ANESTHESIOLOGY

Volatile Anesthetics *versus* Propofol for Cardiac Surgery with Cardiopulmonary Bypass

Meta-analysis of Randomized Trials

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Prior meta-analyses of studies comparing mortality in cardiac surgical patients who received intraoperative volatile anesthetics *versus* propofol have reported conflicting findings.

What This Article Tells Us That Is New

- This systematic review and meta-analysis included data from randomized clinical trials published through the year 2019 and assessed 8,197 patients undergoing cardiac surgery with cardiopulmonary bypass. Although early postoperative mortality did not differ significantly between the anesthetic groups, 1-yr mortality was significantly lower in the patients who received volatile anesthetics.
- Additionally, patients in the volatile anesthetic group had significantly lower occurrence of perioperative myocardial infarction and troponin release and had higher postoperative cardiac index.

ABSTRACT

Background: The aim of this systematic review and meta-analysis was to assess the effect of anesthesia maintenance with volatile agents compared with propofol on both short- and long-term mortality (primary outcomes) and major clinical events in adults undergoing cardiac surgery with cardiopulmonary bypass.

Methods: Randomized clinical trials on the effects of current volatile anesthetics *versus* propofol in adults undergoing cardiac surgery with cardiopulmonary bypass were searched (1965 to September 30, 2019) in PubMed, the Cochrane Library, and article reference lists. A random effect model on standardized mean difference for continuous outcomes and odds ratio for dichotomous outcomes were used to meta-analyze data.

Results: In total, 37 full-text articles (42 studies, 8,197 participants) were included. The class of volatile anesthetics compared with propofol was associated with lower 1-yr mortality (5.5 *vs.* 6.8%; odds ratio, 0.76 [95% CI, 0.60 to 0.96]; $P = 0.023$), myocardial infarction (odds ratio, 0.60 [95% CI, 0.39 to 0.92]; $P = 0.023$), cardiac troponin release (standardized mean difference, −0.39 [95% CI, −0.59 to −0.18], $P = 0.0002$), need for inotropic medications (odds ratio, 0.40 [95% CI, 0.24 to 0.67]; $P = 0.0004$), extubation time (standardized mean difference, −0.35 [95% CI, −0.68 to −0.02]; $P = 0.038$), and with higher cardiac index/output (standardized mean difference, 0.70 [95% CI, 0.37 to 1.04]; $P < 0.0001$). The class of volatile anesthetics was not associated with changes in short-term mortality (1.63 *vs.* 1.65%; odds ratio, 1.04 [95% CI, 0.73 to 1.49]; $P = 0.820$) and acute kidney injury (odds ratio, 1.25 [95% CI, 0.77 to 2.03]; $P = 0.358$).

Conclusions: In adults undergoing cardiac surgery with cardiopulmonary bypass, the class of volatile anesthetics was superior to propofol with regard to long-term mortality, as well as to many secondary outcomes indicating myocardial protection.

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Cardiac surgery is frequently associated with postoperative myocardial infarction (MI, 5 to 10%), atrial fibrillation (20 to 30%), and acute kidney injury (AKI, 15 to 45%).[1–3] Although ischemia–reperfusion injury plays a major role in cardiac and renal insult, systemic inflammatory responses to cardiopulmonary bypass (CPB), endothelial dysfunction, and abnormalities in microcirculation and administered drugs contribute to cardiorenal damage.[4,5] Both myocardial and renal injury can result in organ failure, delayed recovery, and mortality. Hence, strategies increasing both myocardial and renal tolerance to ischemia–reperfusion are needed.

Volatile anesthetics have been reported to protect against ischemia–reperfusion injury by improving postischemic recovery at the cellular level in isolated organs and animal models.[6–8] Consequently, many studies in cardiac surgery administered volatile anesthetics for 10 to 30 min before CPB (anesthetics preconditioning), albeit obtaining variable clinical results.[6,9,10] Evidence of benefits obtained with them for the

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entire surgical time[11–13] have encouraged clinical researchers to compare volatile anesthetics to total intravenous anesthetics in this setting, obtaining better though conflicting results.[6,8,9,14]

A number of meta-analyses have been conducted in cardiac surgery comparing volatile anesthetics with propofol[15–27] with contrasting results on outcomes, principally because of the use of markedly heterogeneous studies in term of populations, interventions, anesthetic protocols, and outcome definition criteria. Limiting the comparison with recent meta-analyses, volatile anesthetics did not influence short-term mortality,[21,22,26] but they did reduce mortality "at the longest available follow up" in three analyses[20,23,26] but not in another[24]; on the basis of only two studies, a meta-analysis[27] claimed that sevoflurane but not isoflurane and desflurane reduced long-term mortality.Volatile anesthetics were associated with lower peaks of cardiac troponin[25] and possibly with higher cardiac index,[16,22] but there are no solid data on the incidence of MI[22,27]or AKI.[21] Finally, only 4 out of 13 meta-analyses were updated to articles published in 2014 or later.[24–27] For these reasons, we undertook a systematic review and meta-analysis to evaluate the effects of anesthesia maintenance with volatile anesthetics as a class and individually compared with propofol on short- and long-term mortality, clinical events, and eventual repercussions on intensive care unit (ICU) and hospital stays in adults undergoing cardiac surgery with CPB.

Materials and Methods

This systematic review and meta-analysis was conducted according to the guidelines of Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA)[28] and followed a protocol registered on the international prospective register of systematic reviews (PROSPERO; CRD42017071815).

Eligibility Criteria

Inclusion Criteria. We included randomized clinical trials on adults (at least 18 yr old) undergoing cardiac surgery with CPB and anesthesia maintenance with volatile anesthetics or propofol.

Exclusion Criteria. The exclusion criteria were nonrandomized clinical trials, absence of information on predefined outcomes, reviews, editorials, conference articles, comments, letters, abstracts only, substudies, protocols, nonhuman studies, pediatric patients, and nonpertinent surgical and/or anesthetic protocols (*i.e.*, off-pump procedure or volatile anesthetics only for very short periods of "preconditioning" or "postconditioning").

Postoperative Outcomes

The list of outcomes is reported in table 1.[29–31]

Search Strategy

PubMed (U.S. National Library of Medicine, Bethesda, Maryland) and Cochrane Databases from 1965 to September 30, 2019, were searched without language restriction. One author (G.D.) performed the search using the following search string: ((propofol OR total intravenous anesthetics) AND (sevofluran* OR desfluran* OR isofluran* OR volatile anesthetic*)) AND ((cardiac OR coronary OR valve) AND (surger* OR surgical* OR interven* OR (operation OR operative))) AND (randomized clinical trials OR randomized trial OR random*).

Study Selection and Data Extraction

Two reviewers (G.D. and I.M.) independently assessed trial eligibility based on titles, abstracts, full-text reports, and further information from the investigators as needed. Disagreements between the two reviewers concerning whether to include a study were resolved by discussion.

Quality Assessment and Risk of Bias

Quality of included studies and risk of bias according to the Cochrane risk of bias criteria[32] and consisting of: (1) random sequence generation and allocation concealment (selection bias); (2) blinding of participants and personnel (performance bias) and of outcome assessment (detection bias); and (3) incomplete outcome data (attrition bias); and (4) selective reporting (reporting bias), were independently assessed by two reviewers (A.B. and C.A.). Differences between reviewers' opinions were resolved by discussion with an arbiter (A.S.).

Statistical Analysis

Cohen's κ was calculated to assess the level of agreement between reviewers in the phases of selection and inclusion of studies. For dichotomous data, the odds ratio with 95% CI was used for the effect measure; to calculate the odds ratio, the total number of patients in each group and those with the event of interest were extracted from each study.

For continuous outcomes, standardized mean difference and the corresponding 95% CI were calculated by extracting means and SD; when SEM was reported, SD was calculated by multiplying SEM by the square root of sample size. Geometric mean transformation or mean SD approximation from medians and interquartile ranges[32] were used in case of nonavailability of means and SD.

The results from all of the studies (either odds ratio or standardized mean difference) were pooled using a random effect model to take into account clinical and methodologic diversity between studies. Forest plots were used to present graphically the obtained results. Statistical heterogeneity across trials was assessed by means of Cochrane Q test, and the I^2 values were reported. An I^2 higher than 0.5 (50% of heterogeneity) indicated considerable heterogeneity across studies.

For outcomes with more than 10 studies, publication bias was addressed visually using a funnel plot comparing log odds ratio or standardized mean difference with their

Table 1. Postoperative Outcomes

Primary outcomes
First coprimary outcome: short-term mortality (in hospital or within 30 days)
Second coprimary outcome: 1-yr mortality
Secondary outcomes
In-hospital myocardial infarction, by using investigators' definitions
Area under the curve for cardiac troponin for at least postoperative 24 h; if not reported, area under the curve was calculated from tabulated data or graphs (trapezoidal rule)
Cardiac index (l/min/m^{-2}) or cardiac output (l/min) from postcardiopulmonary bypass (usually 15 min) to 3–6 h after intensive care unit admission
Inotropic medications (milrinone, dobutamine, dopamine, epinephrine) from postcardiopulmonary bypass to 12 h after intensive care unit admission
In-hospital atrial fibrillation
In-hospital acute kidney injury, defined according to AKIN,[29] RIFLE,[30] or KDIGO criteria[31] or to comparable ones
In-hospital renal replacement therapy
Extubation time (h)
Length of intensive care unit stay (days)
Length of hospital stay (days)

standard error. Egger's test was used to statistically test funnel plot asymmetry and small study effects. A sensitivity analysis performed by removing studies with extreme results was preplanned.

To test the influence of patients' demographic and clinical characteristics, together with the era of the study on the relation between type of anesthetics and outcomes in the whole group and in subgroups, a weighted random-effects metaregression analysis was used. Predictors with a *P* value of less than 0.10 in univariable analysis were considered in the multiple metaregression model. All *P* values were two-sided, and values less than 0.05 were considered statistically significant. The data analysis was performed using STATA 13.0 (StataCorp, USA) and Revman (v. 5.3; Cochrane).

Subgroup Analysis

Three subgroup analyses were planned *a priori* according to: (1) type of intervention (isolated coronary artery bypass graft [CABG], isolated valve surgery, or concomitant surgery, which is CABG and valve surgery); (2) complete avoidance *versus* partial exposure (for induction and in CPB) to propofol or other total intravenous anesthetics in patients under volatile anesthetics; and (3) type of volatile anesthetics. *A posteriori*, we considered jointly the two subgroups in item (2) above because we found no significant difference between them. Again *a posteriori*, results for desflurane or sevoflurane were pooled because of a similar trend in outcomes. In addition, we evaluated cardiac index or cardiac output to estimate postbypass cardiac depression, and subsequently we pooled the two hemodynamic variables because of comparable changes after volatile anesthetics relative to propofol. In addition, also in response to reviewers, we assessed the effect of the study era on the most reported outcomes and also compared studies in which the means ± SD were reported with those in which the means ± SD were transformed or approximated. Finally, *post hoc* we evaluated the effect of aortic cross clamp time on cardiac protection and the possible independent role of surgery type, aortic cross clamp duration, and study era on cardiac outcomes.

Results

Study Selection and Characteristics

The study selection process is depicted in figure 1 of Supplemental Digital Content 1 (http://links.lww.com/ALN/C279). The search strategy identified 1,388 potentially relevant articles. By analyzing titles and abstracts, 1,307 articles were excluded for not meeting inclusion criteria. After a detailed reading of each full text, a further 45 articles were excluded. Finally, 36 studies reported in 37 full-text articles were included.[11,33–68] Articles using 2 different volatile anesthetics or volatile anesthetics alone and volatile anesthetics with propofol for induction were divided in 2 studies, in which the results were presented separately; in the end, 42 studies were considered. An almost perfect agreement between the 2 reviewers was found on both the initial and final selection of studies, with κ values of 0.90 (95% CI, 0.85 to 0.96) and 0.80 (95% CI, 0.67 to 0.94), respectively. The study characteristics are summarized in table 2. A total of 8,197 participants were enrolled 3,992 randomized to volatile anesthetics and 3,936 to propofol for the entire intervention. Baseline characteristics of patients were comparable between the two groups. Patients underwent elective isolated CABG in 26 articles, isolated valve surgery in 8 articles, and concomitant surgery in 3 articles. Volatile anesthetics alone were used in 36 studies, whereas they were used in 6 studies together with propofol for induction[11,51,59,62,64] and in CPB.[51,64] Nine studies used isoflurane, 6 used desflurane, and 25 used sevoflurane and analyzed results separately; 1 study used isoflurane or sevoflurane in a nonspecified proportion of patients, and another study used isoflurane, sevoflurane, or desflurane and put together the results.

Risk of Bias within Studies

Most included studies resulted at "low" risk of bias for almost all items investigated. Only in case of allocation concealments did the judgment result frequently "unclear" because methods to protect against bias were not sufficiently reported. The results on the assessment of risk of bias are reported in figures 2 and 3 in Supplemental Digital Content 2 (http://links.lww.com/ALN/C280).

Mortality

Short-term mortality data were available from 30 articles (37 studies) in which 127 deaths were registered among 7,743 patients (1.6%; fig. 1; fig. 4 in Supplemental Digital Content 3, http://links.lww.com/ALN/C281). Short-term

Table 2. Characteristics of Included Trials Comparing Volatile Anesthetics with Propofol in Adult Patients undergoing Cardiac Surgery (Coronary Artery Bypass Graft on Pump ± Valve Surgery)

Reference	No. of Patients (VA/P)	Surgery Type	Follow-up	Anesthetics (Maintenance)	Age, yr	Male, %	eGFR ml/min	DM %	EF < 25–40%, %	EF, % ± SD	Aortic X Clamping (min)
Sorbara *et al.*[33]	15/15	EIC	1 week	I *vs.* P	60	77	*	*	0	*	67
Engoren *et al.*[34]	35/35	EIC	In hospital	I *vs.* P	61	77	*	*	26.5	*	*
Story *et al.*[35]/Parker *et al.*[40]	236/118	EIC	In hospital	I or S *vs.* P	66	82	≥ 30	*	6.5	*	*
De Hert *et al.* (I)[36]	10/10	EIC	36 h	S *vs.* P	63	80	*	1	0†	64 ± 7.1	42
El Azab *et al.*[37]	10/10	EIC	In hospital	S *vs.* P	61	75	≥ 30	*	0†	*	67
De Hert *et al.* (II)[38]	30/15	EIC	36 h	D or S *vs.* P	75	87	*	27	0	41 ± 5	47
De Hert *et al.* (III)[11]	160/80	EIC	In hospital	D or S *vs.* P	67	82	≥ 45	28	0	67.3 ± 11.3	30
De Hert *et al.* (IV)[39]	50/50	EIC	In hospital	S *vs.* P	66	79	≥ 45	22	0	63.5 ± 12	30
Cromheecke *et al.*[41]	15/15	EIV	In hospital	S *vs.* P	69	57	≥ 30	10	0	67 ± 11.5	68
Lorsomradee *et al.*[42]	160/160	EIC	In hospital	S *vs.* P	67	80	≥ 45	28	0†	67.5 ± 11	30
Xia *et al.*[43]	18/36	EIC	In hospital	I *vs.* P	64	69	≥ 90	13	0	52 ± 4.3	84
Tritapepe *et al.*[44]	75/75	EIC	30 days	D *vs.* P	65	82	≥ 30	21	Some	51.5 ± 11.8	67
Cavalca *et al.*[45]	21/22	ECS	In hospital	S *vs.* P	67	65	≥ 30	14	0†	60.8 ± 7.6	81
De Hert *et al.* (V)[47]	269/145	EIC	30 days/1 yr	D or S *vs.* P	67	81	*	23	0	67 ± 13.3	*
Yildirim *et al.*[46]	40/20	EIC	30 days	I or S *vs.* P	68	75	≥ 45	30	0	44.3 ± 4.3	2
Flier *et al.*[48]	41/43	EIC	30 days/1 yr	I *vs.* P	67	79	≥ 45	30	5	*	53
Huang *et al.*[49]	30/30	EIC	In hospital	I *vs.* P	61	83	≥ 45	20	0	54 ± 8	*
Royse *et al.*[50]	90/89	EIC	In hospital	D *vs.* P	63	85	≥ 30	76	7	*	73
Bignami *et al.*[51]	50/50	ECS	In hospital/1 yr	S *vs.* P	67	76	≥ 30	6	Some	55.1 ± 12.9	80
Imantalab *et al.*[52]	20/20	EIC	In hospital	I *vs.* P	*	75	*	38	0†	*	41
Jovic *et al.*[53]	11/11	EIV	In hospital	S *vs.* P	63	59	≥ 30	14	0	57.5 ± 8	68
Kottenberg *et al.*[54]	19/19	EIC	In hospital	I *vs.* P	65	84	≥ 45	0†	*	*	72
Soro *et al.*[55]	36/37	EIC	In hospital	S *vs.* P	69	78	≥ 30	44	0	57.8 ± 13	48
Koç *et al.*[56]	20/20	EIC	In hospital	S *vs.* P	55	*	*	1	0	*	51
Landoni *et al.*[57]	100/100	ECS	30 days/1 yr	S *vs.* P	69	68	*	*	Some	50.8 ± 14.8	94
Yoo *et al.*[58]	56/56	EIV	In hospital	S *vs.* P	58	46	≥ 45	14	0†	64.2 ± 10.7	69
Jerath *et al.*[59]	67/74	EIC‡	In hospital	I or S *vs.* P	64	93	≥ 30	28	0†	*	*
Kapoor *et al.*[60]	40/36	EIV	30 days	D *vs.* P	40	*	≥ 90	0†	0†	*	64
Sirvinskas *et al.*[61]	36/36	EIC	In hospital	S *vs.* P	67	78	≥ 15	0†	0†	*	*
Likhvantsev *et al.*[62]	437/431	EIC	30 days/1 yr	S *vs.* P	62	88	*	17	0	54.5 ± 6.5	44
Hofland *et al.*[64]	165/166	EIC	In hospital	S *vs.* P	64	86	≥ 45	30	0†	*	66
Hou *et al.*[65]	45/45	EIV	48 h	S *vs.* P	54	66	> 60	*	0†	*	*
Yang *et al.*[63]	36/37	EIV	In hospital	S *vs.* P	51	47	*	0†	0†	56.5 ± 5.5	63
Oh *et al.*[66]	78/78	EIV	In hospital	S *vs.* P	60	45	*	8	0	64.2 ± 7.3	108
Moscarelli *et al.*[67]	31/31	EIV	In hospital	S *vs.* P	65	45	≥ 45	0†	10	58.6 ± 7.4	92.3
Landoni *et al.* (I)[68]‖	1,709/1,721	EIC	30 days/1 yr	D or I or S *vs.* P	62	81	≥ 45	28	< 5	57 ± 3.7	*

*Not reported. †Exclusion criteria; ‡10% off pump. §EuroSCORE II. ‖In the Landoni (I) study among reported outcomes, only 30-day and 1-yr mortality are selectively reported for the on-pump procedure.

AF, atrial fibrillation; AKI, acute kidney injury; AUC, area under the curve for 24–72 h; CI, cardiac index; cTn, cardiac troponin; D, desflurane; DM, diabetes mellitus; ECS, elective concomitant surgery; EF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; EIC, elective isolated coronary artery bypass graft; EIV, elective isolated valve surgery; I, isoflurane; ICU, intensive care unit; Inotr., inotropic medications; MI, myocardial infarction; P, propofol; RRT, renal replacement therapy; S, sevoflurane; VA, volatile anesthetics; X clamping, cross clamping time.

mortality was not modified by volatile anesthetics either as a class (odds ratio, 1.04 [95% CI, 0.73 to 1.49]; $P = 0.820$; $I^2 = 0\%$] or as individual agents. Visual inspection of funnel plot and Egger's test did not reveal asymmetry (fig. 5 in Supplemental Digital Content 4, http://links.lww.com/ALN/C282).

Six studies reported mortality at 1 yr in 5,096 patients with 311 deaths registered (6.1%; fig. 2). Volatile anesthetics were associated with a lower mortality (5.5%) relative to propofol (6.8%; odds ratio, 0.76 [95% CI, 0.60 to 0.96]; $P = 0.023$; $I^2 = 0\%$). On the contrary, in the same studies short-term mortality in volatile anesthetics was similar (2.2%) to propofol (2.1%; fig. 19 in Supplemental Digital Content 5, http://links.lww.com/ALN/C283).

MI

MI incidence was recorded in 22 articles (27 studies totaling 3,037 patients) and occurred in 3.2% of patients (fig. 3, A and B). Volatile anesthetics were associated with a lower

Table 2. (*Continued*)

		Endpoints											
												Mortality	
Bypass Time (min)	EuroSCORE	MI	cTn AUC	Hemodynamics CI	Inotr.	AF	AKI	RRT	Extubation Time	ICU Stay	Hospital Stay	30 days	1 yr
103	*	*	*	*	*	*	*	*	Yes	*	*	*	*
102	*	Yes	*	*	*	*	*	*	Yes	Yes	Yes	Yes	*
96	*	Yes	*	Yes	Yes	*	Yes	Yes	Yes	Yes	*	Yes	*
114	*	Yes	Yes	Yes	Yes	*	*	*	*	*	*	Yes	*
101	*	Yes	*	*	*	*	*	*	*	*	*	Yes	*
102	*	Yes	Yes	Yes	Yes	Yes	*	*	*	*	*	Yes	*
95	4	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	*
96	3.5	Yes	Yes	Yes	Yes	Yes	*	*	*	Yes	Yes	Yes	*
100	6	Yes	Yes	Yes	Yes	Yes	*	*	*	Yes	Yes	Yes	*
98	3.5	Yes	Yes	Yes	Yes	*	*	*	*	Yes	Yes	Yes	*
134	*	Yes	Yes	*	*	*	*	*	Yes	Yes	*	*	*
94	*	Yes	Yes	*	*	Yes	Yes	*	Yes	Yes	Yes	Yes	*
108	4	Yes	*	*	*	*	*	*	Yes	Yes	*	Yes	*
*	3.7	Yes	Yes	*	*	Yes	*	*	*	*	Yes	Yes	Yes
38	*	Yes	Yes	Yes	Yes	*	*	*	Yes	Yes	*	Yes	*
78	3.2	Yes	Yes	*	*	Yes	*	*	Yes	Yes	Yes	Yes	Yes
*	*	Yes	Yes	Yes	Yes	*	*	*	Yes	Yes	Yes	Yes	*
94	3	Yes	*	*	*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	*
100	7.3	Yes	Yes	*	*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
62	*	*	Yes	*	*	*	*	*	Yes	*	*	*	*
91	5.2	*	*	Yes	*	*	Yes	*	Yes	Yes	Yes	Yes	*
112	*	*	Yes	*	*	*	*	*	*	*	*	Yes	*
64	4.1	Yes	Yes	Yes	*	Yes	*	*	*	Yes	Yes	Yes	*
79	*	*	*	*	*	*	*	*	Yes	Yes	Yes	*	*
113	6	Yes	Yes	*	*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
95	2.4	*	*	Yes	*	*	Yes	Yes	*	Yes	Yes	Yes	*
79	*	*	*	Yes	*	Yes	*	*	Yes	Yes	Yes	Yes	*
92	*	*	*	*	*	*	*	*	Yes	Yes	Yes	Yes	*
88	*	*	*	*	*	*	*	*	Yes	Yes	*	*	*
72	0.76§	*	*	*	*	*	*	*	*	*	Yes	Yes	Yes
93	1.8	Yes	Yes	*	*	Yes	*	*	*	Yes	Yes	Yes	*
106	6.4§	*	Yes	Yes	*	*	*	*	*	*	*	*	*
96	*	*	Yes	Yes	*	*	*	*	Yes	Yes	Yes	Yes	*
166	*	*	Yes	Yes	*	*	*	*	Yes	Yes	Yes	*	*
140	3.4§	Yes	Yes	*	*	Yes	*	*	Yes	Yes	Yes	Yes	*
79	*	*	*	*	*	*	*	*	*	*	*	Yes	Yes

MI incidence (odds ratio, 0.60 [95% CI, 0.39 to 0.92]; $P = 0.020$; $I^2 = 0\%$). Although the subgroup of desflurane or sevoflurane was associated with a lower incidence of MI (odds ratio, 0.54 [95% CI, 0.34 to 0.86]; $P = 0.009$; $I^2 = 0\%$), isoflurane was not (odds ratio, 1.38 [95% CI, 0.46 to 4.13]; $P = 0.562$; $I^2 = 0\%$). Univariate and multiple analysis did not reveal a role for study era, surgery type, and aortic cross clamp time on volatile anesthetics effect on MI incidence (fig. 3A; fig. 18 and table 3 in Supplemental Digital Content 5, http://links.lww.com/ALN/C283). Visual inspection of funnel plot and Egger's test did not reveal asymmetry (fig. 5 in Supplemental Digital Content 4, http://links.lww.com/ALN/C282).

Cardiac Troponin

Altogether, 22 articles (26 studies) in 2,740 patients reported the effects of volatile anesthetics on postoperative area under the curve (AUC) for cardiac troponin recorded for 72 h in 4 studies, 48 h in 16 studies, 36 h in 4 studies, and 24 h in

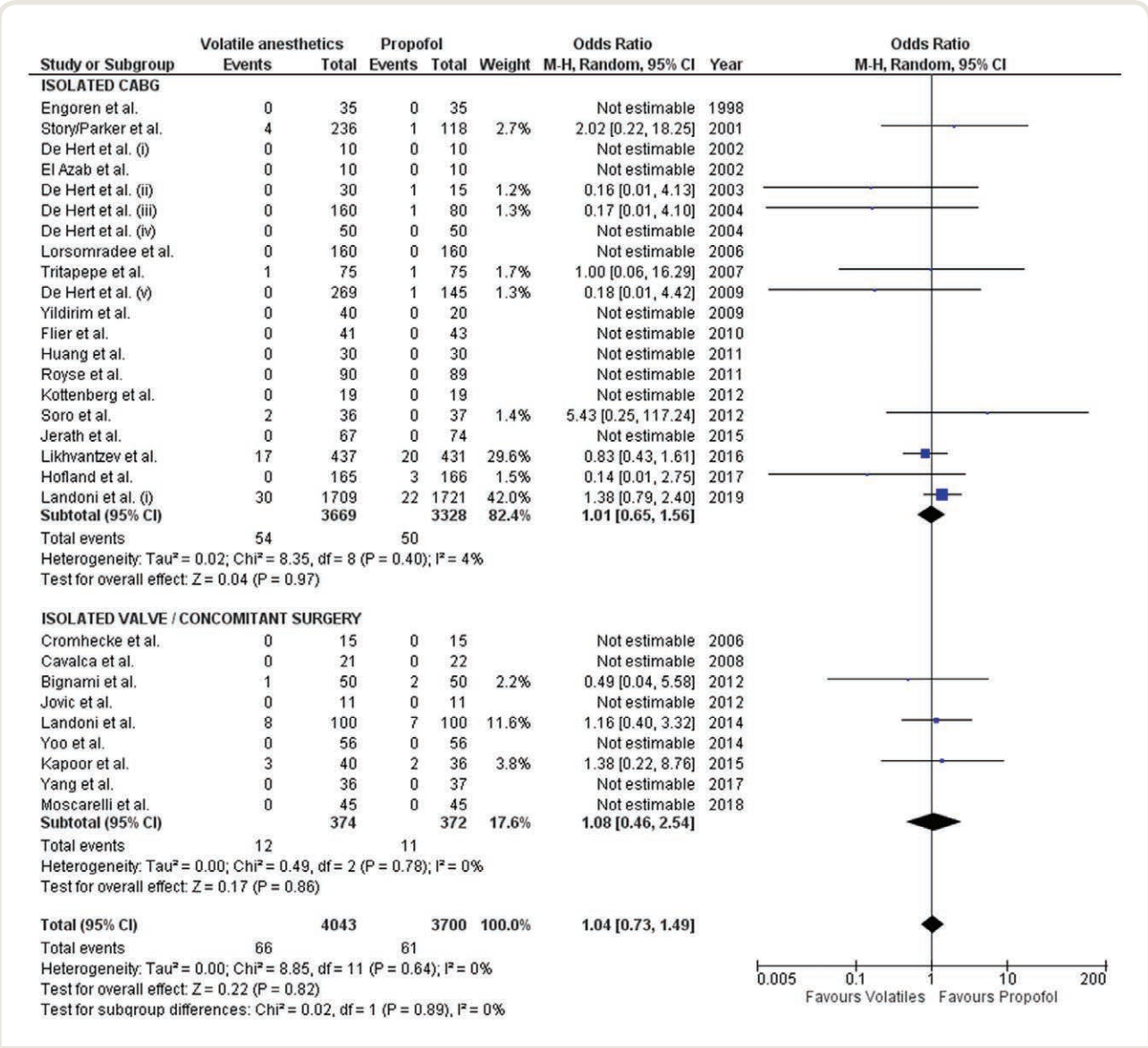

Fig. 1. Forest plot for the effects of volatile anesthetics *versus* propofol on short-term mortality in adults undergoing cardiac surgery with cardiopulmonary bypass. Subgroup analysis shows isolated coronary artery bypass graft (CABG) *versus* isolated valve/concomitant surgery. M-H, Mantel–Haenszel.

1 study (fig. 4, A and B); cardiac troponin I was measured in all but 2 studies that evaluated cardiac troponin T. AUC for cardiac troponin was lower after volatile anesthetics as a class (standardized mean difference, −0.39 [95% CI, −0.59 to −0.18]; $P = 0.0002$; $I^2 = 84\%$) and the desflurane or sevoflurane subgroup (standardized mean difference, −0.48 [95% CI, −0.71 to −0.25]; $P = 0.0001$; $I^2 = 85\%$) but not after isoflurane [standardized mean difference, −0.08 (95% CI, −0.46 to 0.31), $P = 0.697$, $I^2 = 65\%$]; P for subgroup difference = 0.083. In univariate analysis, surgery type, study era, and aortic cross clamp time have a statistically significant impact on the effect of volatile anesthetics on cardiac troponin release (fig. 4A; figs. 13 and 16 and table 4 in Supplemental Digital Content 5, http://links.lww.com/ALN/C283). However, in multiple meta-regression, the role of three variables on the effect of volatile anesthetics on cardiac troponin release was consistently reduced when each one was adjusted for the other two (table 4 in Supplemental Digital Content 5, http://links.lww.com/ALN/C283). Visual inspection of funnel plot showed some studies over the pseudo 95% confidence limits as a consequence of a high heterogeneity (fig. 5 in Supplemental Digital Content 4, http://links.lww.com/ALN/C282) however, no asymmetry was detected by Egger's test.

Cardiac Index and Inotropic Medications

We analyzed 16 articles (20 studies) that reported the effect of volatile anesthetics on post-CPB cardiac index

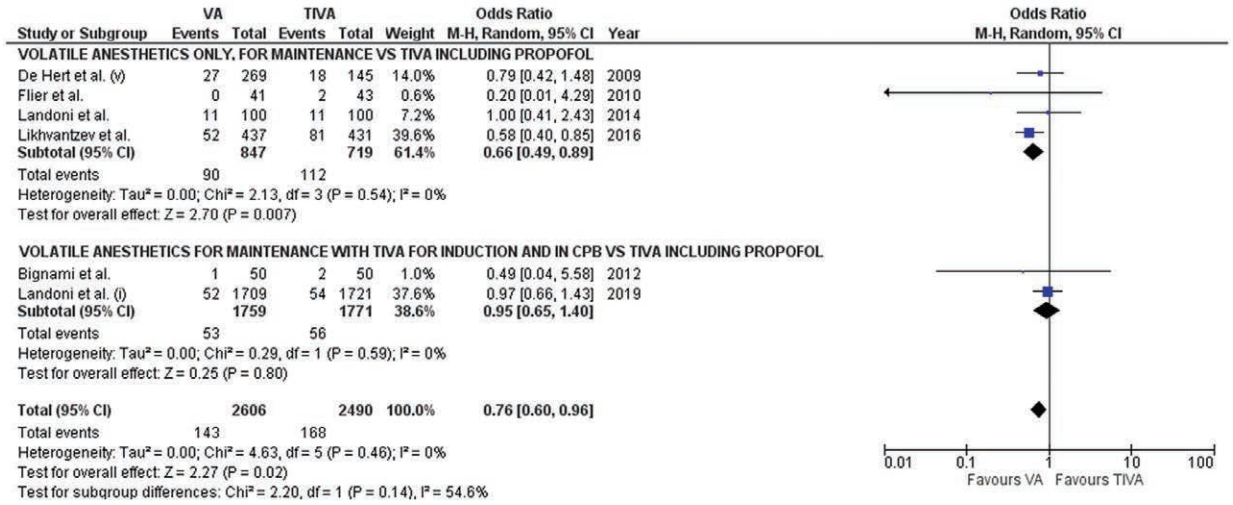

Fig. 2. Funnel plot for volatile anesthetics (VA) *versus* total intravenous anesthetics (TIVA) including propofol on 1-yr mortality in adults undergoing cardiac surgery with cardiopulmonary bypass (CPB). Subgroup analysis shows studies comparing volatile anesthetics with TIVA including propofol, *versus* studies comparing volatile anesthetics plus TIVA including propofol for induction and in CPB *versus* TIVA including propofol. M-H, Mantel–Haenszel.

or cardiac output in 1,896 patients (fig. 5, A and B). After volatile anesthetics, cardiac index and cardiac output were higher than after propofol (standardized mean difference, 0.70 [95% CI, 0.37 to 1.04]; $P < 0.0001$; $I^2 = 91\%$). When cardiac output was converted to cardiac index by dividing cardiac output by the mean value of body surface area reported in considered studies, similar results were obtained (fig. 6 in Supplemental Digital Content 6, http://links.lww.com/ALN/C284). Surgery type, study era, and aortic cross clamp time have a significant impact on the effect of volatile anesthetics on cardiac index in univariate analysis (fig. 6; figs. 14 and 17 and table 5 in Supplemental Digital Content 5, http://links.lww.com/ALN/C283). However, as for cardiac troponin, in the multiple model the effect of the three variables is no longer statistically significant (table 5 in Supplemental Digital Content 5, http://links.lww.com/ALN/C284). No difference was found between the 2 subgroups of volatile anesthetics ($P = 0.980$).

Nine out of the above reported articles (13 studies) evaluated in 1,229 patients also the effect of volatile anesthetics on the post-CPB need for inotropic medications (fig. 6, A and B). After volatile anesthetics, the need for inotropic drugs was very low (odds ratio, 0.40 [95% CI, 0.24 to 0.67]; $P = 0.0004$; $I^2 = 67\%$). The volatile anesthetics effect was statistically significant in the desflurane or sevoflurane subgroup (odds ratio, 0.36 [95% CI, 0.22 to 0.59]; $P < 0.0001$; $I^2 = 61\%$], whereas isoflurane was inefficacious (odds ratio, 0.95 [95% CI, 0.60 to 1.50]; $P = 0.818$; $I^2 = 0\%$]; P for subgroup difference = 0.005.

Funnel plots for the above reported outcomes are shown in figure 5 in Supplemental Digital Content 4 (http://links.lww.com/ALN/C283). For the cardiac index, some studies were over the pseudo 95% confidence limits as a consequence of a high heterogeneity; however, no significant asymmetry was detected by Egger's test ($P = 0.570$). For inotropic drugs, no evident criticisms were observed.

AKI/Renal Replacement Therapy

AKI incidence was reported in 8 articles (10 studies totaling 1,355 patients) and occurred in 15% of patients (fig. 7A). Under volatile anesthetics as a class and individually, AKI incidence was similar to propofol (odds ratio for the class, 1.25 [95% CI, 0.77 to 2.03[; $P = 0.358$; $I^2 = 47\%$].

Renal replacement therapy was reported in 8 of the 10 studies analyzing AKI incidence and occurred in 23 out of 1,183 patients (1.9%; fig. 7B). Again, no difference *versus* propofol was observed for volatile anesthetics as a class and individually (odds ratio for the class, 1.96 [95% CI, 0.80 to 4.81]; $P = 0.142$; $I^2 = 0\%$).

Atrial Fibrillation

Atrial fibrillation incidence was recorded in 14 articles (17 studies totaling 2,149 patients) and occurred in 19% of patients (fig. 7 in Supplemental Digital Content 7, http://links.lww.com/ALN/C285). After volatile anesthetics, atrial fibrillation incidence was similar to propofol (odds ratio, 0.94 [95% CI, 0.73 to 1.22]; $P = 0.660$; $I^2 = 14\%$), in line with results of a retrospective study[69] and an old meta-analysis.[19]

Extubation Time, ICU, and Hospital Stays

The results are reported in the Supplemental Digital Content 8 (http://links.lww.com/ALN/C286).

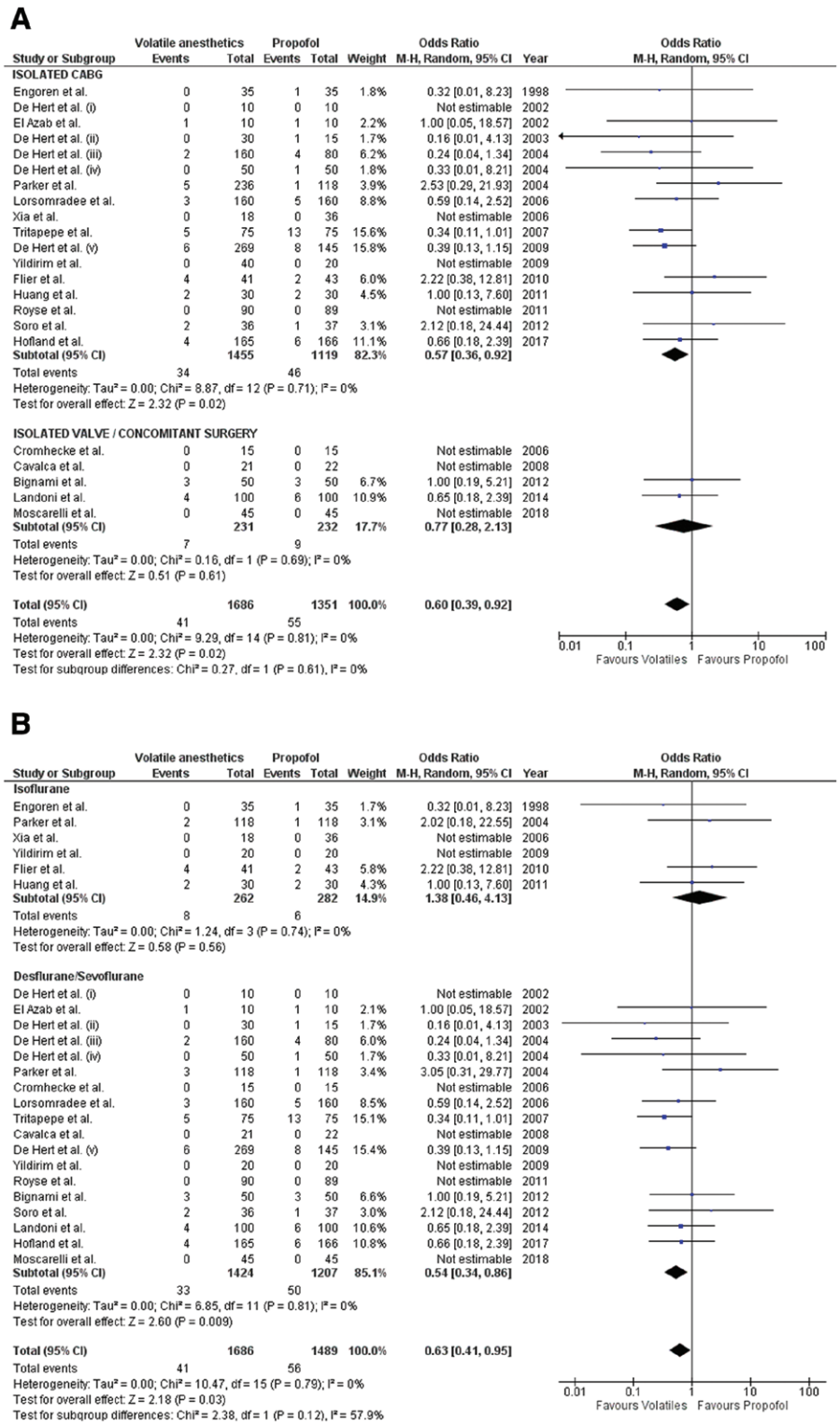

Fig. 3. Forest plot for the effects of volatile anesthetics as a class (*A*) and as subgroups (*B*) *versus* propofol on the incidence of myocardial infarction in adults undergoing cardiac surgery with cardiopulmonary bypass. Subgroup analysis was performed in isolated coronary artery bypass graft (CABG) *versus* isolated valve/concomitant surgery (*A*) and in isoflurane *versus* desflurane or sevoflurane (*B*). M-H, Mantel–Haenszel.

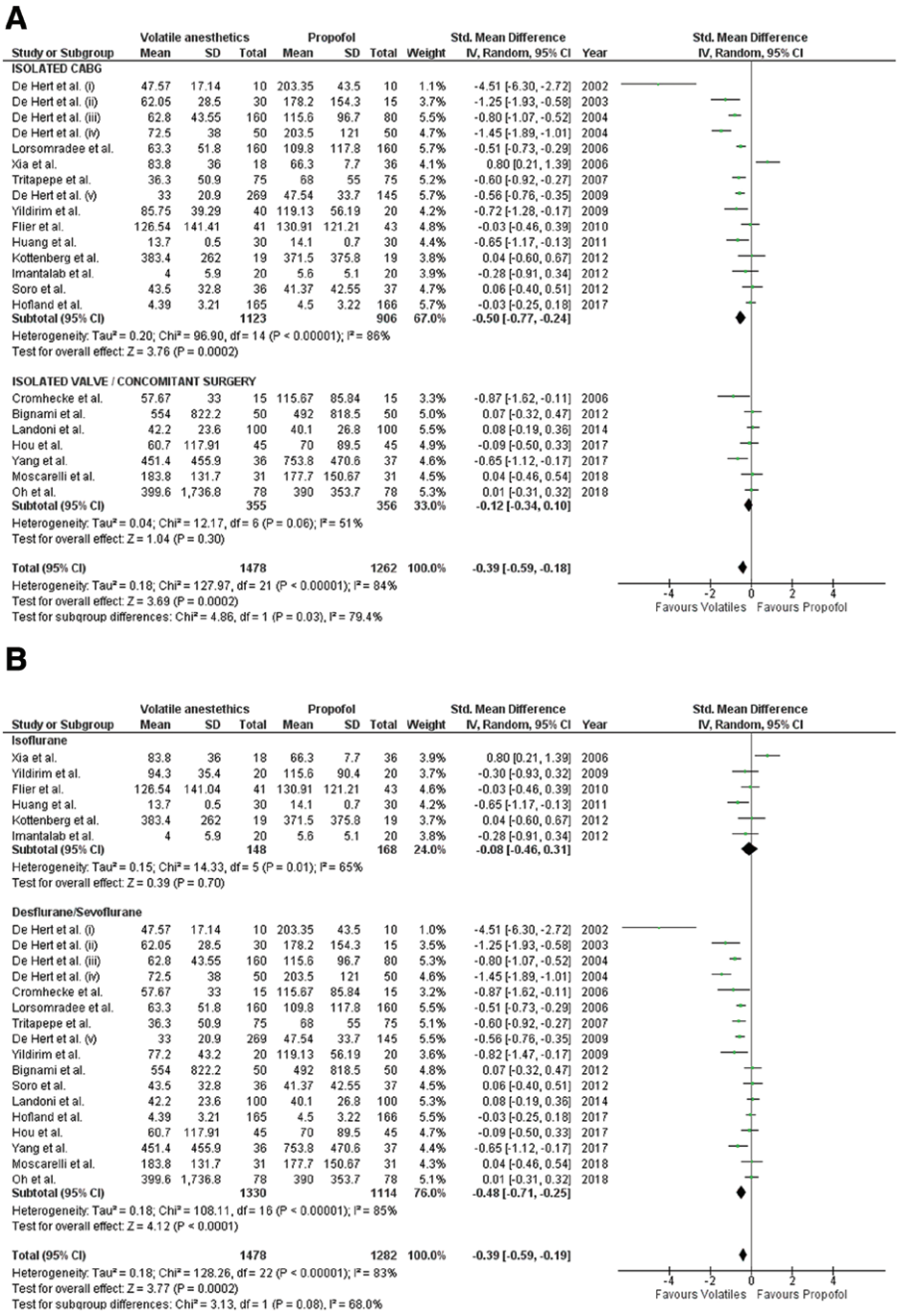

Fig. 4. Forest plot for the effects of volatile anesthetics as a class (*A*) and as subgroups *versus* propofol (*B*) on the area under curve for cardiac troponin in adults undergoing cardiac surgery with cardiopulmonary bypass. Subgroup analysis was performed in isolated coronary artery bypass graft (CABG) *versus* isolated valve/concomitant surgery (*A*) and in isoflurane *versus* desflurane or sevoflurane (*B*). IV, inverse variance; Std., standardized.

Subgroup Analysis

The results are reported in the Supplemental Digital Content 9 (http://links.lww.com/ALN/C286).

Discussion

This meta-analysis has several important clinical results. In adults undergoing cardiac surgery with CPB (both CABG and valve or complex surgery), the class of volatile anesthetics compared with propofol was associated with a similar short-term mortality but with a lower 1-yr mortality. In addition, volatile anesthetics were associated with cardioprotection, whereas no renoprotection was found. Cardioprotection is evident from lower MI incidence, cardiac troponin release, the need for inotropic medications, and preserved cardiac index. The desflurane or sevoflurane

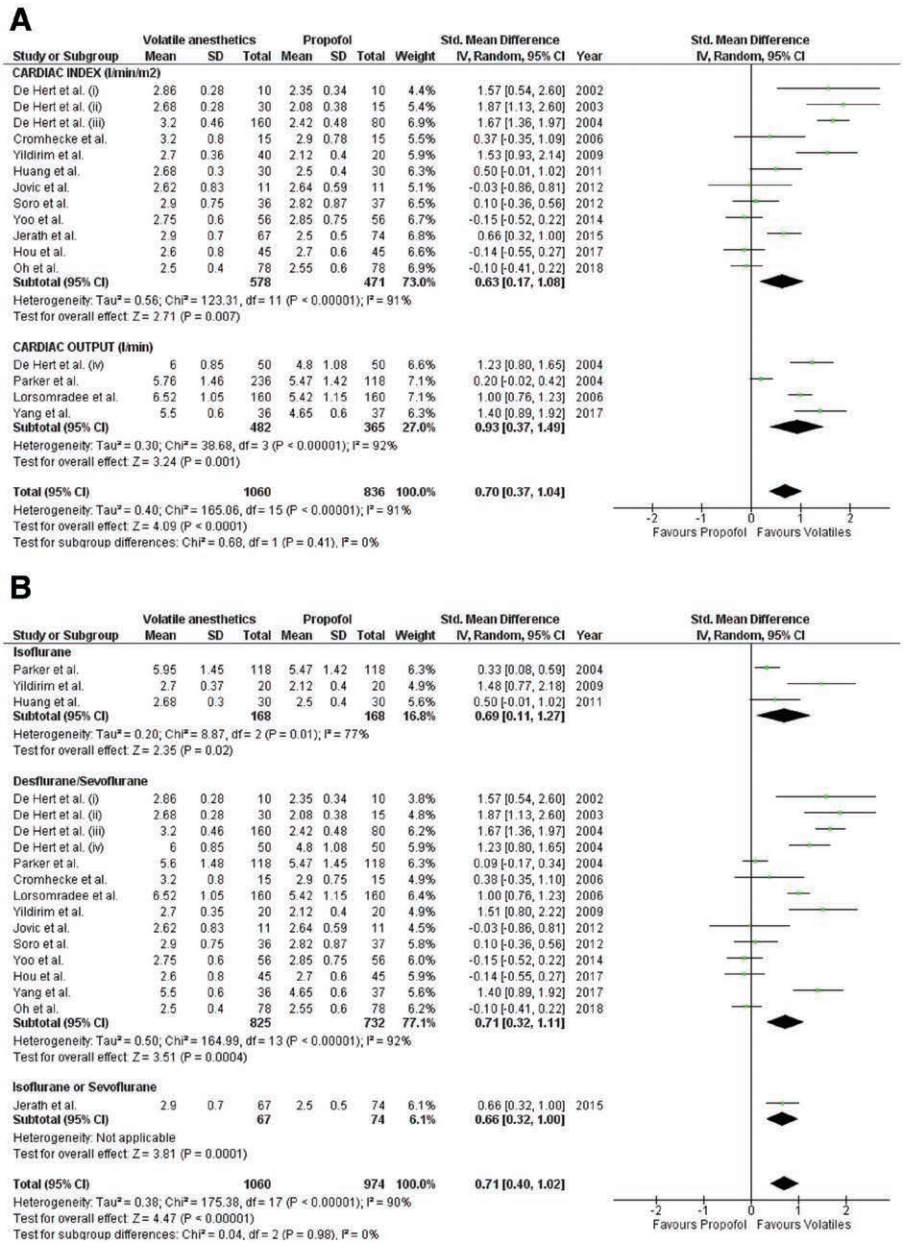

Fig. 5. Forest plot for the effects of volatile anesthetics as a class (*A*) and as subgroups *versus* propofol (*B*) on postbypass cardiac index/cardiac output in adults undergoing cardiac surgery with cardiopulmonary bypass. Subgroup analysis was performed in cardiac index *versus* cardiac output (*A*) and in isoflurane *versus* desflurane or sevoflurane (*B*). IV, inverse variance; Std., standardized mean difference.

subgroup was associated also with reduced extubation time, ICU, and hospital stays.

Many strengths of this study lie also in its methodology. In fact at variance with previous meta-analyses, we restricted the analyses to randomized clinical trials on adults undergoing cardiac surgery with CPB, which represents a perfect model of cardiac and renal ischemia/reperfusion injury; this setting represents 70 to 75% of cardiac interventions[70] and has comparable risk of organ damage. Moreover, we considered studies using volatile anesthetics or propofol (sometimes other total intravenous anesthetics) for the entire intervention, excluding studies on preconditioning or postconditioning; additionally, outcome definitions were comparable. In this way, we eliminated many confounding factors, thereby providing more reliable results. Finally, the inclusion of

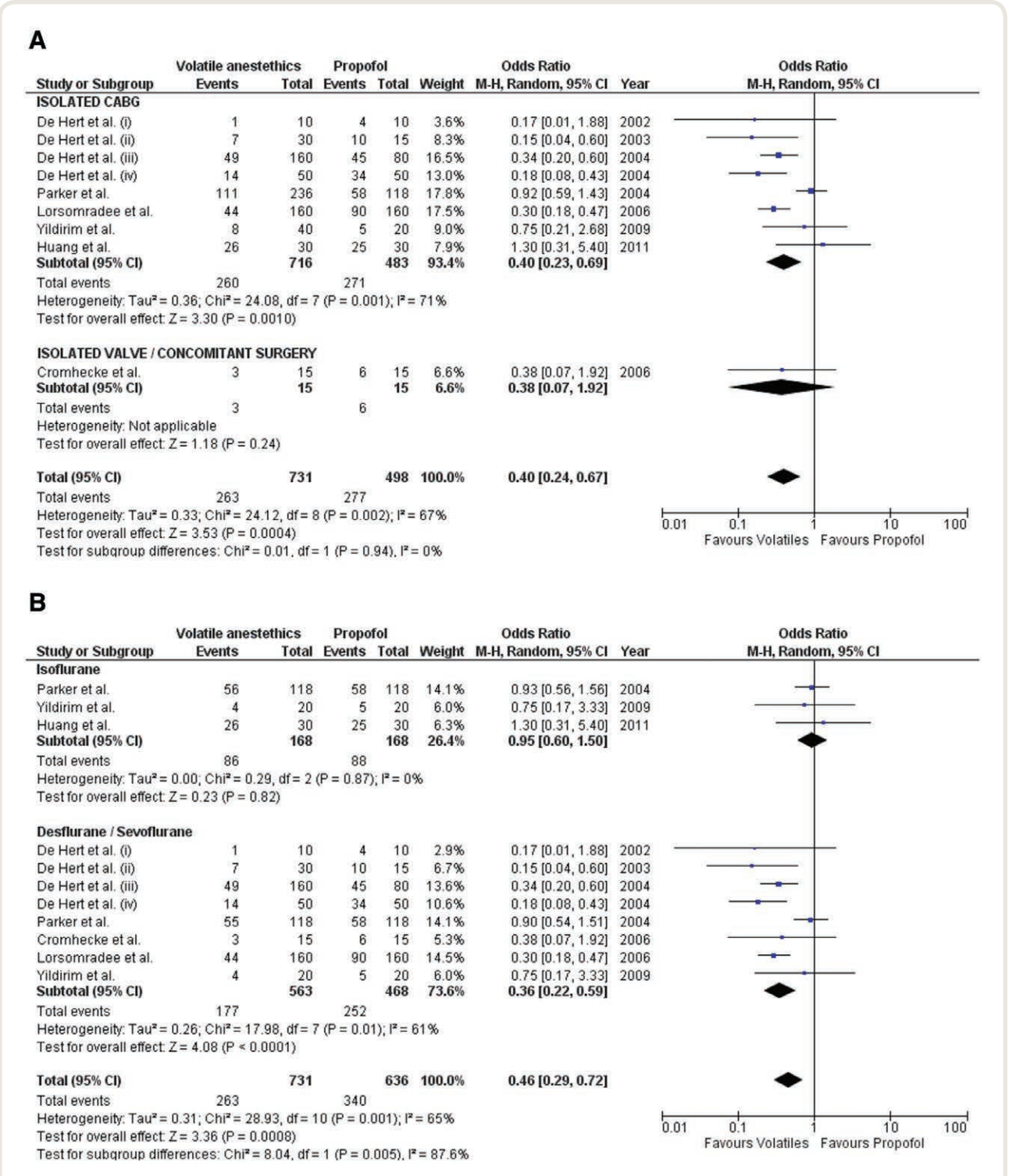

Fig. 6. Forest plot for the effects of volatile anesthetics as a class (*A*) and as subgroups *versus* propofol (*B*) on the need for inotrope medications in adults undergoing cardiac surgery with cardiopulmonary bypass. Subgroup analysis was performed in isolated coronary artery bypass graft (CABG) *versus* isolated valve/concomitant surgery (*A*) and in isoflurane *versus* desflurane or sevoflurane (*B*). M-H, Mantel–Haenszel.

studies published up to 2019 allowed us to obtain 42 studies (8,197 patients) to reach the best current evidence on this topic.

This meta-analysis has some limitations. First, the fact that results on long-term mortality are driven mainly by two articles cannot be overlooked. Second, the included

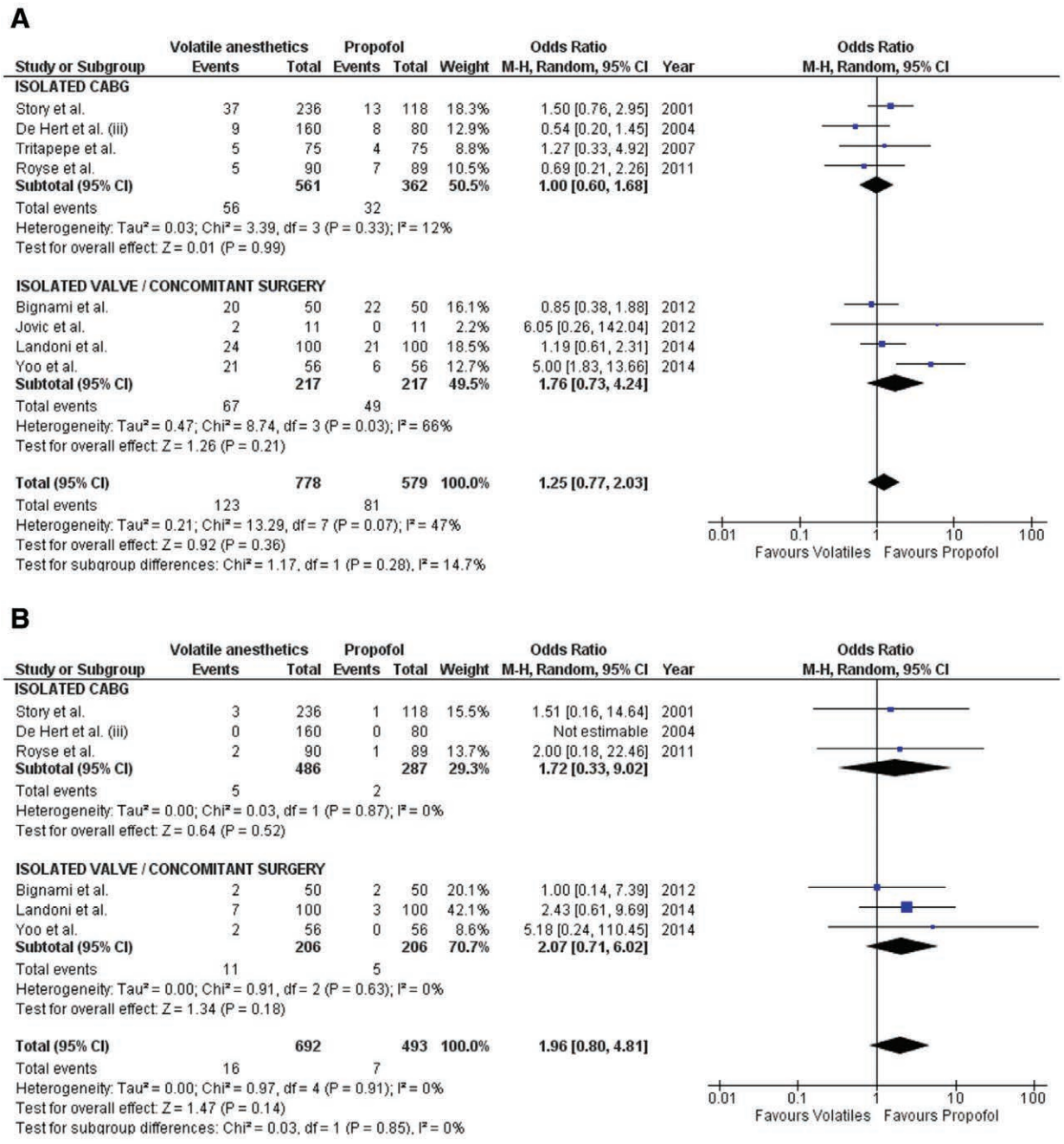

Fig. 7. Forest plot for the effect of volatile anesthetics *versus* propofol on the incidence of acute kidney injury (*A*) and of renal replacement therapy in adults undergoing cardiac surgery with cardiopulmonary bypass (*B*). Subgroup analyses in (*A*) and (*B*) show isolated coronary artery bypass graft (CABG) *versus* isolated valve/concomitant surgery. M-H, Mantel–Haenszel.

randomized clinical trials obtained few events for some outcomes. Third, in some trials[51,59,62,64,68] the use of total intravenous anesthetics for induction and for some periods of anesthesia maintenance in the volatile anesthetics arm may have attenuated their favorable effect.[62] Fourth, the use in a substantial number of patients[47,68] of total intravenous anesthetics also different from propofol could be a confounding factor. Despite these limitations of pragmatic trials that did not follow a strict anesthesiological protocol, they have the merit of replicating the reality of cardiac surgery. Fifth, despite the homogeneity of surgical and anesthetic protocols and the negative results of metaregression for most variables, other interferences with outcomes could not be excluded, including the long time

period considered and the ensuing qualitative differences in perioperative care.

An important result of our work is that volatile anesthetics were not associated with a lower short-term mortality in patients undergoing cardiac surgery with CPB. This result is in line with some recent meta-analyses conducted in heterogeneous surgical and anesthesiological settings that evaluated exclusively short-term mortality in patients anesthetized with volatile anesthetics *versus* propofol[21,22] or total intravenous anesthetics in general.[26] Other recent meta-analyses claimed a reduction in mortality with volatile anesthetics compared with total intravenous anesthetics by evaluating the "longest available data" on mortality, combining short-term and long-term outcomes and obscuring the difference between them.[20,23,26] Notably, we showed that at 1 yr, volatile anesthetics were associated with a 19% clinically important lower mortality in 5,096 patients, most on sevoflurane, whereas short-term mortality was similar. Until now, no meta-analyses have evaluated long-term mortality after volatile anesthetics *versus* propofol in cardiac surgery. Among the considered studies, there are different results even if the statistical heterogeneity is low. Two medium-sized trials[47,62] show a negligible difference in short-term mortality but a substantial reduction in long-term mortality by volatile anesthetics. However, in a large recent pragmatic trial,[68] volatile anesthetics did not significantly affect long-term mortality compared with propofol. In this trial, however, propofol and other total intravenous anesthetics were largely used also in the volatile anesthetics arm (in 89% of volatile anesthetics patients for induction and in 59% for anesthesia maintenance), and their unfavorable effects could not be excluded.[62]

Another reason for the difference between short- and long-term mortality could be the low statistical power of the short-term mortality outcome, which is a rare event when compared with long-term mortality. In fact, the odds ratio, when calculable, are usually based on a small number of events and show high variability.

The improved long-term survival after volatile anesthetics may be due to the better short-term preserved myocardium according to lower cardiac depression, cardiac troponin release, and MI incidence, mainly under desflurane or sevoflurane; of note, a lower release of cardiac troponin has been associated with a decrease in long-term mortality.[71,72]

To conclude, because of the above-reported lack of homogeneity, our results suggest the need for new trials able to clearly dissect the effect of volatile anesthetics and propofol on short- and long-term mortality.

Volatile anesthetics were associated with a lower postoperative release of cardiac troponin relative to propofol. However, this result updates and confirms those of previous meta-analyses that analyzed peak values instead of AUC (which better quantifies the extent of myocardial injury[73]), included markedly heterogeneous studies, and except in three cases,[15,18,22] used total intravenous anesthetics comparators other than propofol.[16,17,20,25] Importantly, desflurane and sevoflurane were associated with lower cardiac troponin release, whereas isoflurane appeared inefficacious. A result of major clinical importance is that volatile anesthetics, particularly sevoflurane or desflurane, caused less cardiac depression after weaning from CPB and early in ICU compared with propofol as inferred by a better cardiac index/output and a lower use of inotropic medications; accordingly, volatile anesthetics better protect against myocardial dysfunction after CPB. Even more importantly, MI incidence was lower particularly under desflurane or sevoflurane in line with the lower cardiac troponin release and a preserved cardiac function. An old meta-analysis reported a lower incidence of MI, although it considered different intervention and anesthetic protocols in more than 50% of studies.[17] On the contrary, isoflurane did not modify MI, confirming previous meta-analyses[15,19] and in accordance with not significant effects on cardiac troponin. Taken together, results of the present meta-analysis reveal a parallel effect of volatile anesthetics mainly desflurane and sevoflurane on MI, cardiac troponin release, and cardiac depression in patients undergoing cardiac surgery with CPB, *i.e.*, on the surrogate and solid endpoints indicating myocardial dysfunction and ischemia.

Surgery type, aortic cross clamp time, and study era appeared to influence volatile anesthetics' effects on two major cardiac surrogate endpoints, namely cardiac troponin release and cardiac index. Importantly from the clinical point of view, cardioprotection was favored by volatile anesthetics in isolated CABG and with shorter aortic cross clamp times (*i.e.*, the ischemia duration), both observed mainly in older articles. In addition, aortic cross clamp time is the best predictor of volatile anesthetics' effect on cardiac troponin release and cardiac index. However, because of the multiple connections among these variables, the multiple analysis cannot reveal their independent role in influencing volatile anesthetics effect on postoperative cardiac troponin release and cardiac index.

Our meta-analysis did not detect any renoprotective effect of volatile anesthetics. Our updated results differ from a previous meta-analysis, which claimed a lower AKI incidence.[21] Notably, the authors stated that renal protection would disappear if a article on volatile anesthetics preconditioning were excluded.[10] In addition, renal replacement therapy was similar after volatile anesthetics, confirming the data of the above-quoted meta-analysis.[21] It is interesting to note that remote ischemic preconditioning reduced the AKI incidence and the combined endpoint in patients undergoing cardiac surgery anesthetized with volatile anesthetics but not with propofol.[74]

The potential mechanisms of cardiac and renal protection by volatile anesthetics include different cellular pathways, such as protein kinase C and G, ATP-dependent K^+ channels, endothelial nitric-oxide synthetase, and the inhibition of caspase-mediated apoptosis, all mimicking the ischemic preconditioning. Major clinical consequences include decreased myocardial oxygen demand during

ischemia and the attenuation of tubular necrosis after ischemia–reperfusion injury.[7,8,14,75] Despite the fact that our and previous meta-analyses never showed beneficial effects of propofol relative to volatile anesthetics, protective mechanisms at cardiac and renal levels have been observed in cells and isolated organs also with propofol.[75–78] Likely, *in vivo* the protective effects of propofol are overwhelmed by those of volatile anesthetics.

In the future, large randomized clinical trials based on high-risk patients, homogeneous for surgical and anesthesiological protocols, are needed to assess the impact of volatile anesthetics alone *versus* propofol alone as a total intravenous anesthetics. Finally, after the results of this meta-analysis and those obtained after remote ischemic preconditioning,[74] future trials should strive to conclusively disclose the short- and long-term effects of this procedure on renal and cardiac protection after cardiac surgery.

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Competing Interests

The authors declare no competing interests.

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