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Is local anaesthesia a favourable approach for transcatheter aortic valve implantation? A systematic review and meta-analysis comparing local and general anaesthesia

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ABSTRACT

Objectives We conducted a systematic review and meta-analysis to identify the potential favourable effects of local anaesthesia plus sedation (LAS) compared with general anaesthesia (GA) in transcatheter aortic valve implantation (TAVI).

Methods Electronic databases (PubMed/Medline, Embase, Cochrane Central Register of Controlled Trials) and the reference lists of eligible publications were screened for randomised controlled trials (RCTs) and observational studies published between 1 January 2006 and 26 June 2016 that compare LAS to GA in an adult study population undergoing TAVI. We conducted study quality assessments using the Cochrane risk of bias tool and structured the review according to PRISMA. A meta-analysis calculating the pooled risk ratios (RRs) and mean differences (MDs) with 95% confidence intervals (CIs) under the assumption of a random-effects model was performed. Statistical heterogeneity was evaluated using the I² statistic and Cochran's Q-test.

Results After database screening, one RCT and 19 observational studies were included in the review. We found no differences between LAS and GA in terms of 30-day mortality, in-hospital mortality and other endpoints that addressed safety and complication rates. LAS was associated with a shorter ICU and hospital stay and with lower rates of catecholamine administration and red blood cell transfusion. New pacemaker implantations occurred more frequently under LAS. The overall conversion rate from LAS to GA was 6.2%.

Conclusion For TAVI, both LAS and GA are feasible and safe. LAS may have some benefits such as increased haemodynamic stability and shorter hospital and ICU stays, but it does not impact 30-day mortality. Since there is a paucity of randomised trial data and the findings are mainly based on observational study data, this review should be considered as a hypothesis-generating article for subsequent RCTs that are required to confirm the potential favourable effects we detected for LAS.

Registration number CRD42016048398 (PROSPERO).

Strengths and limitations of this study

► Our review is relevant to a current controversy regarding the practical implementation of TAVI, an evolving procedure that is constantly gaining in importance in the treatment of severe aortic stenosis.

► Most up-to-date review on the subject: we identified a total of 20 eligible articles, including 10 recently published studies providing new evidence that has not been considered in previous reviews.

► The review was conducted with strict adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the guidelines of the Cochrane Collaboration.

► Due to the observational nature of most of the publications available on the subject, the findings are susceptible to selection bias.

► Study centres were not homogenous in terms of procedural management and general anaesthesia was more frequently used than local anaesthesia during the early phase of TAVI in most institutions.

INTRODUCTION

Surgical replacement of the aortic valve is the current standard treatment for severe aortic stenosis and has been shown to reduce symptoms and to improve prognosis.[1] However, a large number of patients cannot undergo surgical aortic valve replacement because of high surgical risk related to advanced age, frailty, impaired cardiac function and relevant comorbidities.[2] Introduced in 2002, transcatheter aortic valve implantation (TAVI) has become the treatment of choice for severe aortic stenosis in the presence of prohibitive surgical risk and provides a reasonable treatment alternative for high-risk surgical patients.[3–5] TAVI is likely to gain further support in the future as several recent clinical trials, such as the randomised PARTNER II trial, have focused on extending its indication to low- and intermediate-risk patients and have shown encouraging results

for a broader range of patients than current guidelines recommend.[6 7]

When evaluating the impact of this new technology, it is necessary to consider that TAVI is an evolving technology with ongoing controversies concerning its practical implementation. One issue at stake is anaesthetic management since different approaches are currently used. Whereas TAVI has commonly been performed under general anaesthesia (GA), many clinicians have recently shifted to local anaesthesia with optional mild to moderate sedation (LAS).[8 9] The use of the less-invasive LAS method may minimise the cardiovascular and pulmonary complications associated with GA.[10 11] Nevertheless, there are advantages to using GA in TAVI, such as the facilitated use of periprocedural transesophageal echocardiography and easier management of surgical complications.[12] The extent to which the type of anaesthesia used in TAVI impacts procedural safety and clinical outcomes remains debatable. Therefore, in this systematic review and meta-analysis, we evaluated whether the use of LAS in TAVI has a favourable effect on complications and outcomes in patients with severe aortic stenosis compared with TAVI performed under GA.

METHODS
This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[13] The study protocol is registered in the international prospective register of systematic reviews (PROSPERO), registration number CRD42016048398.

Literature search
A literature search was conducted using the electronic databases PubMed/Medline, Embase and the Cochrane Central Register of Controlled Trials. The databases were searched up to 27 June 2016, and no further limitations were set. In addition, we screened the reference lists of eligible studies to identify other relevant publications. To determine appropriate search terms, we defined the following specific question according to the PICOS framework, as shown in supplementary table 1: Does the use of local anaesthesia with optional mild to moderate sedation in TAVI have a favourable effect on complications and outcomes in patients with severe aortic stenosis compared with TAVI performed under GA?

As search terms, we used the following contextual query language: 'Aortic valve' AND ('TAVI' OR 'TAVR' OR 'Transcatheter Aortic Valve Implantation' OR 'Transcatheter Aortic Valve Replacement') AND 'General Anaesthesia' AND ('Local Anaesthesia' OR 'Sedation') (supplementary appendix 1).

Study selection and eligibility criteria
The study selection process conformed with the PRISMA flow diagram throughout all its phases.[13] Any disagreements in the study selection process were resolved by the

consensus of all authors. The titles and abstracts of the search results were screened independently by two investigators (CE and GS). For potentially relevant studies, the full text was reviewed. Due to a lack of randomised controlled trials (RCTs) addressing our question, we also considered observational studies.

We included all studies in our analysis that matched our search criteria and the following eligibility criteria:
► Study characteristics: Publication date between 1 January 2006 and 27 June 2016: published as full text.
► Study design: RCTs and observational studies (prospective and retrospective).
► Population: Adults diagnosed with aortic stenosis.
► Intervention: TAVI.
► Comparison: TAVI under LAS with optional mild to moderate sedation compared with TAVI under GA.
► Outcome: Report of at least one of the following primary outcome parameters: 30-day mortality, length of hospital stay, pneumonia.

Data extraction and data items
The following data were extracted for inclusion in the systematic review: author information, date of publication, study design, sample size, population baseline characteristics and intervention characteristics, such as the access site and valve types used. The extracted outcome parameters were 30-day and in-hospital mortality, conversion from LAS to GA, conversion to open heart surgery, minor and major vascular complications, minor and major/life-threatening bleeding, intraprocedural and postprocedural catecholamine treatment, red blood cell transfusion, length of hospital and intensive care unit (ICU) stay, moderate/severe aortic regurgitation, new pacemaker implantation, stroke, acute kidney injury, myocardial infarction, pneumonia and sepsis. Any vascular complication leading to death, irreversible end-organ damage or life-threatening and major bleeding was considered a major vascular complication: all other vascular complications were considered minor.

Risk of bias
Two reviewers (CE and GS) conducted a domain-based evaluation of the risk of bias for each study using the Cochrane risk of bias tool.[14] To identify publication bias, funnel plots were created and visually evaluated for all meta-analyses that pooled 10 or more studies. In the absence of publication bias, the distribution of effect estimates in the funnel plot should resemble a symmetrical inverted funnel, whereas an asymmetrical funnel plot indicates the presence of publication bias.[15]

Statistical analysis
Statistical analyses were conducted using the Review Manager software provided by the Cochrane Collaboration, Version 5.3. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Means, SD, rates and their corresponding 95% CIs were calculated

using MedCalc for Windows, version 16.8 (MedCalc Software, Ostend, Belgium).

As effect measure estimates, we employed risk ratios (RRs) for dichotomous outcomes and mean differences (MDs) for continuous outcomes. We analysed the effect measure estimates of the selected studies using a pooled overall effect estimate for each outcome by computing the weighted average of the RRs or MDs, both under the assumption of a random-effects model. In the random-effects model, we assumed that the true value of the corresponding estimated effect differed among the studies, leading to the presence of statistical heterogeneity.[14] For the RRs, the Mantel-Haenszel method was used to estimate the between-study variation, and the inverse-variance method was performed for the MDs. RRs and MDs are presented with 95% CIs. p Values <0.05 were considered statistically significant. Due to the explorative nature of the study, the significance level was not adjusted. Inconsistency of the study results was quantified using Higgins's and Thompson's I^2 statistic and Cochran's Q-test. I^2 indicates the percentage of variability in study estimates that is attributable to heterogeneity rather than chance.[16] Substantial heterogeneity was determined if I^2 was >50%. Cochran's Q-test analyses the heterogeneity of the effect estimates between studies based on the weighted sum of squares between the overall pooled estimate and the study estimates, using a X^2 distribution.

Unadjusted estimates were included in the meta-analysis, as confounder-adjusted estimates were available in only a few cases.[17–19] We are aware that pooled estimates may not be overinterpreted. All available adjusted estimates are listed in supplementary appendix 2. For two outcome parameters, length of hospital stay and length of ICU stay, the data were not reported as the means and SD but as medians and ranges/IQRs in several studies. Due to the high amount of missing data, we decided not to estimate the missing means and SD as previous reviews on the same subject have done, instead, we performed meta-analyses that exclusively pooled the original data obtained from the eligible studies. The medians and ranges/IQRs reported in the remaining articles were included only in the qualitative synthesis and are provided as supplementary figures. This practice conforms with the guidelines of the Cochrane Collaboration, as the majority of studies had missing means and SD and we assumed that the outcome distributions were skewed.[14]

RESULTS
Search results and study characteristics
The initial electronic database search yielded a total of 211 articles. By screening the reference lists of eligible articles, one additional relevant publication was identified. We excluded 177 articles based on title and abstract. We reviewed 35 full-text articles and identified 20 articles for inclusion in our review (figure 1).[17–36] All the studies were observational studies except one RCT.[32]

Table 1 shows the baseline clinical characteristics of the included studies. In four studies, we found a significantly higher risk score (logistic EuroScore or STS score) for the GA group.[18 30 31 36] In comparison, one study registered a significantly higher logistic EuroScore for the LAS group.[32] Other significant differences are shown in table 1.

Supplementary table 2 shows the access routes and valve types used for TAVI. The preferred access route in all studies was the femoral artery. Fourteen studies reported the transfemoral approach as the only access route used.[17–20 22 23 26–28 31 34 35] The predominant valve types used in all studies were the Medtronic CoreValve (Medtronic, Minneapolis, MN, USA) and the Edwards Sapien/Sapien XT valve (Edwards Lifesciences, Irvine, CA, USA). In five studies, only the Medtronic CoreValve was implanted,[22 24 35 36] whereas in two studies, all the implanted valves were Edwards Sapien/Sapien XT valves (supplementary table 2).[17 33] The most frequently reported anaesthetic approach was the infiltration of the vascular access sites with lidocaine 1% in combination with the administration of remifentanil or fentanyl and propofol and/or midazolam as analgosedative agents. The level of sedation ranged from no sedation to moderate/deep sedation with mild sedation as the most common target level, although many studies did not provide detailed information on this issue. In two studies, iliohypogastric-/ilioinguinal blocks were performed as an alternative or supplement to local infiltration techniques.[25 27] Supplementary table 3 provides an overview of all anaesthetic approaches reported in the LAS group.

The results of the risk of bias assessment are illustrated in supplementary figure 1. We identified one eligible RCT that had a low risk of selection bias since adequate information concerning random sequence generation and allocation concealment was provided.[32] We evaluated all other studies as having a high risk of selection bias and performance bias due to the lack of randomisation and blinding of participants and personnel. Two studies were assessed as having a high risk of attrition bias because outcome data were not reported for all participants and no reason was provided for the missing data.[24 31] One study was considered to have a high risk of reporting bias because the results section did not provide data for all the outcome parameters specified previously in the article.[26]

We excluded the study by Covello et al from the analyses that included data extracted from the study by Petronio et al because we assumed that as a multicentre study, the latter included cases that were previously reported by Covello et al. However, Covello et al assessed several outcomes that were not considered by Petronio et al and were of interest for our study.[25 36]

Mortality
The 30-day mortality rate was 5.6% (CI 4.7 to 6.5) in the LAS group (150 out of 2697 patients) and 5.9% (CI 4.8 to 7.3) in the GA group (93 out of 1566 patients), with no
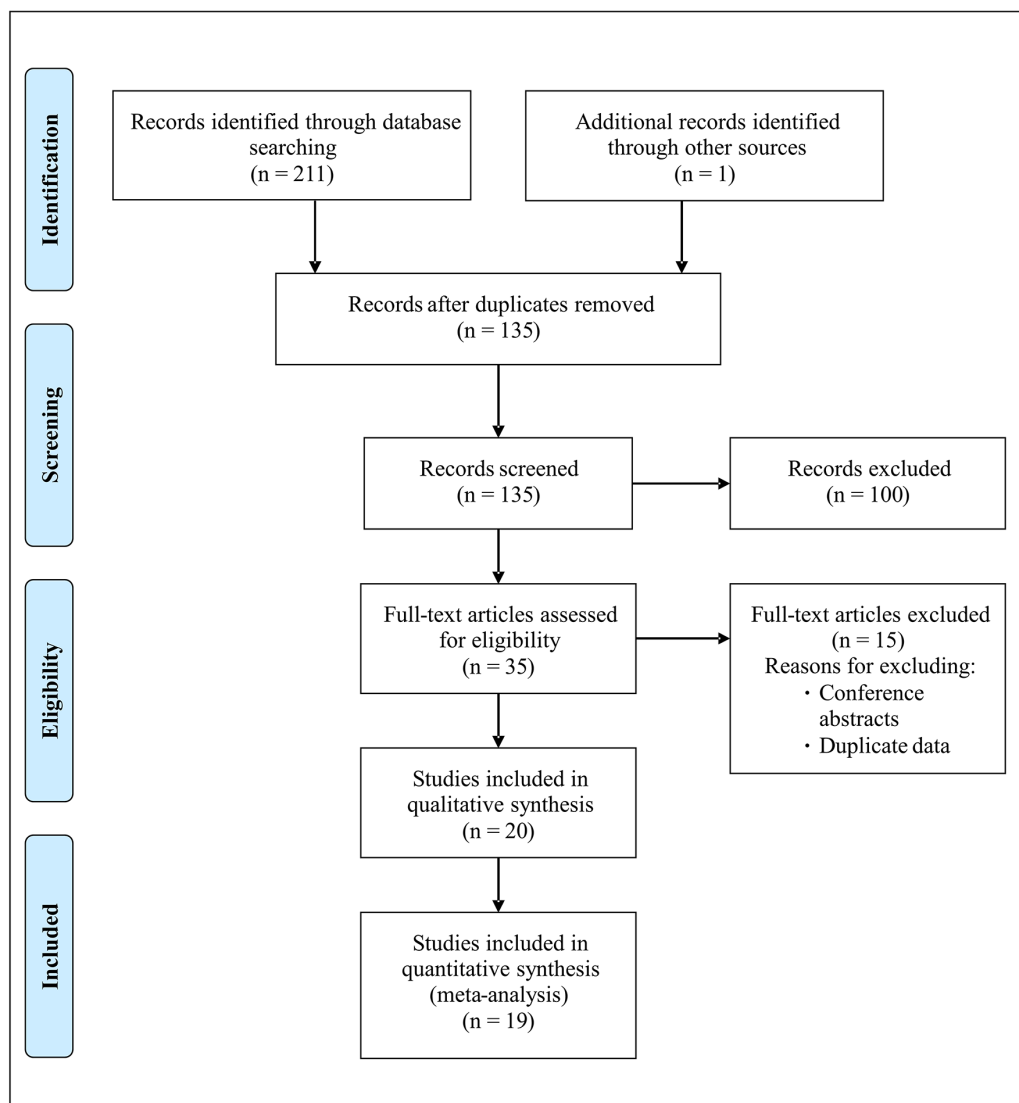
Figure 1 Flow diagram of study selection process corresponding to PRISMA statement.

significant difference (RR 0.91 (CI 0.70 to 1.18), p=0.48) (figure 2).

Similarly, the in-hospital mortality rate did not differ significantly between the study groups (RR 0.87 (CI 0.55 to 1.40), p=0.58). In-hospital mortality was 4.8% (CI 4.0 to 5.6) in the LAS group (142 out of 2968 patients) and 5.1% (CI 4.2 to 6.0) in the GA group (129 out of 2544 patients; figure 2).

Procedural outcomes

The meta-analysis revealed a significant decrease in both intraprocedural and postprocedural catecholamine treatment in the LAS group (figure 3). During TAVI, 31.0% (CI 24.9 to 38.1) of the LAS group received catecholamines (89 out of 287 patients). In contrast, the rate was 65.0% (CI 56.0 to 75.1) in the GA group (184 out of 283 patients) (RR 0.47 (CI 0.32 to 0.70), p=0.0002). Heterogeneity among the trials was considerable, with an I^2 of 54%, but was not significant according to the Q-test (p=0.07). After TAVI, 9.4% (CI 6.5 to 12.9) of the LAS group (36 out of 385 patients) and 15.4% (CI 10.8 to 21.3) of the GA group (36 out of 234 patients) required catecholamines (RR 0.59 (CI 0.38 to 0.92), p=0.02).

Significantly fewer patients in the LAS group required red blood cell transfusions (RR 0.69 (CI 0.49 to 0.96), p=0.03). The rate was 14.7% (CI 12.9 to 16.7) in the LAS group (241 of 1637 patients) versus 16.7% (CI 15.0 to 18.6) in the GA group (348 out of 2084 patients). We found considerable heterogeneity among the trials (I^2=64%, p=0.006; figure 3).

Conversion from TAVI to open heart surgery was infrequent, occurring in 2.5% (CI 2.0 to 3.0) of the LAS group (92 out of 3739 patients) and 2.9% (CI 2.4 to 3.4) of the GA group (114 out of 3992 patients). There was no significant difference between the groups (RR 0.89 (CI 0.51 to 1.56), p=0.68) (supplementary figure 2).

In total, 148 out of 2369 patients, or 6.2% (CI 5.3 to 7.3), required a conversion of the anaesthetic technique from LAS to GA. The most frequent reasons for the change in anaesthetic management were vascular and procedural complications, hypotension, respiratory complications

Table 1 Baseline characteristics

Study/year		n	Age (years)	Female (%)	BMI (kg/m²)	EuroScore (%)	STS score (%)	DM (%)	CKD (%)	Stroke or TIA (%)	CAD (%)	NYHA III/IV (%)
Attizzani 2015[20]	LAS	116	81	49	29.6	NA	8.6	47	39	22	NA	87
	GA	91	81	45	29.4	NA	9.8	53	40	17	NA	83
Babaliaros 2014[17]	LAS	70	82	39	27	NA	10.6	43	NA	20	83	87
	GA	72	83	47	28		11.4	44		28	81	89
Balanika 2014[21]	LAS	41	82	44	NA	28	NA	NA	NA	NA	NA	NA
	GA	57	81	42		27		NA		NA	NA	NA
Behan 2008[22]	LAS	9	80	33	NA	NA	NA	NA	NA	11	NA	NA
	GA	3	83	33						33		
Bergmann 2011[23]	LAS	100	80.2	57	26.9	20	NA	NA	NA	6	56	NA
	GA	51	81.1	47	26.6	21		NA		18	65	
Brecker 2016[24]	LAS	245	81.3	51.4	NA	16.1	5.3	24.5	NA	12.7	52.7	79.2
	GA	245	81.6	53.1		16.3	5.2	24.1		11.8	55.7	78.8
Covello 2010[25]	LAS	42	79.5	NA	NA	27.3	NA	33	NA	19	57	NA
	GA	27	77.6			22.9		30		15	44	
Dall'Ara 2014[18]	LAS	1095	82.5*	54.5	26.2	19.7*	NA	25.5	60.9	NA	11.2*	76.0
	GA	1712	81.4*	51.3	26.5	20.9*		25.1	69.2		25.8*	79.9
Dehédin 2011[27]	LAS	34	83.5	47	NA	23.6	9.2	NA	56	12	44	68
	GA	91	83.0	50		24	14		44	11	52	88
D'Errigo 2016[26]	LAS	310	82.7	35.5	26.4	13.3	NA	29.4	NA	NA	24.2	69.4
	GA	310	82.0	38.1	26.4	13.4		29.0			26.1	67.1
Gauthier 2015[28]	LAS	66	86	61	26	27.1	NA	20	NA	18	NA	65
	GA	51	86	39	25	25.3		29		24		67
Goren 2015[29]	LAS	129	83	60	27	NA	NA	32	NA	9	NA	100
	GA	75	83	64	28			32		11		100
Kesimci 2016[30]	LAS	72	77.4	44.4*	27.2	12.0*	6.7*	8.3*	NA	13.9*	62.5	NA
	GA	79	76.3	68.4*	27.2	17.3*	17.0*	27.8*		3.8*	58.2	
Kiramijyan 2016[31]	LAS	467	82.9	49.4	27.4*	NA	8.5*	33.8	43.9*	12.2	72.4	87.0
	GA	66	81.3	50.0	31.0*		9.8*	35.5	62.3*	13.1	83.3	93.5
Mayr 2016[32]	LAS	31	84	42	27	11.7*	5.0	NA	NA	NA	NA	71
	GA	31	80	58	25	9.7*	4.3					77
Motloch 2012[33]	LAS	33	82.6	65.9	NA	NA	20.8	29.3	NA	14.6	43.9	83.0
	GA	41	83.4	45.5			16.5	27.3		24.2	42.4	84.8
Oguri 2014[34]	LAS	949	83.1	54.9	26.1	17.3	NA	23.9	NA	9.4	NA	76.2
	GA	1377	83.1	50.9	26.1	18.8		26.6		9.7		77.6
Palermo 2016[35]	LAS	44	85.4*	31.8	26.2	13.5	6.9	29.5	31.8	11.4	56.8*	NA
	GA	21	79.6*	23.8	28.3	13.1	6.2	42.9	19.0	19.0	85.7*	NA

Continued

Table 1 Continued

Study/year		n	Age (years)	Female (%)	BMI (kg/m²)	EuroScore (%)	STS score (%)	DM (%)	CKD (%)	Stroke or TIA (%)	CAD (%)	NYHA III/IV (%)
Petronio 2016[36]	LAS	961	81.8	53.3	NA	19*	NA	28.5	NA	9.2	44.7	73.5
	GA	355	81.2	53.0	NA	21*	NA	30.8	NA	9.6	50.6	69.6
Yamamoto 2013[19]	LAS	130	83.7	60.5	25.7	22.0	11.2	25.6	68.5	10.1	NA	66.7
	GA	44	84.7	53.3	26.0	26.6	14.3	13.3	63.6	11.1	NA	62.2

*Reported as significant.
CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; NA, not available; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons; TIA, transitory ischaemic attack.

and insufficient patient compliance or patient discomfort. Supplementary table 4 lists all the information on conversions obtained from the studies.

Periprocedural complications

The rate of major vascular complications was 5.8% (CI 5.1 to 6.5) in the LAS group (254 out of 4402 patients) and 4.6% (CI 4.0 to 5.3) in the GA group (203 out of 4395 patients). The difference was not statistically significant (RR 0.95 (CI 0.69 to 1.31), p=0.75) (supplementary figure 2). Similarly, the meta-analysis did not reveal a significant difference between the groups in the rate of minor vascular complications (RR 0.89 (CI 0.71 to 1.11), p=0.30). Minor vascular complications were reported for 9.1% (CI 7.9 to 10.6) of the LAS group (186 out of 2035 patients) and 7.2% (CI 6.1 to 8.4) of the GA group (147 out of 2049 patients; supplementary figure 2).

Major and life-threatening bleeding occurred in 12.1% (CI 10.9 to 13.4) of the LAS group (380 out of 3146 patients) and 12.3% (CI 11.0 to 13.8) of the GA group (314 out of 2548 patients). The difference between the groups was not significant (RR 0.86 (CI 0.69 to 1.09), p=0.21) (supplementary figure 2).

Likewise, the two groups did not differ significantly in the rate of minor bleeding (RR 1.12 (CI 0.92 to 1.35), p=0.26). Minor bleeding was observed in 9.7% (CI 8.5 to 10.9) of the LAS group (270 out of 2794 patients) and 7.6% (CI 6.5 to 8.9) of the GA group (168 out of 2205 patients; supplementary figure 2).

The rate of acute kidney injury did not differ significantly between the groups (RR 0.92 (CI 0.69 to 1.23), p=0.58). In total, acute kidney injury occurred in 8.2% (CI 7.4 to 9.1) of the LAS group (380 out of 4607 patients) and 5.8% (CI 5.1% to 6.5%) of the GA group (261 out of 4516 patients). The heterogeneity among the trials was considerable (I^2=54%, p=0.008; supplementary figure 2).

Similarly, the rate of myocardial infarctions was comparable in both groups (RR 1.33 (CI 0.76 to 2.34), p=0.32). It amounted to 0.8% (CI 0.6 to 1.2) of the LAS group (29 out of 3486 patients) and 0.6% (CI 0.4 to 0.9) of the GA group (22 out of 3903 patients; supplementary figure 2).

The rate of sepsis also did not differ significantly between the groups. Sepsis occurred in 4.8% (CI 2.6 to 8.1) of the LAS group (14 out of 290 patients) versus 7.3% (CI 4.3 to 11.5) of the GA group (18 out of 247 patients) (RR 0.93 (CI 0.38 to 2.27), p=0.88) (supplementary figure 2).

The rate of moderate/severe aortic regurgitation was 3.9% (CI 3.1% to 4.9%) in the LAS group (83 out of 2112 patients) and 3.5% (CI 2.8 to 4.4) in the GA group (82 out of 2325 patients), with no statistically significant difference (RR 0.85 (CI 0.57 to 1.26), p=0.41) (supplementary figure 2).

LAS was associated with a significantly higher rate of new pacemaker implantation, amounting to 17.5% (CI 16.3 to 18.8) or 814 out of 4648 patients, compared with 12.8% (CI 11.8 to 13.9) or 588 out of 4597 patients in
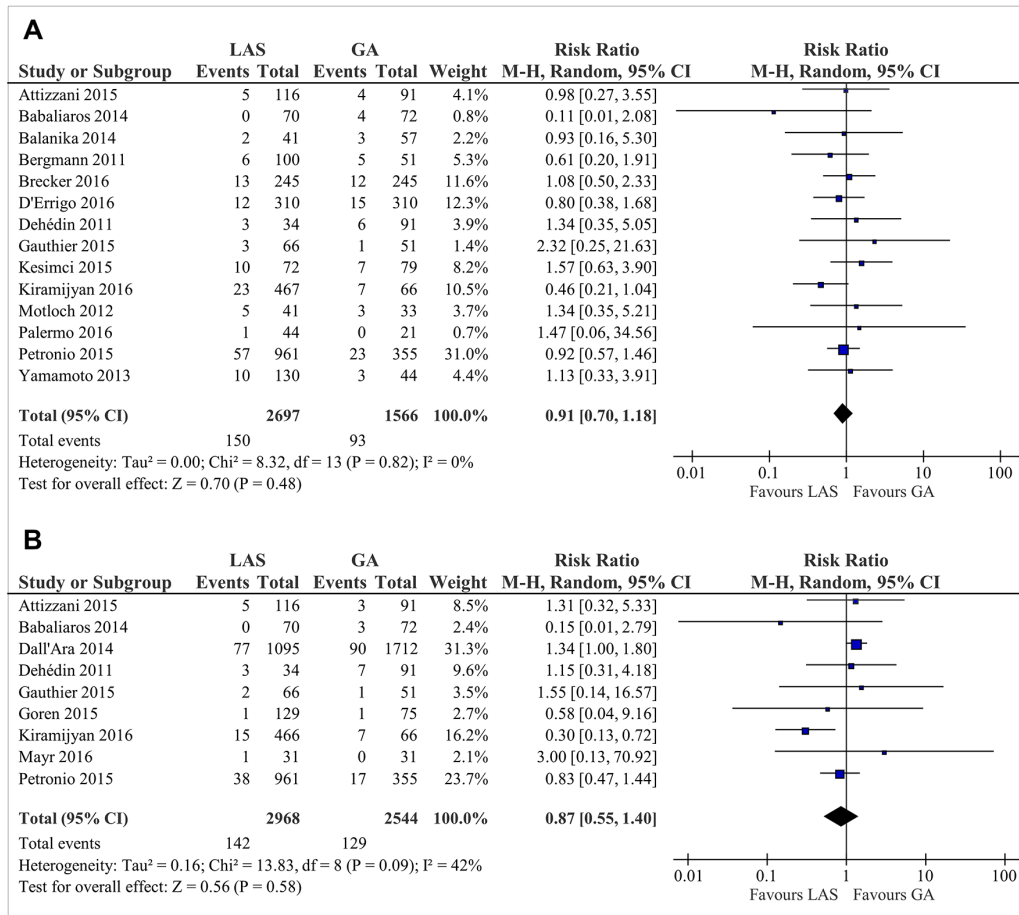
Figure 2 Mortality outcomes. (A) 30-day mortality. (B) In-hospital mortality.

the GA group (RR 1.24 (CI 1.11 to 1.39), p=0.0001) (figure 4).

There was no significant difference between the LAS group and the GA group in terms of the stroke rate, which was 2.6% (CI 2.2 to 3.1) in the LAS group (124 out of 4777 patients) and 2.2% (1.8 to 2.7) in the GA group (103 out of 4624 patients) (RR 1.05 (CI 0.80 to 1.38), p=0.73) (figure 4).

Only three studies reported the frequency of pneumonia, which was slightly lower in the LAS group with a rate of 1.4% (CI 0.3 to 4.1) or 3 out of 215 patients versus 5.7% (2.3 to 11.7%) or 7 out of 123 patients in the GA group. However, the difference between the two groups did not reach statistical significance (RR 0.31 (CI 0.09 to 1.04), p=0.06) (figure 4).

Length of stay
The length of hospital stay was significantly shorter in the LAS group (MD −1.49 days (CI −2.45 to −0.53 days), p=0.002) (figure 5). There was considerable heterogeneity among the trials (I²=60%, p=0.01). We also found a significantly reduced length of ICU stay for patients in the LAS group (MD −0.47 days (CI −0.83 to −0.11 days), p=0.01) (figure 5).

The findings of the studies that provided only medians and ranges or IQRs are graphically presented in supplementary figure 3. A statistically significant decrease in the

length of stay of the LAS group was observed in seven studies.[17 20 27 28 30 34 36] As the graphic shows, the duration of ICU stay was comparable in most cases, which is in contrast to the results of the meta-analysis. Notably, the only eligible RCT found a statistically significant decrease in the length of ICU stay in the GA group.[32]

DISCUSSION
The present systematic review and meta-analysis evaluates the safety and clinical outcomes of TAVI under LAS compared with TAVI under GA. Our findings suggest that the two anaesthesia regimens, LAS and GA, are equally safe for TAVI, as we found no differences in 30-day mortality, in-hospital mortality and other endpoints addressing the safety and complication rates of TAVI. Patients who underwent LAS were less likely to require intra- and post-procedural catecholamine treatment and red blood cell transfusions. The ICU stay and length of hospital stay were reduced with the use of LAS. However, LAS was associated with a higher rate of new pacemaker implantations. The conversion rates of the anaesthetic technique varied from 0% to 17%.[21 23] We identified several recently published trials relevant to our article that were not considered in previous systematic reviews, including the first randomised controlled trial comparing LAS
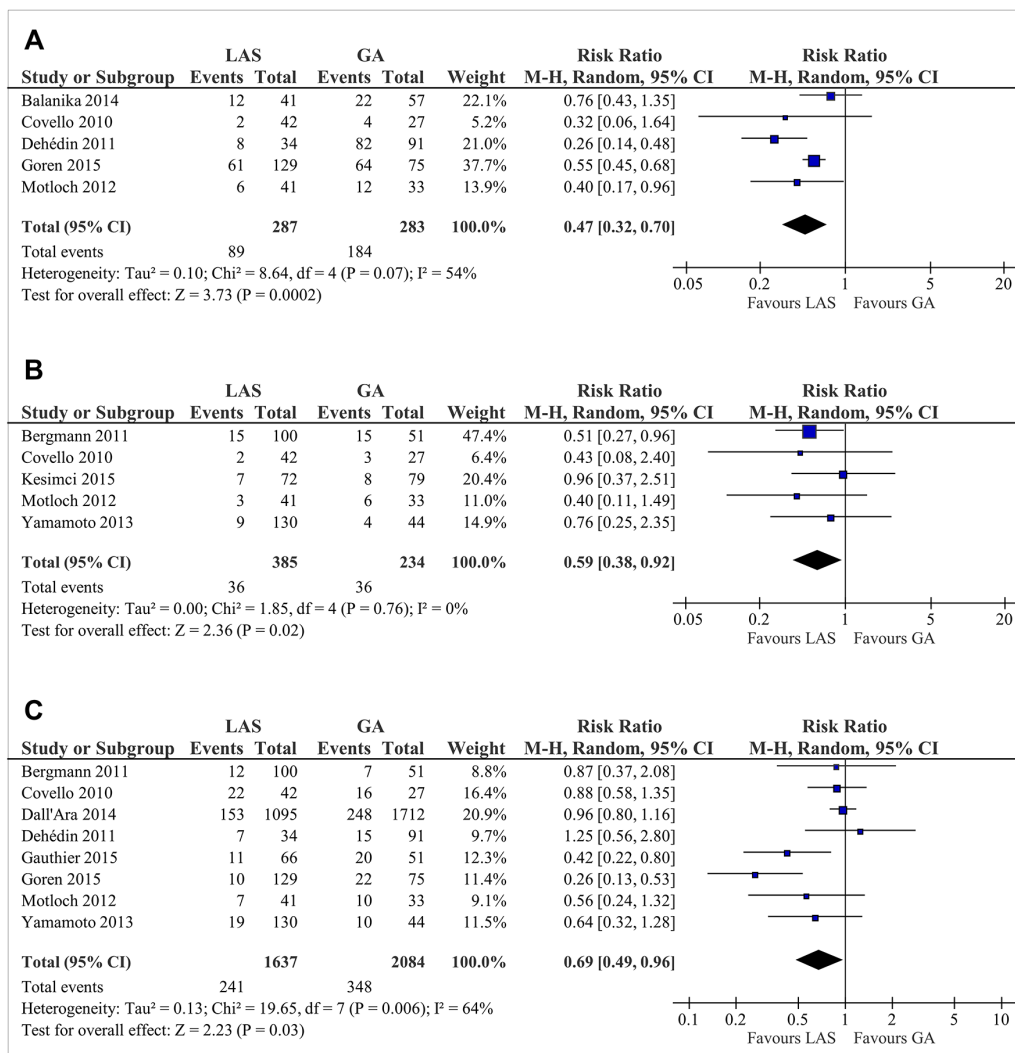
Figure 3 Procedural outcomes. (A) Intraprocedural catecholamine treatment. (B) Postprocedural catecholamine treatment. (C) Patients requiring transfused red blood cells.

and GA for TAVI. Thus, our article adds important new information to the decision-making process concerning the optimum anaesthetic strategy and strengthens the evidence supporting the safety of LAS for TAVI that has been indicated in previous systematic reviews.[37–39]

LAS provides multiple benefits compared with GA. These benefits are even more valuable in a patient population characterised by old age and a high level of frailty, as in the case of patients undergoing TAVI for aortic stenosis. The avoidance of the cardiac depressant effects of anaesthetic drugs results in a decrease in periprocedural haemodynamic instability. Hypotension and bradycardia are side effects of anaesthetic drugs that may lead to reduced vital organ perfusion, putting the patient at risk of permanent neurological deficits, myocardial ischaemia and renal impairment: therefore, these conditions require appropriate pharmacological management.[10 40 41] The use of LAS as an anaesthetic approach for TAVI minimises these risks, and the lower rates of intraprocedural and postprocedural catecholamine administration that we found for the patients in the LAS group reflect improved

haemodynamic stability compared with the GA group. In terms of catecholamine administration, inotropes are preferable over vasopressors, since poor contractility and left ventricular systolic dysfunction are dominating factors in the genesis of hypotension in TAVI patients.[42] Additionally, Goren et al explained the lower rate of red blood cell transfusions they found in patients who underwent LAS in terms of anaesthesiologists' increased tolerance of low haemoglobin values as long as haemodynamic stability is maintained.[29] According to Palermo et al, increased blood loss in the GA group is considered secondary to the vasodilating effect of halogenic volatile anaesthetics.[35] In our meta-analysis, we confirmed the reduced need for red blood cell transfusions in the LAS group. However, many studies reported a shift from LAS to GA administration over the study period, thus the lower transfusion rates for LAS might also be due to the lower occurrence of intraprocedural complications in more experienced teams.

The shorter length of hospital stay that we observed in the LAS group adds an important rationale for choosing LAS as the primary anaesthetic technique for
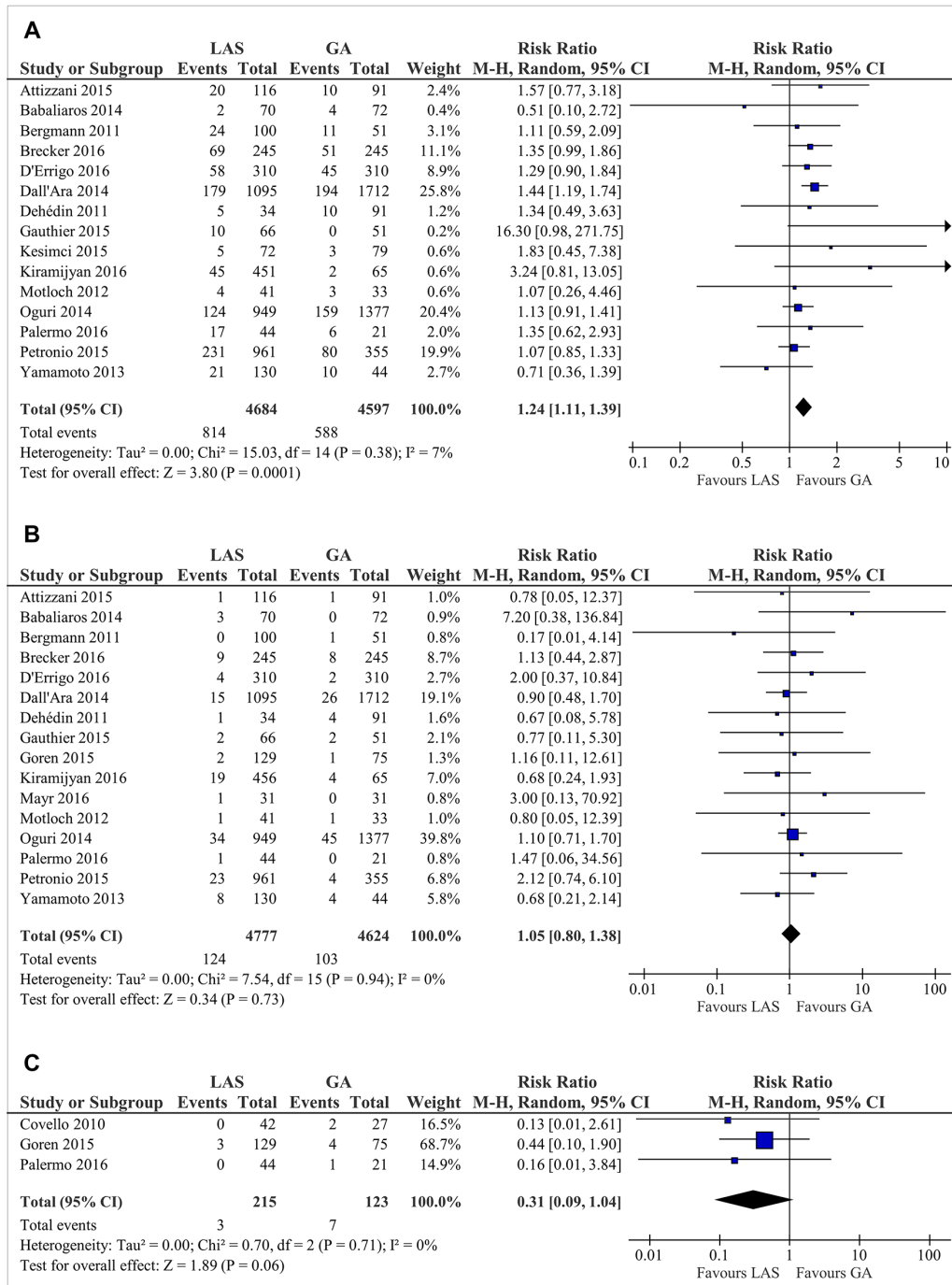
Figure 4 Complication outcomes. (A) New pacemaker implantation. (B) Stroke. (C) Pneumonia.

TAVI. Because we could not find significant differences in the occurrence of periprocedural complications that would prolong the hospital stay, the reasons for the later discharge of patients who underwent GA-TAVI remain subject to speculation. One reason might be the transfer of intubated patients to the ICU, where extubation occurred with some delay after the procedure, as reported by some authors.[17 21 29 30] Indeed, we showed in a further meta-analysis that LAS was associated with a shorter length of ICU stay. However, the reduction in the duration of ICU stay was smaller than the overall reduction in the length of hospital stay, so we assume

that additional, yet unknown aspects contribute to this finding. Interestingly, the only RCT on the subject conversely reported a significantly increased length of ICU stay for the LAS group but without providing a rationale for this finding.[32] Graphical analysis of the length-of-stay data from studies that reported only the median and IQR/range produced a similar result as that of the meta-analysis, showing a shorter hospital stay in the LAS group. However, we could not confirm the finding of a shorter ICU stay in these studies. Thus the pooled estimate of this outcome should not be overinterpreted despite the observation of a significant
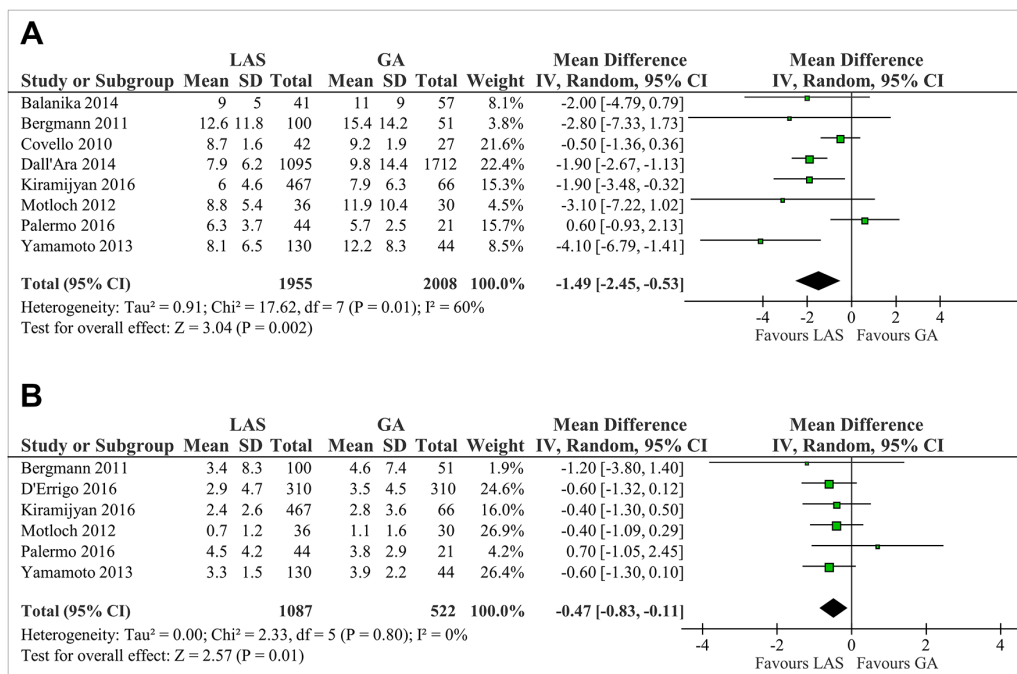
Figure 5 Length of stay outcomes. (A) Length of hospital stay (days). (B) Length of ICU stay (days).

difference in the meta-analysis (supplementary figure 3).

ICU admission has been associated with a high risk of nosocomial infections, which is related to both the length of stay and the administration of mechanical ventilation.[43 44] Gauthier et al reported a lower risk of infectious complications for patients who received LAS for TAVI: they attributed this finding to the avoidance of bladder catheterisation, central venous catheter insertion and intubation.[28] Nevertheless, we could not identify a significant difference in the pneumonia rate between the LAS and GA groups, possibly because of the small number of studies that reported this outcome. Palermo et al described pneumonia rates of 0% for LAS versus 4.8% for GA; Covello et al reported rates of 0% for LAS versus 7% for GA; and Goren et al also found a lower incidence, with 2% for LAS versus 5% for GA. However, these findings did not reach statistical significance.[25 29 35]

Notably, we found a higher rate of pacemaker implantations in the patients who underwent LAS for TAVI. Pacemaker implantation in general is one of the most frequent complications of TAVI, and it is commonly subsequent to a third-degree atrioventricular block induced during the implantation process. We agree with Maas et al that the attribution of pacemaker implantation to LAS use is arguable because an association between pacemaker implantation and the self-expandable devices used for TAVI has been previously described in several studies.[39 45–47] However, Brecker et al found a higher rate of pacemaker implantations in the LAS group (28.2% vs 20.8% in the GA group) despite the restriction to only one valve type, the Medtronic CoreValve, which they attributed to heightened attempts to reposition a deeply implanted valve under GA.[24] Moreover, valve positioning can be impaired

by increased patient movement due to discomfort or anxiety leading to a higher rate of conduction defects that require a permanent pacemaker, for example, decreased cerebral blood flow during rapid ventricular pacing may have an anxiogenic effect.[27] Furthermore, the use of GA allows for a short interruption of mechanical ventilation and thus may be favourable in terms of precise valve positioning.[48]

Aortic regurgitation has been identified as a strong risk factor for postprocedural cardiovascular mortality.[49] Oguri et al reported a significantly higher rate of ≥mild aortic regurgitation in their LAS group (16.4% vs 12.7% in the GA group).[34] This correlation was not confirmed in our analysis, as we found no significant difference in moderate/severe aortic regurgitation between the groups. However, evidence on this issue was limited due to the different methods of reporting the aortic regurgitation grades among the studies.

Our analyses revealed no statistically significant difference between the groups in terms of major vascular complications. However, the LAS group tended towards a higher incidence (5.8% vs 4.6% in GA), which might reflect increased agitation and movement during TAVI and earlier postprocedural mobilisation of patients in the LAS group. Similarly, the incidence of acute kidney injury was higher in the LAS group than in the GA group (8.2% vs 5.8%). Although not statistically significant, this tendency is notable, since the higher rate of blood transfusions and anaesthetic drug-induced hypotension under GA have been discussed as risk factors for acute kidney injury. However, postoperative renal function might be impaired by other factors such as dehydration, perioperative blood loss and rapid ventricular pacing, debris and thromboembolism during TAVI. Therefore, the impact

of anaesthesia choice on this outcome should not be overinterpreted.[50]

Whereas in recent years, there has been a shift from GA to LAS in many European institutions, in North America, GA still is the predominant method, and it is used in >95% of patients.[8 9] One of the most frequently mentioned rationales for preferring GA is the increased capacity to handle sudden and life-threatening complications during TAVI that may comprise mitral regurgitation, valve embolisation, coronary obstruction, cardiac tamponade and aortic dissection. In patients receiving LAS for TAVI, these complications require emergent conversion of the anaesthetic technique. Among the trials included in our analysis, we found a wide range of conversion rates, including elective conversions, from the 0% reported by Balanika et al to the 17% reported by Bergmann et al.[21 23] However, the impact of emergency conversions on safety is not reflected in the mortality outcomes of both groups: in fact, we detected no difference between LAS and GA. In this regard, we would rather emphasise the importance of an experienced anaesthesiologist prepared for a swift conversion of procedures performed under LAS and advise the primary administration of GA in cases of anticipated complications and intubation difficulties.

Several limitations of our study should be considered. Since we included primarily non-randomised trials, the outcome data were susceptible to selection bias. For the outcome parameters length of hospital stay and length of ICU stay, studies with missing means were excluded from the quantitative analysis, which may have introduced attrition bias. For the outcome parameters length of hospital stay, acute kidney injury and red blood cell transfusion, heterogeneity among the trials was substantial. The study centres varied in their preferred anaesthetic drugs, valve types and vascular access sites. In particular, a broad range of anaesthetic approaches were used in the LAS group, ranging from local lidocaine infiltration of the access sites to ilioinguinal/-hypogastric blocks and from no sedation to deep sedation, which has to be taken into consideration when interpreting the results. Since some study centres reported the use of both transfemoral and transaxillary/subclavian access routes, access-related procedural differences should be considered. Transfemoral TAVI is the most frequently used access route and is preferred over transaxillary/subclavian TAVI because it provides the easiest and least invasive vascular access and can be performed percutaneously in most cases. Transaxillary/subclavian TAVI usually implies a surgical cutdown and is used as an alternative route only in cases where the transfemoral route is not applicable due to vascular sclerosis or stenting. Additionally, many authors indicated an unbalanced distribution of LAS and GA over the study period. Starting with GA during the early phase and shifting towards LAS in line with the institutions' growing experience with TAVI procedures may have introduced performance bias into the results. Furthermore, the results might be biased by country-specific conditions, such as the requirement in the German DRG system of a minimum hospital stay after TAVI, which has been recently reduced from five to four nights. These differences impair the comparability of international data. Lastly, we found evidence of publication bias for the outcomes acute kidney injury and major vascular complications (supplementary figure 4).

CONCLUSIONS

To conclude, both LAS and GA are safe and feasible anaesthetic approaches for TAVI. There was no difference in 30-day mortality, in-hospital mortality and various other safety endpoints. LAS was associated with favourable effects such as shorter hospital and ICU stays and a reduced need for catecholamines and red blood cell transfusions. Nevertheless, we consider both anaesthetic regimens suitable for TAVI and suggest a careful pre-procedural evaluation to determine the optimum strategy for each patient. Additional high-quality RCTs that also focus on long-term outcomes are required to establish the indications for either of the two anaesthetic approaches. In particular, if fusion imaging requiring both transesophageal echo and fluoroscopy becomes the standard, GA might be more convenient and safe. Due to the paucity of randomised study data on the subject, we mainly based our review on the findings of observational studies, which creates an inherent limitation to the validity of the results. Therefore, this review provides an update of current literature, but should be considered primarily as a hypothesis-generating article for subsequent RCTs.

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