to be the worst in terms of the long- and short-term survival after cardiac surgery.

Table 2 Secondary and sensitivity analyses to evaluate the effect on mortality of volatile *vs* TIVA regimen in 35 studies. For these analyses (volatile *vs* TIVA), the three studies comparing a volatile anaesthetic with another volatile anaesthetic were not included. TIVA, total i.v. anaesthesia; NNT, number needed to treat; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; ICU, intensive care unit

	Number of included studies	Events in the volatile group	Events in the TIVA group	OR (all in favour of volatile agents)	95% CI	*P*-value for effect	NNT	I^2
Mortality								
Overall analysis	35	25/1994 (1.3%)	43/1648 (2.6%)	0.51	0.33–0.81	0.004	74	0%
Sensitivity analysis on mortality								
Low risk of bias studies	18	17/1380 (1.2%)	32/998 (3.2%)	0.42	0.24–0.73	0.002	50	0%
Without the largest study (6)	34	12/1725 (0.7%)	25/1503 (1.7%)	0.63	0.36–1.11	0.11		
More than 100 patients	16	22/1590 (1.4%)	39/1309 (3.0%)	0.43	0.25–0.72	0.002	63	0%
CABG surgery studies	28	22/1746 (1.3%)	39/1402 (2.8%)	0.48	0.30–0.78	0.003	66	0%
CPB-CABG surgery	22	21/1597 (1.3%)	37/1259 (2.9%)	0.45	0.27–0.75	0.002	62	0%
OPCABG surgery	6	1/149 (0.7%)	2/143 (1.4%)	0.83	0.19–3.74	0.8		
Non-CABG surgery	7	3/248(1.2%)	4/246 (1.6%)	0.82	0.23–2.89	0.8		
Myocardial infarction	27	44/1879 (2.3%)	74/1560 (4.7%)	0.56	0.38–0.82	0.003	42	0%
Inotropes use	21	309/1186 (26%)	426/1115 (38%)	0.42	0.31–0.59	<0.001	8	45%
Continuous outcomes								
	Number of included studies	**Patients in the volatile group**	**Patients in the TIVA group**	**Standardized mean difference (all in favour of volatile agents)**	**95% CI**	***P*-value for effect**		I^2
Mechanical ventilation (h)	21	1353	1097	−0.23	−0.38 to −0.08	0.003		65%
ICU stay (h)	19	1387	1133	−0.30	−0.50 to −0.11	0.003		81%
Hospital stay (days)	21	1656	1296	−0.30	−0.45 to −0.15	<0.001		70%
Troponin I (ng ml^{-1})	17	1189	954	−0.53	−0.82 to −0.24	<0.001		90%

Discussion

Our principal findings

This meta-analysis has several important findings. First of all, volatile agents (isoflurane, desflurane, and sevoflurane) seem to reduce mortality after cardiac surgery when compared with TIVA. Mortality at the longest follow-up available was doubled in patients receiving TIVA compared with patients receiving volatile agents [25/1994 (1.3%) in the volatile group *vs* 43/1648 (2.6%) in the TIVA arm $P=0.004$], with 35 studies included and no statistical heterogeneity. Secondly, even if each volatile agent showed approximately a 50% reduction in mortality when compared with TIVA [desflurane (1.8 *vs* 4.0%), isoflurane (0.7 *vs* 2.0%), and sevoflurane (1.2 *vs* 3.0%)], none of these analyses was statistically significant *per se*, possibly because of the relatively limited number of patients enrolled (953, 1451, and 1698, respectively); we were therefore able to identify a benefit in survival only aggregating the three volatile agents together. Thirdly, few direct comparisons between the three volatile agents exist (nine overall). Even performing a Bayesian network meta-analysis with direct and indirect comparisons using the TIVA group as comparator, we were unable to identify whether there is a best or a worst volatile agent according to survival. Finally, our Bayesian network meta-analyses show that conducting cardiac anaesthesia with TIVA, including propofol-based TIVA, seems to increase mortality, especially when the comparator is desflurane or sevoflurane.

Strengths of our study in relation to other studies

The findings of the present Bayesian network meta-analysis confirm those of previous studies suggesting that the beneficial effects of volatile agents could translate into a reduction in mortality, but add relevant new data and provide methodologically innovative and more robust pieces of information.

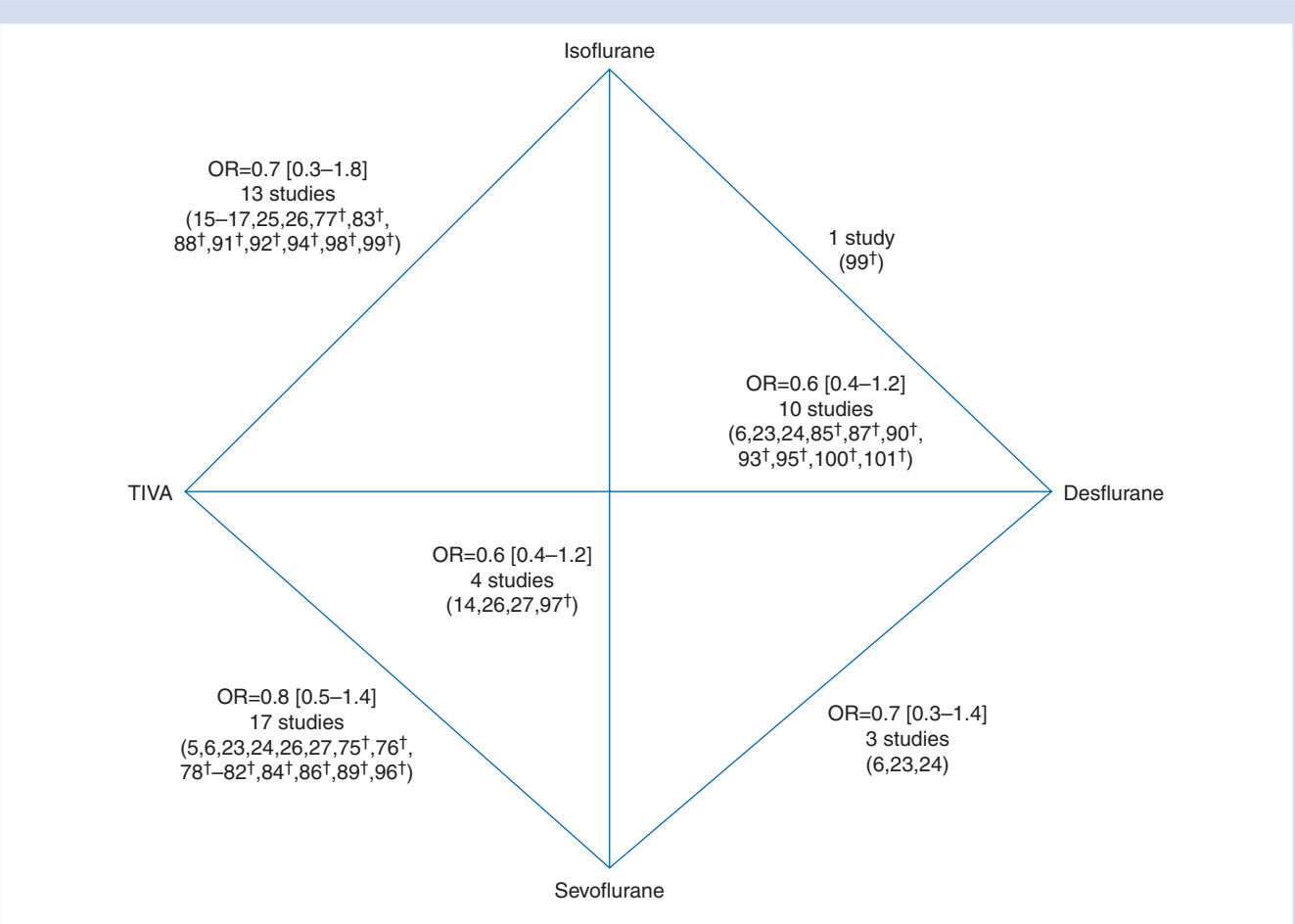

Fig 3 Network configuration. Comparisons between treatments and number of studies for each contrast. †Supplementary material references.

A first meta-analysis[3] suggested that desflurane and sevoflurane were associated with a reduced mortality in cardiac surgery when compared with TIVA, but it included only half as many patients and studies, used less robust analyses, did not include isoflurane in the analyses, and had no direct and indirect comparisons between agents. Similar considerations apply to a more recent[8] meta-analysis performed on isoflurane only and showing a trend ($P=0.05$) towards a reduction in mortality in a subgroup of high-quality studies comparing isoflurane *vs* propofol in cardiac surgery. A relatively small RCT[6] reported large 1 yr mortality differences between sevoflurane, desflurane, and TIVA in CABG patients but a disproportionately high mortality rate was reported in the TIVA group. In accordance with our results, a retrospective study[2] suggested a beneficial effect on survival with the use of sevoflurane in low-risk CABG surgery. Finally, a meta-regression of >34 000 cardiac surgery procedures done in Italy[4] suggested that isoflurane was the most effective volatile agent to reduce mortality in cardiac surgery; these findings are only in part contradicted by our results, suggesting that desflurane and sevoflurane are associated with a more obvious survival benefit. Both analyses are probably driven by the high number of patients receiving isoflurane in the meta-regression and by the high number of patients receiving desflurane and sevoflurane in our analyses.

Weaknesses of our study

Several limitations are acknowledged. Most of the studies included in this meta-analysis were single-centred, and thus exposed to more bias.[28] Furthermore, double blindness could not be expected in the setting of anaesthesia for cardiac surgery because of safety reasons. We also excluded studies using ischaemic pre-conditioning or remote ischaemic pre-conditioning without investigating synergist or antagonist effects. The specific limitations of Bayesian network meta-analyses[18 29–31] are detailed in the Supplementary data. Traditional limitations of meta-analyses attributable to variations in the treatment regimens, in populations or major subgroups within trials, and in the conduct of the trials also apply to this Bayesian network meta-analysis. In particular, we noted that after the removal of the largest trial[18] from the meta-analysis, only the use of desflurane was still associated with a significant reduction in mortality compared with TIVA—this means that the number of patients enrolled in this setting is still low and increases the need for a large randomized controlled trial. In fact, the overall results of this meta-analysis are still statistically fragile as there were only 68 deaths and statistical significance is reached only when combining all volatile agents and comparing them with TIVA.

Table 3 Posterior distribution of odds ratio (OR) and 95% credible interval, for the anaesthetic agent difference effects, derived by Bayesian hierarchical model with a Markov Chain Monte Carlo algorithm. *Indirect treatment difference effect calculated from consistency equation. †Significant treatment difference effect. TIVA, total i.v. anaesthesia

Contrast	Volatile agents *vs* TIVA, longest follow-up		Volatile agents *vs* TIVA, short-time mortality	
	OR	95% credible interval	OR	95% credible interval
Sevoflurane *vs* TIVA	0.31†	0.14–0.64	0.43	0.15–1.14
Desflurane *vs* TIVA	0.43†	0.21–0.82	0.41	0.15–1.04
Isoflurane *vs* TIVA	0.42	0.15–1.09	0.54	0.18–1.50
Sevoflurane *vs* desflurane*	0.74	0.27–2.01	1.05	0.26–4.25
Sevoflurane *vs* isoflurane*	0.76	0.22–2.60	0.80	0.19–3.44
Desflurane *vs* isoflurane*	1.03	0.31–3.38	0.76	0.18–3.14
Contrast	**Volatile agents *vs* propofol, longest follow-up**		**Volatile agents *vs* propofol, short-time mortality**	
	OR	**95% credible interval**	**OR**	**95% credible interval**
Sevoflurane *vs* propofol	0.37†	0.13–0.98	0.42	0.13–1.31
Desflurane *vs* propofol	0.52	0.18–1.38	0.39	0.11–1.22
Isoflurane *vs* propofol	0.38	0.11–1.23	0.47	0.12–1.71
Sevoflurane *vs* desflurane*	0.72	0.17–3.01	1.09	0.21–5.64
Sevoflurane *vs* isoflurane*	0.98	0.20–4.85	0.91	0.16–5.28
Desflurane *vs* isoflurane*	1.37	0.28–6.76	0.83	0.14–4.92

Nonetheless, it should be acknowledged that we have included all the randomized studies ever done in cardiac surgery that included mortality data (38 studies with 3966 patients) and therefore there is no possibility to have 'more evidence' than that provided in this manuscript. Interestingly, the effect sizes of the three volatile agents are comparable in magnitude (OR=0.71 for isoflurane, OR=0.64 for desflurane, and OR=0.80 for sevoflurane). It should also be acknowledged that the magnitude of effect is large (absolute reduction of 1% or relative reduction of 50% in mortality) and that any systematic review, even a network meta-analysis, may overly depend on one or a few trials with very extreme findings such as the large De Hert paper that accounts for almost half of the overall deaths (Supplementary Fig. S2); however, inclusion of so many trials, patients and events, and use of random effects methods may largely safeguard us from Type I and II errors. Furthermore, even if the cardiac protective properties of volatile agents reduce mortality in patients undergoing cardiac surgery, it cannot be excluded that they have significant positive or detrimental effects on other organs such as the brain.

Interpretation and implications of our findings

Our Bayesian network meta-analysis strongly supports the hypothesis that volatile anaesthetics may be superior to a TIVA-based anaesthesia according to a major postoperative outcome such as all-cause mortality. Experimental data suggest that direct positive effects of volatile anaesthetics may be because of specific cardioprotective properties, including, at least in part, pre-conditioning and post-conditioning mechanisms, which attenuate apoptosis and necrosis, and reduce myocardial dysfunction after ischaemia and reperfusion. Cardiac protection may be mediated by early activation of protective enzymes in the signalling pathways and late induction of the synthesis of protective proteins in the heart.[32 33] Coronary vasodilation,[34] and anti-inflammatory/antioxidant[35 36] activities of inhalation agents may play a role in this protection. Such a protective mechanism may extend to different degrees to other organ systems.[37–41] Moreover, the contribution of inhalation agents to preserving cardiac function and satisfactory haemodynamics may ensure adequate perfusion and oxygenation of other organ systems and improve the chances for an uneventful recovery after surgery.

All these effects can well expand beyond the immediate perioperative period and impact on long-term survival because of different modalities. We may speculate on a prolonged active protection of volatile anaesthetics because of their effects on cellular genomic expression. More simply, potential myocardiocyte-sparing effect of volatile anaesthetics during surgery means that more myocardium may be preserved and viable in the early and late postoperative periods, and potential reduced perioperative myocardial dysfunction may have implications on early and late function of other organ systems. The combination of these effects can well expand beyond the immediate perioperative period.

Our Bayesian network meta-analysis cannot exclude whether volatile agents could be simply less detrimental to mortality than TIVA in these settings. Nevertheless, propofol has been shown to modulate various inflammatory responses in experimental studies,[42 43] with a potential role in critically ill patients requiring additional studies to be validated.

Whether the effects of inhalation agents on mortality in cardiac surgery are attributable to a positive protection or to a less detrimental effect than propofol, the choice of inhalation anaesthesia could still have a great impact on a large scale. If all anaesthetics are detrimental and volatile agents are simply less detrimental than TIVA, we should do our best to identify new agents with even less detrimental effects. Conversely assuming a positive protection by inhalation agents could

involve a potential role of these drugs in other several clinical scenarios, requiring additional studies to be validated. Even if a recent report suggested, for the first time, that the cardiac protective effects of volatile agents could be present in non-cardiac surgery[44] it is unlikely that these results will be clinically relevant[11 73] as it is difficult to anticipate adverse cardiac events in non-cardiac surgery.

Conclusions

Volatile anaesthetics improve survival in cardiac surgery when compared with TIVA. No clear data exist to suggest that one volatile agent (isoflurane, desflurane, or sevoflurane) is more beneficial than others, but there is preliminary evidence to suggest that TIVA is detrimental when compared with desflurane and sevoflurane. Cardiac anaesthesiologists, cardiac surgeons, and perfusionists should be aware that anaesthetics have pharmacological properties that go beyond the pharmacodynamic or pharmacokinetic properties and that the anaesthetic plan should take into account the effect of these drugs on survival. As the evidence comes from small trials, it is imperative to conduct a large, multicentre trial to confirm that 1 yr survival is significantly influenced by the choice of the anaesthetic.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Authors' contributions

G.L.: concepts, design, definition of intellectual content, data analysis, manuscript preparation, manuscript review, guarantor. T.G.: definition of intellectual content, literature search, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing. G.B.-Z.: design, literature search, data analysis, statistical analysis, manuscript review. C.N.N.: literature search, data acquisition, manuscript review. D.F.: literature search, data acquisition, manuscript review. M.P.: literature search, data acquisition, manuscript editing. L.P.: definition of intellectual content, data acquisition, manuscript preparation. L.C.: concepts, design, definition of intellectual content, manuscript preparation, manuscript review. G.F.: definition of intellectual content, manuscript editing. A.Z.: concepts, design, definition of intellectual content, manuscript editing, manuscript review.

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Declaration of interest

None declared.

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Appendix

(heart OR cardiac OR myocard* OR coronary) AND (operatin* OR operation* OR surgery) AND (propofol OR isoflurane OR sevoflurane OR desflurane) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR (clinical trial[tw] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind[tw])) OR (latin square[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[tw] OR follow-up studies[mh] OR prospective studies[mh] OR crossover studies[mh] OR control[tw] OR controls[tw] OR controlled[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh]) NOT (cavies OR rats OR pigs OR dogs)NOT (comment[pt] OR editorial[pt] OR meta-analysis[pt] OR practice-guideline[pt] OR review[pt])).

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