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Deep sedation versus general anaesthesia for transcatheter mitral valve repair: an individual patient data meta-analysis of observational studies

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KEYWORDS

- mitral regurgitation
- mitral valve disease
- mitral valve repair

Abstract

Aims: The aim of this meta-analysis was to compare general anaesthesia (GA) and deep sedation (DS) with regard to safety and length of intensive care unit (ICU) stay in patients undergoing percutaneous edge-to-edge mitral valve repair (PMVR).

Methods and results: Four studies comparing GA and DS in patients undergoing PMVR were included in an individual patient data meta-analysis. Data were pooled after multiple imputation. The composite safety endpoint of all-cause death, stroke, pneumonia, or major to life-threatening bleeding occurred in 87 of 626 (13.9%) patients with no difference between patients treated with DS as compared to GA (56 and 31 events in 420 and 206 patients, respectively). In this regard, the odds ratio (OR) was 1.27 (95% confidence interval [CI]: 0.78 to 2.09; p=0.338) and 1.26 (95% CI: 0.49 to 3.22; p=0.496) following the one-stage and two-stage approach, respectively. Length of ICU stay was longer after GA as compared to DS (ratio of days 3.08, 95% CI: 2.18 to 4.36, p<0.001, and 2.88, 95% CI: 1.45 to 5.73, p=0.016, following the one-stage and two-stage approach, respectively).

Conclusions: Both DS and GA might offer a similar safety profile. However, ICU stay seems to be shorter after DS.

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Abbreviations

ICU intensive care unit
IQR interquartile range
NYHA New York Heart Association
PMVR percutaneous edge-to-edge mitral valve repair

Introduction

Several trials have shown the role and potential efficacy of percutaneous edge-to-edge repair for both degenerative and functional mitral regurgitation (MR) as compared to optimal medical treatment in patients with increased surgical risk[1-3]. In the beginning, the vast majority of procedures were performed under general anaesthesia (GA)[4]. However, GA itself carries a considerable risk in patients deemed to be inoperable (e.g., haemodynamic instability, prolonged need for invasive ventilation)[5]. Further, GA may be associated with a longer stay in the intensive care unit (ICU), which again influences clinical outcome as well as human resources and financial expense[6-8]. Deep sedation (DS) arose as a potential alternative strategy to facilitate percutaneous edge-to-edge mitral valve repair (PMVR)[9]. In most circumstances, local experience drives the decision on the anaesthetic strategy chosen. Data supporting either strategy are sparse. Therefore, the primary objective of this meta-analysis is to summarise and pool data of all available studies investigating the feasibility and safety of the MitraClip® (Abbott Vascular, Santa Clara, CA, USA) procedure under DS in comparison to GA.

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Methods

The methods are described in detail in **Supplementary Appendix 1**.

STATISTICAL ANALYSIS

We calculated summary statistics for patient characteristics, preprocedural diagnostics, procedural characteristics, and outcomes stratified by anaesthesia group as mean and standard deviation (SD), or if skewed (as judged by inspection of histograms) as median and interquartile range (IQR). We used frequencies and percentages to summarise categorical variables. All descriptive statistics were derived from observed data. Numbers and distribution of missing values are depicted per study and in total.

Missing data were handled with multiple imputation using chained equations[10].

We conducted one-stage and two-stage meta-analyses to estimate pooled effects of PMVR performed under DS in comparison to GA **(Supplementary Figure 1, Supplementary Figure 2)**. In both approaches, we adjusted regression models for the following confounders: age, sex, body mass index, New York Heart Association (NYHA) functional Class ≥III, presence of chronic pulmonary disease, estimated glomerular filtration rate, left ventricular ejection fraction (LVEF), systolic pulmonary artery pressure, and procedure duration.

Primary efficacy and safety outcomes were analysed by means of logistic regression models (logit link). The number of days for length of hospital stay as well as length of ICU stay were analysed by means of Poisson regression models (log link). The resulting regression coefficients are on the log scale. Exponentiation of these regression coefficients provides estimates of the treatment effect on a multiplicative scale (i.e., a ratio or factor). For this reason, we refer to these treatment effects as a ratio throughout the text, in Tables, and in Figures.

All p-values were two-sided and judged as significant if less than 0.05. All analyses were conducted using R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria) and used predominantly the following packages: mice for multiple imputation of missing data, lme4 for one-step meta-analysis, meta for two-step meta-analyses, and mitml for pooling estimates according to Rubin's rules.

Results

We identified 24 reports of interest for this meta-analysis. After screening titles and abstracts, four reports of monocentric observational studies remained[11-14]. All of these studies were judged eligible after evaluation of the full text in detail and all principal investigators agreed to provide individual patient data. The study of Rassaf et al randomised patients in a non-blinded fashion to either DS or GA. Patients were also included in the overall observational study of Horn and co-workers leading to exclusion of this trial[13,15]. Therefore, four studies enrolling 626 patients in total were included in the meta-analysis. Baseline characteristics and procedural characteristics are summarised in **Table 1** and **Table 2**, respectively. Data regarding in-hospital complications were complete for all patients. In the studies included, sedation was achieved with midazolam and propofol in the DS group. Sedation was guided and titrated by the cardiologist performing transoesophageal echocardiography. An anaesthesia team performed GA with endotracheal intubation in the GA group **(Supplementary Table 1)**. The risk of bias assessment is described in **Supplementary Appendix 2** and **Supplementary Table 2**.

Table 1. Baseline characteristics of patients from observed data.

	Deep sedation n=420	General anaesthesia n=206	Missing data
Patient characteristics			
Age, years	76.9 (8.9)	75.6 (9.8)	0 (0%)
Male sex	248 (59.08%)	126 (61.2%)	0 (0%)
BMI, kg/m²	25.8 (5.0)	26.1 (5.3)	81 (12.9%)
COPD	67 (16.0%)	37 (18.0%)	3 (0.5%)
Diagnostic characteristics			
eGFR, ml/min/1.73 m²	49.7 (22.0)	51.8 (25.2)	18 (2.9%)
LVEF, %	43.2 (15.5)	41.0 (15.0)	75 (12.0%)
Mitral regurgitation ≥III	406 (96.7%)	201 (97.6%)	0 (0%)
Mitral regurgitation functional	297 (70.7%)	148 (72.2%)	1 (0.2%)
PAPs, mmHg	51.2 (19.2)	47.4 (16.5)	109 (17.4%)
NYHA Class ≥III before procedure	349 (83.1%)	179 (86.9%)	0 (0%)

Categorical data are shown as count (percentage) and continuous data as mean (standard deviation). BMI: body mass index; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; n: number of patients in treatment group; NYHA: New York Heart Association; PAPs: systolic pulmonary artery pressure

Table 2. Procedural and treatment characteristics as well as in-hospital complications from observed data.

	Deep sedation n=420	General anaesthesia n=206	Missing data
Procedural characteristics			
Procedural duration, minutes	115 [88.0; 151]	116 [89.5; 150]	2 (0.3%)
Procedural success	401 (95.5%)	197 (95.6%)	0 (0%)
Length of stay			
in hospital, days	9.00 [6.00; 14.0]	9.00 [7.00; 15.0]	1 (0.2%)
on intensive care unit, days	0.00 [0.00; 1.00]	2.00 [1.00; 2.00]	13 (2.1%)
Number of cases without intensive care admission	213 (52.1%)	4 (2.0%)	13 (2.1%)
In-hospital complications			
Primary safety endpoint	56 (13.3%)	31 (15.0%)	0 (0%)
Death	14 (3.3%)	6 (2.9%)	0 (0%)
Stroke	3 (0.7%)	1 (0.5%)	0 (0%)
Pneumonia	15 (3.6%)	8 (3.9%)	0 (0%)
Bleeding, major	27 (6.4%)	19 (9.2%)	0 (0%)
Bleeding, life-threatening	4 (1.0%)	0 (0.00%)	0 (0%)

Categorical data are shown as count (frequency) and continuous data as median (interquartile range). n: number of patients in treatment group. The primary safety endpoint is a composite of death, stroke, pneumonia, and severe bleeding according to VARC-2 criteria at short-term follow-up.

Table 3. Pooled estimates of treatment effects on primary endpoints in one- and two-stage meta-analyses adjusted for covariates.

Endpoint	Meta-analysis	Estimate [95% CI]	*p*-value	τ^2	FMI
Safety	One-stage	1.27 [0.78; 2.09]	0.338	0.000[a]	0.007
	Two-stage	1.26 [0.49; 3.22]	0.496	0.000	–
LOS	One-stage	1.11 [0.96; 1.27]	0.160	0.016	0.016
	Two-stage	1.11 [0.74; 1.67]	0.476	0.060	–
ICU-LOS	One-stage	3.08 [2.18; 4.36]	<0.001	0.094	0.040
	Two-stage	2.88 [1.45; 5.73]	0.016	0.145	–

Estimates are given as odds ratios (OR) for safety and as exponentiated coefficients for length of stay (LOS) and length of intensive care unit stay (ICU-LOS); these exponentiated coefficients should be interpreted as x-fold increase LOS or ICU-LOS. [a] For the safety endpoint, the slope variance could not be estimated and was therefore fixed at 0. CI: confidence interval; FMI: fraction of missing information; τ^2: estimated heterogeneity of treatment effects

MISSING DATA AND MULTIPLE IMPUTATION

In the merged data set containing observed data from all studies as provided by the study investigators, a total of 303 data points (3.0%) were missing. The proportion of missing data per variable ranged from 0 to 17.4% **(Table 2, Table 3, Supplementary Table 3)**. In 232 of 626 (37.1%) patients, at least one value was missing. Performing a traditional complete case analysis would have substantially reduced the sample size (by 37.1%). Instead, we used multiple imputation, which provided the basis for the statistical analyses. The validity of the imputation procedure was assessed by investigating convergence plots and by comparing the distribution of the imputed data to the observed data **(Supplementary Figure 3)**. However, the additional uncertainty introduced by missing data was only modest, as indicated by the relatively low proportion of missing data per variable and the small fraction of missing information (FMI) estimated for the results of the meta-analyses.

META-ANALYSIS

Procedural success rates were very high, irrespective of the assigned treatment group (i.e., in 401 of 420 patients [95.5%] for DS and in 197 of 206 patients [95.6%] for GA). The low number of procedures without procedural success precluded reliable regression models. Therefore, we did not perform formal meta-analyses for the primary efficacy endpoint.

The distribution of outcome variables in the observed data set is depicted in **Table 2** and **Figure 1** (both show plain summary statistics without weighting). The one- and two-stage meta-analyses based on the imputed data revealed that the length of hospital stay did not differ significantly between patients undergoing PMVR with GA or DS **(Table 3, Figure 2A)**. In contrast, the length of ICU stay was longer in patients undergoing general anaesthesia as compared to deep sedation **(Table 3, Figure 2B)**. For example, according to the one-stage meta-analysis, the length of ICU stay was 3.08 times longer in patients treated with GA versus DS.

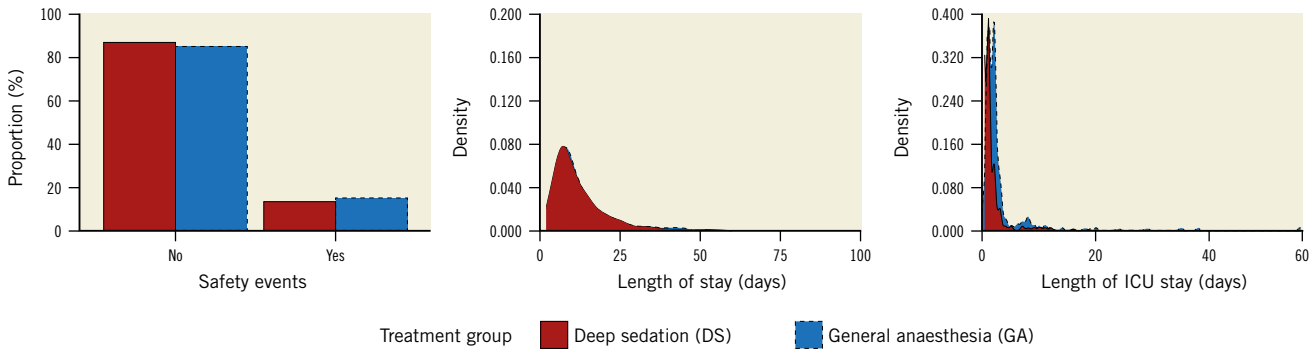

Figure 1. *Distribution of outcome variables in observed data. The number of safety events relative to the number of patients by treatment group (left) as well as the density distribution of length of total hospital stay (middle) and length of ICU stay (right) are shown.*

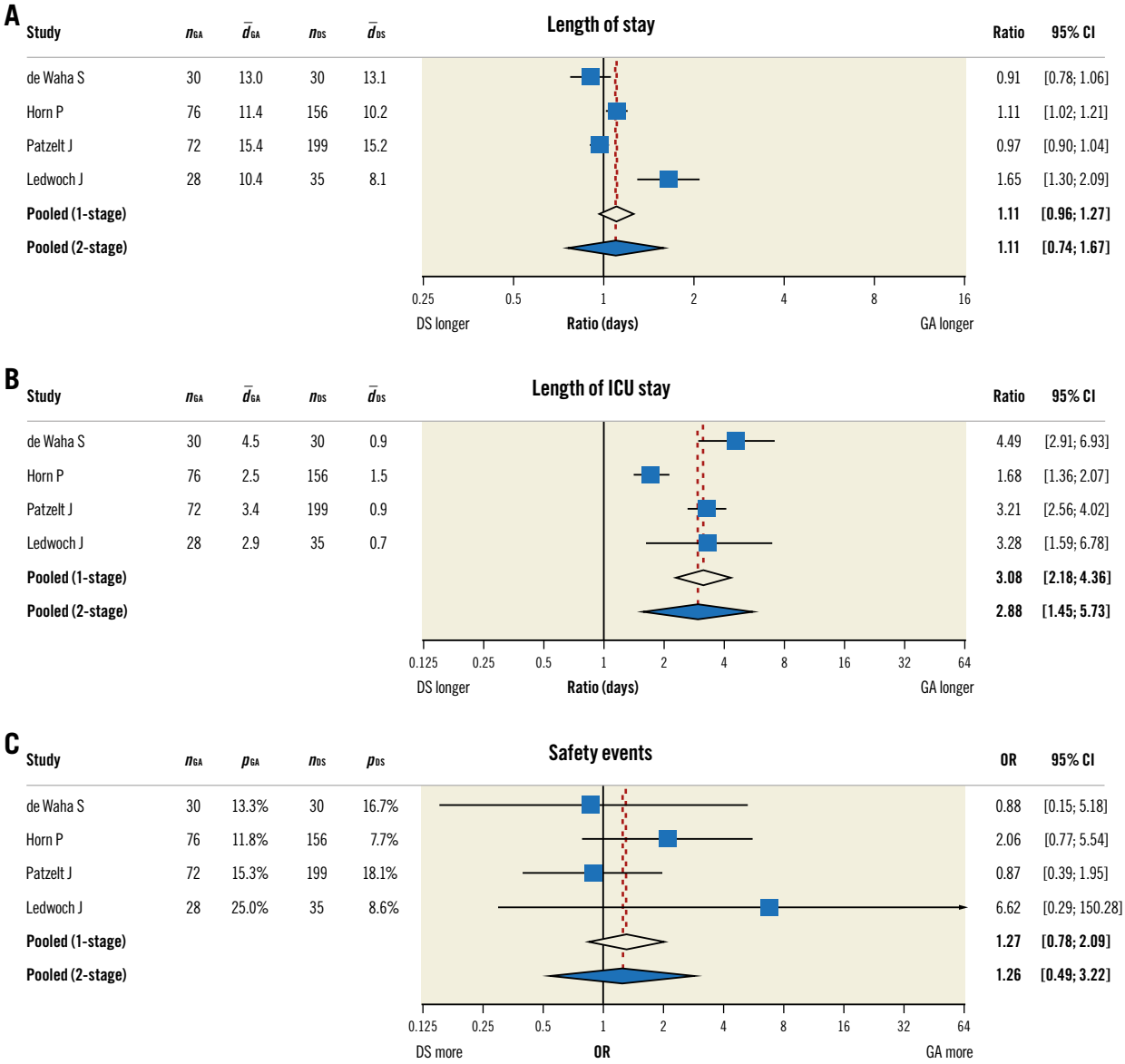

Figure 2. *Forest plot showing treatment effect estimates and 95% confidence intervals for individual studies and the pooled treatment effects in the one- and two-stage meta-analyses for (A) length of hospital stay, (B) length of intensive care unit stay, and (C) the primary safety endpoint alongside the number of patients per group (n_{GA}, n_{DS}), the mean length of stay per group in days ($\bar{d}_{GA}$, $\bar{d}_{DS}$; only A & B), and the proportion of patients with safety event per group (p_{GA}, p_{DS}; only C). The point estimates and 95% confidence intervals for individual studies were based on the two-stage meta-analyses. The size of the blue-coloured squares corresponds to the relative weight of the respective study in the two-stage meta-analyses. "Ratio" denotes the exponentiated coefficients of the treatment effect, which can be interpreted as the factor (i.e., x-fold) by which the length of stay is prolonged due to treatment strategy. DS: deep sedation; GA: general anaesthesia; OR: odds ratio*

The frequency of safety events in the observed data set is depicted in **Table 2** and **Figure 1**. In addition, **Table 2** depicts the frequency of single outcome events which – when summed up – compose the primary safety outcome. Neither treatment strategy was associated with a significant increase in the risk for safety events, as indicated by the estimates of the treatment effects and their 95% confidence intervals (CIs) in the one- and two-stage meta-analyses **(Table 3, Figure 2C)**. However, for all endpoints, the CIs were relatively wide, especially in the two-stage meta-analyses, indicating substantial uncertainty about the point estimates. The FMI was low in all one-stage meta-analyses, indicating that the missing data introduced only little uncertainty in these estimates.

In order to check a possible impact of confounder adjustment on the results, we repeated all meta-analyses without adjusting for covariates. However, these analyses led to very similar results **(Supplementary Table 4)** and will thus not be considered in detail.

The estimated between-study variance indicated substantial heterogeneity in the true effect sizes across studies for both length of stay (two-stage $\tau^2 = 0.060$, $I^2 = 86.8\%$, 95% CI [68.3%; 94.5%]) and length of ICU stay (two-stage $\tau^2 = 0.145$, $I^2 = 88.4\%$,

95% CI [72.9%; 95.1%]) but not for the safety endpoint (two-stage $\tau^2 = 0.000$, $I^2 = 0\%$, 95% CI [0%; 84.6%]) **(Table 2)**.

Several subgroup analyses were pre-specified to study possible sources of heterogeneity. These are reported in **Supplementary Appendix 3** and **Supplementary Figure 4-Supplementary Figure 6**.

Discussion

This meta-analysis pooled individual patient data of 626 patients who were enrolled in four prospective observational studies. As a result, this meta-analysis comprises a sample of similar size to well-known registries such as the Transcatheter Valve Treatment Sentinel Pilot (n=628)[16] and the Transcatheter Mitral Valve Interventions registry (n=643 to 828 depending on the report)[17-19]. Our study focused on the impact of the chosen anaesthetic method on procedural success, procedural safety, length of hospital stay, and length of ICU stay. The main finding was that DS appears to be a safe and effective alternative to GA in patients undergoing PMVR. Moreover, DS was associated with shorter length of ICU stay but with a similar overall length of hospital stay as compared with GA.

Procedural success, defined as successful placement of at least one clip and reduction of mitral regurgitation to ≤II°, was very high (i.e., >95%) irrespective of the anaesthetic method used. This success rate is in line with reports of other registries[16,18,20].

Our composite primary safety endpoint comprised in-hospital complications (i.e., death, stroke, pneumonia, and major or life-threatening bleeding) and occurred in 87 of the 626 (13.9%) patients. Most of these safety events were bleedings (50 of 87 safety events [57.5%] and 50 of 626 patients [8.0%]). The bleeding rate in our population was comparable to the bleeding rate of 7.4% reported for the TRAMI registry which used a similar bleeding definition[17]. Fortunately, more devastating events such as deaths or strokes were rare and occurred at similar rates to other registries (e.g., TRAMI 2.2% and 0.9%, respectively[17]).

The issue of procedural safety as a function of the anaesthetic method is of clinical relevance but has not been addressed by other registries so far. As a matter of fact, the majority or nearly all patients in other registries have been treated with GA[16,18,20]. A national consensus paper from Germany also recommended performing PMVR under GA[4]. Theoretically, GA offers advantages over DS such as a patient lying still, pausing ventilation for critical steps during the procedure, and the possibility for quick conversion to bail-out surgery, which might facilitate a safer procedure. Patients treated with DS with an unprotected airway are supposed to be at risk for aspiration with subsequent pneumonia. However, GA itself carries a risk of adverse events. Among patients with heart failure, the risk of adverse perioperative events might be higher in patients with severely reduced ejection fraction[21]. In our meta-analysis, neither anaesthetic method was associated with a higher risk of in-hospital complications in the total sample. Naturally, this finding does not preclude the possibility that such a difference might still exist, especially given the limited number of studies and the resulting uncertainty in the estimated treatment effects. However, this finding was consistent across meta-analytic approaches and with the findings of the individual studies included in our meta-analysis, thus providing more robust evidence due to the larger sample size (n=626 in our meta-analysis versus n=60 to 271 in individual studies). Moreover, the individual patient data approach allowed us to adjust analyses for patient level confounders known to be associated with procedural success and adverse events.

While length of ICU stay was shorter with DS as compared to GA, this was not the case for the overall length of stay. This might be counterintuitive at first glance. However, the length of stay was quite long with a median of nine days. This suggests that most procedures were performed after stabilisation following admission for acute decompensated heart failure and not electively. However, a shorter length of hospital stay is probably beneficial from an economic point of view. Since organisation and workflow differ considerably between hospitals, the need for an anaesthesia care team for GA might be a challenge or an organisational bottleneck in one hospital but not in another. Moreover, organisation and workflow within a hospital may evolve in parallel to increasing experience with PMVR, leading to some kind of "fast track" GA with extubation immediately on the operating table without the need for ICU admission. In contrast, the shorter ICU stay with DS as compared to GA in the studied population was driven primarily by the fact that patients were not admitted to the ICU at all (i.e., zero days on ICU) in a considerable proportion of patients treated with DS. Therefore, the difference in length of ICU stay may not be present in contemporary populations.

We used a multiple imputation strategy that accounted for the hierarchical structure of the data as well as between-study heterogeneity. The key advantage of multiple imputation in general is that it allows using all of the available data and making inferences under the assumption that the data are missing at random (MAR) given the observed data on outcomes and covariates[22]. This is in contrast to complete-case analyses, which can lead to a severe loss of information and operate under much stricter assumptions as compared with multiple imputation[23]. Moreover, a complete case analysis uses only a subset of the available observations, thus reducing the power to detect statistically significant differences. In the case of our meta-analysis, a complete case analysis of the adjusted mixed regression model for in-hospital complications would have discarded 37.1% of the patients.

The individual patient data approach also allowed us to perform subgroup analyses on the patient level. The most conspicuous finding here suggests that patients with reduced ejection fraction might suffer more in-hospital complications when undergoing GA as compared to DS, whereas patients with preserved ejection fraction might not. However, subgroup analyses were not adjusted for multiple testing and therefore should be interpreted with caution until further evidence from additional studies becomes available.

The association of procedural safety and the chosen anaesthetic method was not modified by either preprocedural systolic pulmonary pressure or age. Tigges et al studied the implication of pulmonary hypertension in patients undergoing PMVR based on the TRAMI population[19]. They found that increased values of

preprocedural systolic pulmonary pressure are associated with an increased risk of post-discharge mortality at one year but not with periprocedural complications. Together, this suggests that PMVR is safe in patients with elevated systolic pulmonary pressure irrespective of the anaesthetic methods.

DS was achieved by continuous application of propofol and repeated bolus applications of midazolam in all studies. No strict targets for the depth of sedation were defined prospectively. The physician performing transoesophageal echocardiography monitored the depth of sedations clinically to ensure that the patient tolerated all aspects of the procedure while maintaining spontaneous breathing. In all studies, GA was performed by an anaesthetist. Propofol was used as hypnotic drug in combination with an opiate for this purpose. Both approaches are standard of care in most institutions.

Limitations

The following limitations should be acknowledged. First, the studies included in our meta-analysis were prospective but observational. Large-scale randomised controlled trials investigating the optimal anaesthetic procedure are currently lacking. To work on methodical shortcoming by pooling data from observational studies, we adjusted our analyses for known risk factors for procedure-related complications and/or an unfavourable short-term outcome. Probably due to the fact that GA and DS were historical comparisons in most included studies, the observed patient characteristics were quite well balanced between groups. However, we were unable to control for unobserved confounders, for which randomisation would be the reference standard. Therefore, all findings of our meta-analysis should be interpreted with caution because such studies cannot replace evidence from large-scale randomised trials. The choice between GA and DS was not a historical comparison but rather based on the Heart Team consensus in the study of Patzelt et al[14]. Therefore, patient selection might have influenced the result on length of ICU stay in this study. However, the direction of the effect is not different in the other studies **(Figure 2B)**. The patients' health status seems, therefore, unlikely to explain the observed difference in length of ICU stay between GA and DS. Second, we were unable to adjust subgroup analyses for confounders as we did for the main analyses due to statistical problems with model convergence and total separation. This is a frequent issue with fitting some regression and mixed-effects models[24]. The total sample size of our meta-analysis is an improvement compared to the individual studies but is still rather small from a statistical point of view. This is most likely the cause of the problems encountered during fitting mixed-effects regression models. Having more studies would probably avoid these issues and allow an even more thorough investigation into the effects of DS versus GA. Assessment of the primary efficacy endpoint and safety endpoint (i.e., clinical events of in-hospital complications) followed standard operating procedures of the local institutions and were not assessed by means of a core echocardiography laboratory or independent clinical events committee, respectively. Therefore, we cannot fully exclude detection or attribution bias that may be inherent in the included studies. Third, the Mitral Valve Academic Research Consortium introduced the updated MVARC bleeding scale in 2015, which is a modified version of the VARC-2 bleeding scale[25]. Bleeding events were prospectively adjudicated according to the VARC-2 bleeding scale in all included studies. Unfortunately, data were not recorded in such detail that the bleeding scale could be updated reliably in retrospect. However, comparing both scales **(Supplementary Table 5)** reveals that only minor discrepancies exist. One relevant discrepancy is that fatal bleeding is separated from life-threatening bleeding as a distinct entity in the MVARC bleeding scale.

Conclusions

In conclusion, our meta-analysis suggests that PMVR is feasible using either deep sedation or general anaesthesia, length of ICU stay may be shorter with deep sedation as compared to general anaesthesia, and procedural safety may not be different between these two anaesthetic techniques.

Impact on daily practice

Transcatheter mitral valve repair can be performed under deep sedation or general anaesthesia. The results of this meta-analysis suggest that either method may be safe, and the choice should be based on the expertise of the centre and operators.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-00607

Supplementary data

Supplementary Appendix 1. Methods

Search strategy, selection criteria, and data acquisition

We performed this meta-analysis according to a predefined protocol, which was registered at PROSPERO (CRD42019111307). We identified studies of potential interest by searching MEDLINE through PubMed. The following search strategy was used without restriction to the time of publication or language: "sedation"[Title/Abstract] AND ("anesthesia"[Title/Abstract] OR "anaesthesia"[Title/Abstract]) AND "mitral valve"[Title/Abstract].

The search was initially performed on October 10th 2018 and last updated on June 20th 2020. In addition, we searched scrutinising the reference lists of included studies and related review articles as well as discussing the subject with field experts to identify more articles of potential interest. Eligible studies compared mild to deep sedation with general anaesthesia in patients with severe MR suffering from symptomatic heart failure undergoing PMVR. Since the focus of the current meta-analysis is the matter of safety, both randomised controlled trials and observational studies were eligible. Two reviewers (A. Jobs and S. de Waha-Thiele) screened the titles and abstracts of identified search items for eligibility. The full study report was evaluated in case of uncertainty. Discrepancies were resolved by discussion after involvement of a third reviewer (S. Desch). Study investigators of eligible studies were invited to participate in this collaborative meta-analysis and asked to provide de-identified individual patient data on standardised spreadsheet documents. The data provided were checked for missing information and consistency. Summary tables were checked with original publications. Queries were resolved through consultation with study investigators. To create a common data pool with uniform coding, some study investigators extracted missing information, where possible, from the hospital information system to fill some of the missing information that was present in the original database of the study. Risk of bias was assessed according to the bias domains defined in ROBINS-I (Sterne JA et al. BMJ. 2016;355:i4919).

Outcomes and definitions

The pre-specified efficacy outcome was procedural success defined as post-procedural MR equal to or less than grade 2. The pre-specified safety outcome was a composite of in-hospital

complications including death, stroke, pneumonia, or major to life-threatening bleeding according to VARC-2 criteria (Kappetein AP et al. Eur Heart J. 2012;33:2403-18). Throughout the text, the safety endpoint is also referred to as in-hospital complications. Additional outcomes were length of hospital stay and length of ICU stay, both measured in days.

Statistical analysis

We calculated summary statistics for patient characteristics, preprocedural diagnostics, procedural characteristics, and outcomes stratified by anaesthesia group as mean and standard deviation (SD), or if skewed (as judged by inspection of histograms), as median and interquartile range (IQR). We used frequencies and percentages to summarise categorical variables. All descriptive statistics were derived from observed data. Numbers and distribution of missing values are depicted per study and in total.

Missing data were handled with multiple imputation using chained equations [3]. The imputation procedure accounted for the clustering of participants within studies and the heterogeneity between studies by employing two-stage imputation methods based on mixed-effects models for IPD meta-analyses [10] (and Resche-Rigon M et al. Stat Methods Med Res. 2018;27:1634-49), where continuous variables were imputed using methods for continuous data, and ordered categorical and count data were imputed using predictive mean matching. In addition, the imputation was carried out separately for each treatment group to preserve possible treatment-by-covariate interactions (Tilling K et al. J Clin Epidemiol. 2016;80:107-15; von Hippel PT et al. Sociological Methodology. 2009;39:265-91). In total, 20 imputations were performed. The imputation model included all of the observed outcomes, the received treatment, and the below-mentioned confounders.

We conducted one-stage and two-stage meta-analyses to estimate pooled effects of PMVR performed under deep sedation in comparison to general anaesthesia. In both approaches, we adjusted regression models for the following confounders: age, sex, body mass index, New York Heart Association (NYHA) functional Class ≥III, presence of chronic pulmonary disease, estimated glomerular filtration rate, left ventricular ejection fraction, systolic pulmonary artery pressure, and procedure duration. These confounders were identified as risk

factors for in-hospital complications by means of a literature search (Pighi M et al. Am J Cardiol. 2017;119:630-7; Schueler R et al. EuroIntervention. 2016;12:508-14).

For the one-stage meta-analysis, we used mixed-effects regression models with uncorrelated random intercepts to account for variation in baseline risk between studies, and random slopes to account for variation in treatment effect between studies **(Supplementary Figure 1)**. Parameter estimates calculated on each imputed data set were finally pooled by means of Rubin's rules (Rubin DB. Wiley; 1987).

For two-stage meta-analysis, we used conventional regression models to calculate study-specific treatment estimates and respective standard errors for each imputed data set in the first stage. Thereafter, study-specific treatment estimates of each data set were pooled by means of Rubin's rules (Rubin DB. Wiley; 1987) after which a traditional random effects meta-analysis was performed in the second stage **(Supplementary Figure 2)** [22]. We estimated between-study heterogeneity according to the Paule-Mandel estimator and derived confidence intervals using the method proposed by Hartung and Knapp (Veroniki AA. Res Synth Methods. 2016;7:55-79; Langan D et al. Res Synth Methods. 2017;8:181-98).

Primary efficacy and safety outcomes were analysed by means of logistic regression models (logit link). Regression models with a log-link function to calculate risk ratios were pre-specified but could not be used due to convergence issues. Although pre-specified, we did not perform meta-analyses for the primary efficacy endpoint due to the low number of procedures without success. Heterogeneity of the treatment effect across studies was essentially zero for the primary safety endpoint; therefore, we could not use random slopes for this analysis (otherwise modelling results in singular fit). The number of days for length of hospital stay as well as length of ICU stay were analysed by means of Poisson regression models (log link). The resulting regression coefficients are on the log scale. Exponentiation of these regression coefficients provide estimates of the treatment effect on a multiplicative scale (i.e., a ratio or factor). For this reason, we refer to these treatment effects as a ratio throughout the text, in Tables, and in Figures.

For the one-stage meta-analysis, we quantified the heterogeneity of the treatment effect using the slope variance (τ^2). For the two-stage meta-analysis, we calculated the variance of the treatment effect (τ^2) and the Higgins and Thompson statistic (I^2).

We performed subgroup analyses by estimating treatment-covariate interactions in one-stage meta-analyses on the primary safety endpoint, length of hospital stay, and length of ICU stay. However, because of the reduced sample size in the subgroups, we encountered problems with non-convergence and total separation that were not present in the main analyses. For this reason, the mixed-effects regression models used in the subgroup analyses adjusted only for age and sex. The following subgroups were pre-specified: age, sex, NYHA functional Class ≥III, left ventricular ejection fraction <40%, and systolic pulmonary artery pressure.

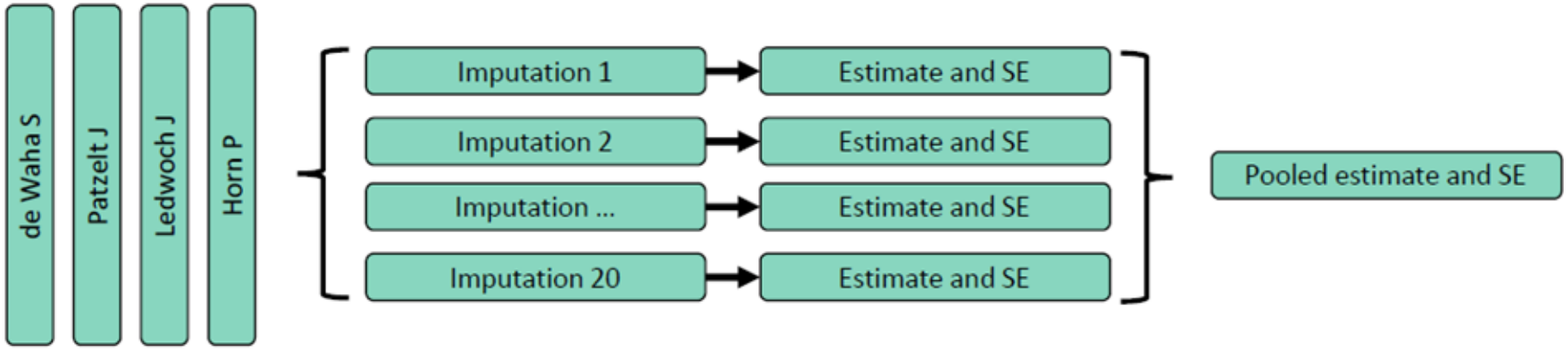
All p-values were two-sided and judged as significant if less than 0.05. All analyses were conducted using R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria) and used predominantly the following packages: mice for multiple imputation of missing data, lme4 for one-step meta-analysis, meta for two-step meta-analyses, and mitml for pooling estimates according to Rubin's rules.

Supplementary Appendix 2. Risk of bias

Overall, risk of bias is judged to be low to moderate for ROBINS-I domains **(Supplementary Table 2)**. The main source of bias is the fact that outcome assessors were aware of the intervention received by study participants. For example, in clinically ambiguous cases the study physician might have adjudicated the pneumonia diagnosis based on the information that a patient underwent general anaesthesia and not deep sedation. Moreover, even though some patients might do very well (i.e., fast respiratory and haemodynamic recovery) after general anaesthesia, admission to the ICU as well as prolonged length of stay on the ICU will certainly be more likely after general anaesthesia than after deep sedation.

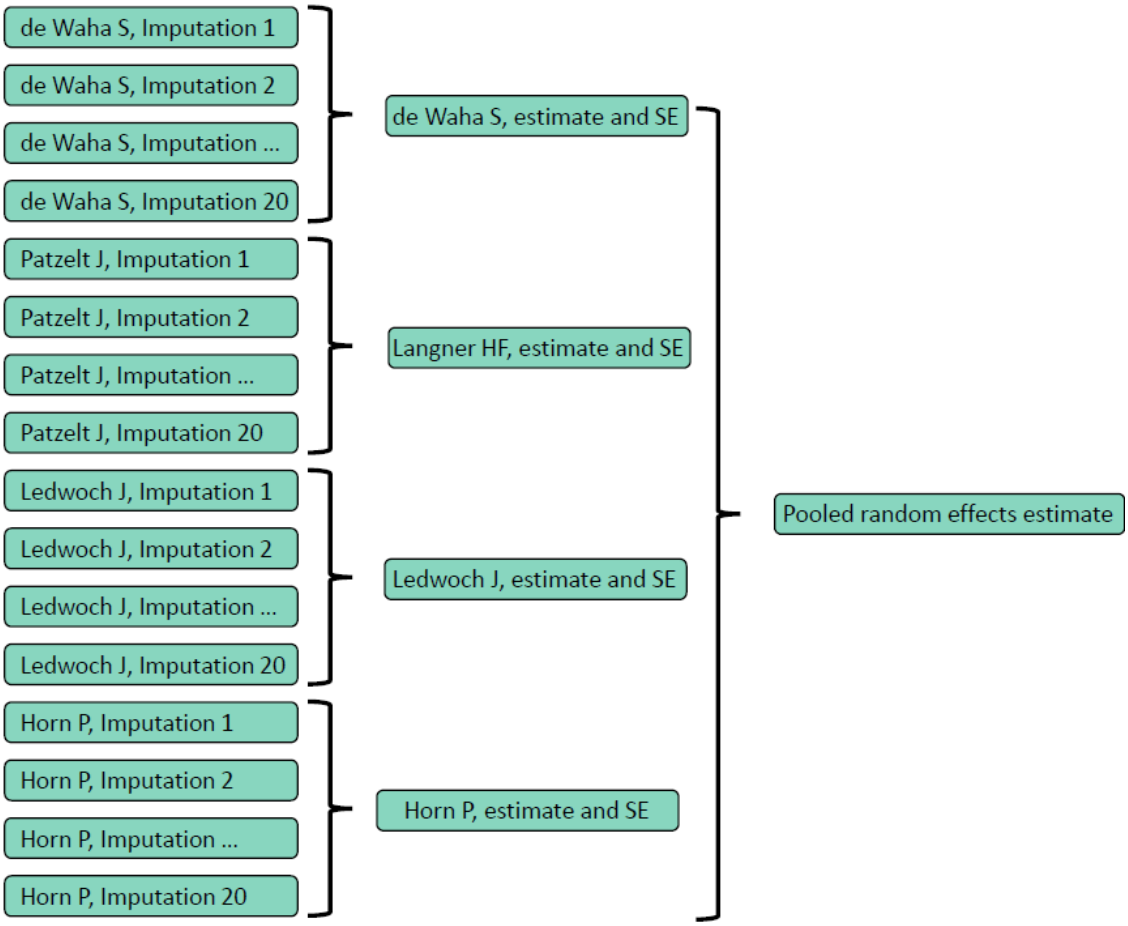
Supplementary Appendix 3. Results for subgroup analyses

Subgroup analyses were modelled by adding a term for treatment-by-subgroup interaction to the mixed-effects regression models used for one-stage meta-analyses. However, due to problems with model convergence and total separation, regression models for subgroup analyses could only be adjusted for age and sex. Age and systolic pulmonary artery pressure were modelled as continuous covariates, and subgroups were defined as values of one half of an SD above and below the mean, respectively. The overall treatment effects and the treatment effects in each subgroup are shown in **Supplementary Figure 4**-**Supplementary Figure 6**. Female sex and a higher systolic pulmonary artery pressure were associated with a prolonged length of hospital stay **(Supplementary Figure 4)**. Heart failure with reduced ejection fraction was associated with longer ICU stay as well as more safety events **(Supplementary Figure 5, Supplementary Figure 6)**.



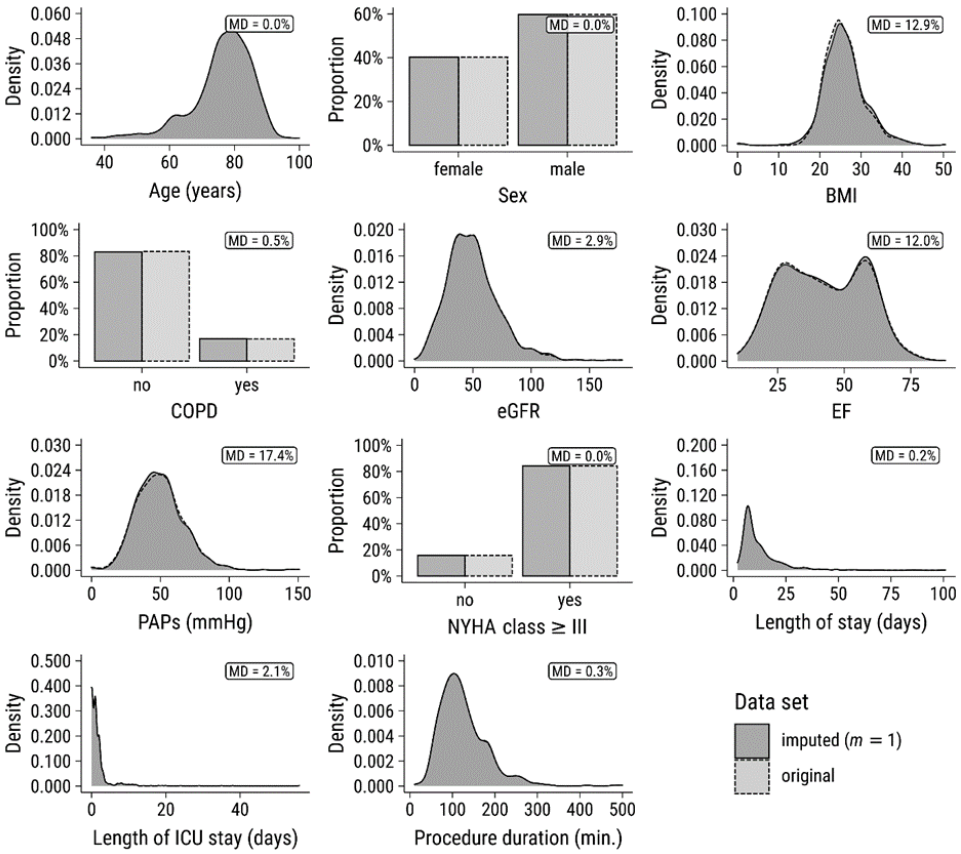
Supplementary Figure 1. Pooling of data in one-stage meta-analyses.

Missing data of each data set were imputed 20 times by means of an imputation model considering the observed data of all studies. Thereafter, a multilevel (= mixed) regression model was fitted for each imputed data set resulting in 20 treatment estimates with respective standard error. These were combined into one pooled treatment estimate with its respective standard error by Rubin's rules.



Supplementary Figure 2. Pooling of data in two-stage meta-analyses.

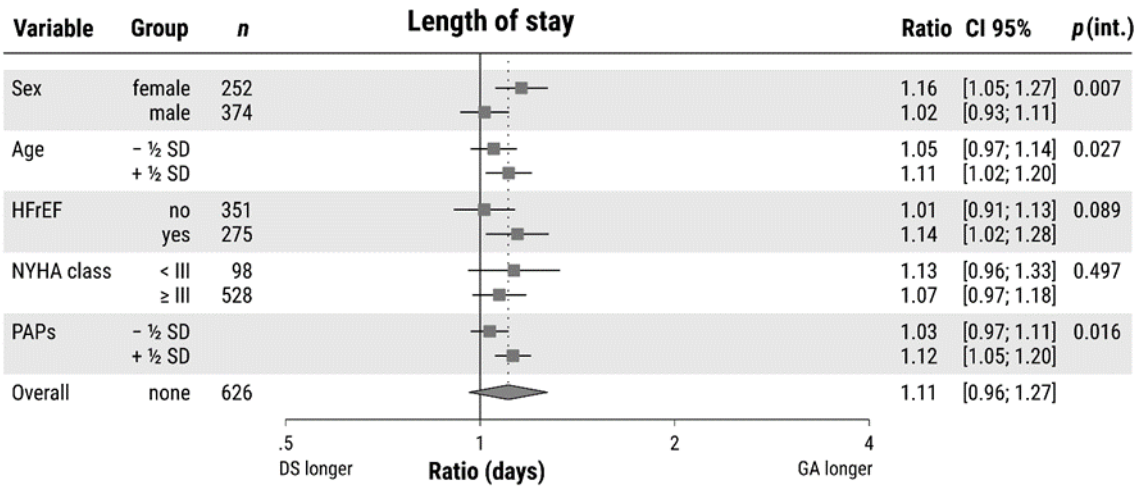
Missing data of each data set were imputed 20 times by means of an imputation model considering the observed data of all studies. Thereafter, for each study one regression model was fitted for each imputed data set (n=20). Treatment estimates and respective standard errors were calculated from these fitted regression models and combined into one pooled treatment estimate with respective standard error by Rubin's rules. The combined treatment estimates and standard errors of each study were finally pooled by random-effects meta-analyses.



Supplementary Figure 3. Comparison of original and imputed data.

Density plots showing the distribution of original (dark grey) and imputed (light grey) data. As a representation for the imputed data, only the first imputed data set (m=1) is shown. Depicted are all covariates to adjust regression models and the outcomes with missing data (length of total hospital stay, “length of stay”; length of stay on the intensive care unit, “length of stay (ICU)”).

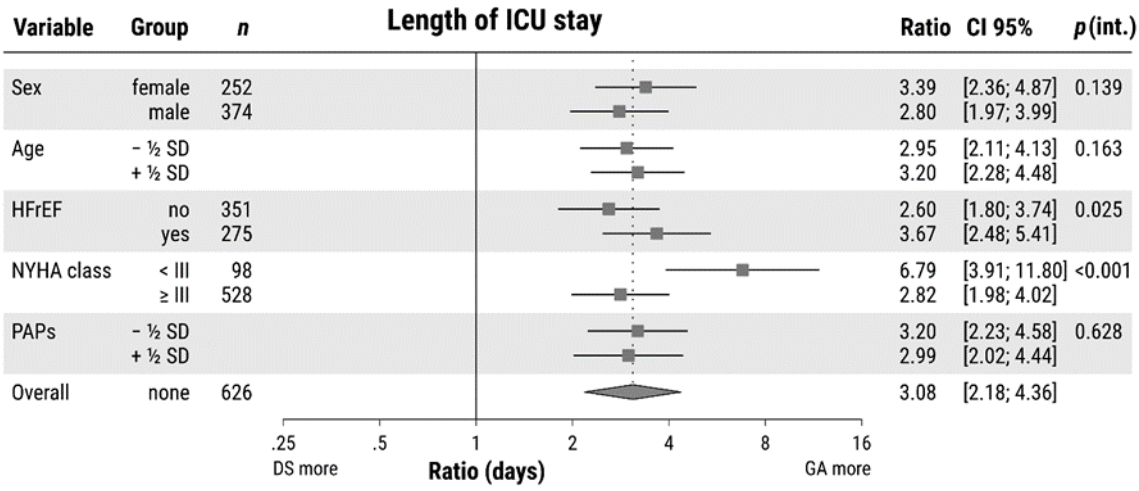
BMI: body mass index in kg/m²; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate in ml/min/1.73 m²; EF: left ventricular ejection fraction in %; ICU: intensive care unit; MD: percentage of missing data; NYHA: New York Heart Association; PAPs: systolic pulmonary artery pressure in mmHg



Supplementary Figure 4. Forest plot showing treatment-by-covariate interaction on length of stay.

Forest plot showing treatment-by-covariate interactions in one-stage meta-analyses on length of hospital stay.

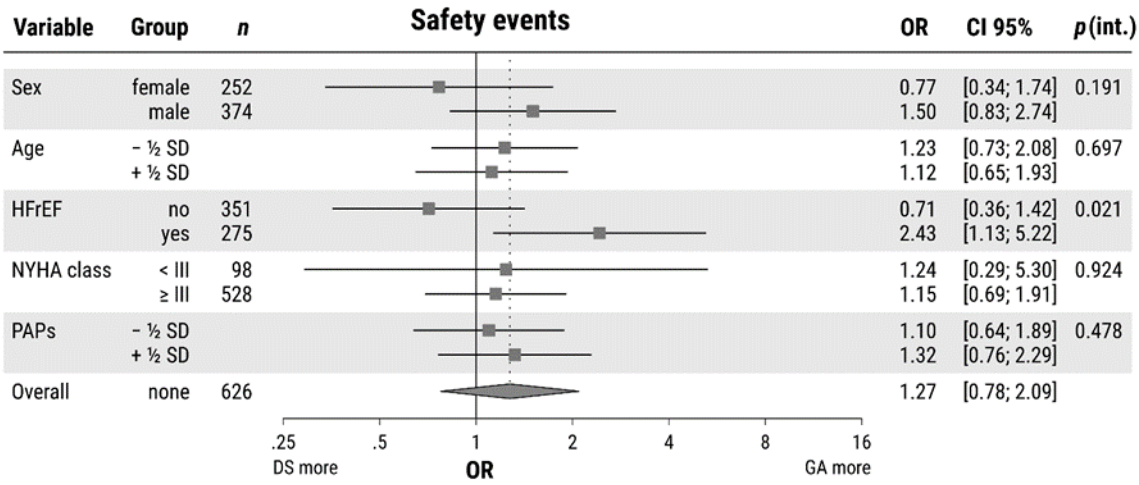
CI: confidence interval; DS: deep sedation; GA: general anaesthesia; HFrEF: heart failure with reduced ejection fraction; *n*: number of patients in stratum; NYHA: New York Heart Association; SD: standard deviation



Supplementary Figure 5. Forest plot showing treatment-by-covariate interaction on length of intensive care unit stay.

Forest plot showing treatment-by-covariate interactions in one-stage meta-analyses on length of stay on intensive care unit.

CI: confidence interval; DS: deep sedation; GA: general anaesthesia; HFrEF: heart failure with reduced ejection fraction; *n*: number of patients in stratum; NYHA: New York Heart Association; SD: standard deviation



Supplementary Figure 6. Forest plot showing treatment-by-covariate interaction on safety events.

Forest plot showing treatment-by-covariate interactions in one-stage meta-analyses on the primary safety endpoint.

CI: confidence interval; DS: deep sedation; GA: general anaesthesia; HFrEF: heart failure with reduced ejection fraction; *n*: number of patients in stratum; NYHA: New York Heart Association; OR: odds ratio; SD: standard deviation

Supplementary Table 1. Study characteristics.

	de Waha et al	Horn et al	Patzelt et al	Ledwoch et al
Number of centres	2	1	1	1
Number of operators	2	3	Not known	1
Number of patients **total** **general anaesthesia** **deep sedation**	 60 30 30	 232 76 156	 271 72 199	 63 28 35
Recruitment period	GA: 06/2012-11/2013 DS: 01/2014-07/2014	01/2011 to 11/2015	04/2014 to 12/2016	GA: 10/2009 to 01/2011 DS: 01/2011 to 12/2014
General anaesthesia (GA)	Endotracheal intubation Propofol (continuously) plus remifentanil (continuously) Extubation was aimed to be performed immediately after the procedure.	Endotracheal intubation Propofol (continuously) plus sufentanil (continuously) or remifentanil (continuously) Extubation as soon as possible after the procedure.	Endotracheal intubation Propofol (continuously) plus piritramide Extubation as soon as possible after the procedure.	Endotracheal intubation Propofol (continuously) plus sufentanil (continuously) or remifentanil (continuously) Extubation as soon as possible after the procedure.
Deep sedation (DS)	Propofol (continuously) plus midazolam (bolus)	Propofol (continuously) plus midazolam (bolus)	Propofol (continuously) plus midazolam (bolus) plus piritramide (bolus)	Propofol (bolus) plus midazolam (bolus)
Conversion from DS to GA	2	3	2	3
Allocation to GA or DS	Different anaesthetic protocol between centres (GA in Leipzig and DS in Lübeck)	"[…] determined by the operational structuring of our MitraClip program such that patients were scheduled for the next available implantation date with fixed time slots for GA and DS. Selection of the type of anaesthesia was not based on patients' characteristics".	Based on the decision of the Heart Team	Change in anaesthetic protocol within department

Supplementary Table 2. Risk of bias assessment.

	de Waha et al	Horn et al	Patzelt et al	Ledwoch et al
Bias due to confounding				
1.1 Is there potential for confounding of the effect of intervention in this study?	**PY**	**PY**	**PY**	**PY**
1.2. Was the analysis based on splitting participants' follow-up time according to intervention received?	**N**	**N**	**N**	**N**
1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Not applicable because individual patient data were used in the meta-analysis			
1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	**N**	**N**	**N**	**N**
Bias in selection of participants into the study				
2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	**N**	**N**	**N**	**N**
2.4. Do start of follow-up and start of intervention coincide for most participants?	**Y**	**Y**	**Y**	**Y**
Risk of bias judgement	Moderate	Moderate	Moderate	Moderate
Bias in classification of interventions				
3.1 Were intervention groups clearly defined?	**PY**	**PY**	**PY**	**PY**
3.2 Was the information used to define intervention groups recorded at the start of the intervention?	**Y**	**Y**	**Y**	**Y**
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	**N**	**N**	**N**	**N**
Risk of bias judgement	Moderate	Moderate	Moderate	Moderate
Bias due to deviations from intended interventions				
4.1. Were there deviations from the intended	**N**	**N**	**N**	**N**

intervention beyond what would be expected in usual practice?				
Risk of bias judgement	Low	Low	Low	Low
Bias due to missing data				
5.1 Were outcome data available for all, or nearly all, participants?	**Y**	**PY**	**Y**	**Y**
5.2 Were participants excluded due to missing data on intervention status?	**N**	**N**	**N**	**N**
5.3 Were participants excluded due to missing data on other variables needed for the analysis?	**N**	**N**	**N**	**N**
Risk of bias judgement	Low	Moderate	Low	Low
Bias in measurement of outcomes				
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	**PN**	**PN**	**PN**	**PN**
6.2 Were outcome assessors aware of the intervention received by study participants?	**Y**	**Y**	**Y**	**Y**
6.3 Were the methods of outcome assessment comparable across intervention groups?	**Y**	**Y**	**Y**	**Y**
6.4 Were any systematic errors in measurement of the outcome related to intervention received?	**N**	**N**	**N**	**N**
Risk of bias judgement	Moderate	Moderate	Moderate	Moderate
Bias in selection of the reported result				
Is the reported effect estimate likely to be selected, on the basis of the results, from... 7.1. ... multiple outcome measurements within the outcome domain?	**N**	**N**	**N**	**N**
7.2 ... multiple analyses of the intervention-outcome relationship?	**N**	**N**	**N**	**N**
7.3 ... different subgroups?	**N**	**N**	**N**	**N**
Risk of bias judgement	Low	Low	Low	Low

Risk of bias assessment as suggested by ROBINS-I authors (BMJ. 2016 Oct 12;355:i4919). Domain questions are answered with Y=yes; PY=probably yes; PN=probably no; N=No. Green coloured responses indicate potential markers for low risk of bias, whereas red

coloured responses indicate potential markers for risk of bias. Summarising judgement of a domain is highlighted by grey background and should be interpreted as follows:
Low risk of bias: the study is comparable to a well-performed randomised trial with regard to this domain.
Moderate risk of bias: the study is sound for a non-randomised study with regard to this domain but cannot be considered comparable to a well-performed randomised trial.
Serious risk of bias: the study has some important problems.
Critical risk of bias: the study is too problematic to provide any useful evidence on the effects of intervention.

Supplementary Table 3. Frequency of missing data.

Variable	de Waha et al n=60	Horn et al n=232	Patzelt et al n=271	Ledwoch et al n=63	Total n=647
Type of anaesthesia (deep sedation or general anaesthesia)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Age	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Male sex	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
BMI	0 (0.0)	12 (5.2)	6 (2.2)	63 (100.0)	81 (12.9)
COPD	0 (0.0)	3 (1.3)	0 (0.0)	0 (0.0)	3 (0.5)
eGFR	0 (0.0)	5 (2.2)	8 (3.0)	5 (7.9)	18 (2.9)
LVEF	0 (0.0)	35 (15.1)	39 (14.4)	1 (1.6)	75 (12.0)
Mitral regurgitation ≥III°	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mitral regurgitation functional	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
sPAP	0 (0.0)	66 (28.4)	37 (13.7)	6 (9.5)	109 (17.4)
NYHA Class ≥III before procedure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Procedural duration	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.2)	2 (0.3)
Procedural success	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Length of stay					
… in hospital, days	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.2)
… on intensive care unit, days	1 (1.7)	11 (4.7)	0 (0.0)	1 (1.6)	13 (2.1)
Primary safety endpoint	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stroke	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bleeding, major	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bleeding, life-threatening	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Missingness is shown as count (proportions).

BMI: body mass index; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; sPAP: systolic pulmonary artery pressure

Supplementary Table 4. Pooled estimates of treatment effects on primary outcomes in one- and two-stage meta-analyses without adjustment for covariates.

Endpoint	Meta-analysis	Estimate, 95% CI	*p*-value	τ^2	FMI
Safety	1-stage	1.18, 0.73–1.90	0.506	0.000[a]	0
	2-stage	1.23, 0.46–3.30	0.547	0.0997	
LOS	1-stage	1.07, 1.00–1.16	0.055	0.002	0.011
	2-stage	1.08, 0.91–1.29	0.237	0.009	
ICU-LOS	1-stage	3.15, 2.19–4.55	<0.001	0.114	0.009
	2-stage	3.27, 1.57–6.80	0.014	0.183	

Estimates are given as odds ratios (OR) for safety and as exponentiated coefficients for length of stay (LOS) and length of intensive care stay (ICU-LOS); these exponentiated coefficients should be interpreted as x-fold increase in length of LOS or ICU-LOS; [a]for the safety endpoint, the slope variance could not be estimated and was therefore fixed at 0.

CI: confidence interval; FMI: fraction of missing information

Supplementary Table 5. Comparison of VARC-2 and MVARC bleeding scales.

	VARC-2	MVARC
Life-threatening or disabling bleeding	Fatal bleeding (BARC type 5) OR Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) OR Bleeding causing hypovolaemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) OR Overt source of bleeding with drop in haemoglobin >5 g/dL or whole blood or packed red blood cells (RBCs) transfusion >4 units* (BARC type 3b)	Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating surgery or intervention, or intramuscular with compartment syndrome OR Bleeding causing hypovolaemic shock or hypotension (systolic blood pressure <90 mmHg lasting >30 min and not responding to volume resuscitation) or requiring significant doses of vasopressors or surgery
Extensive bleeding		Overt source of bleeding with drop in haemoglobin of ≥4 g/dl‡ or whole blood or packed RBC transfusion ≥4 U within any 24-hr period, or bleeding with drop in haemoglobin of ≥6 g/dl‡ or whole blood or packed RBC transfusion ≥4 U (BARC type 3b) within 30 days of the procedure
Major bleeding	Overt bleeding either associated with a drop in the haemoglobin level of at least 3.0 g/dl or requiring transfusion of two or three units of whole blood/RBC, or causing hospitalisation or permanent injury, or requiring surgery AND does not meet criteria of life-threatening or disabling bleeding	Overt bleeding either associated with a drop in the haemoglobin of ≥3.0 g/dl‡ or requiring transfusion of ≥3 U of whole blood or packed RBCs AND does not meet criteria of life-threatening or extensive bleeding
Minor bleeding	Any bleeding worthy of clinical mention (e.g., access-site haematoma) that does not qualify as life-threatening, disabling, or major	Any overt†, actionable sign of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that meets ≥1 of the following: requiring non-surgical medical intervention by a healthcare professional; leading to hospitalisation or increased level of care; prompting evaluation; or requires 1 or 2 U of whole blood or packed RBC transfusion and otherwise does not meet criteria for major, extensive, or life-threatening bleeding.

* Given that one unit of packed RBC typically will raise the haemoglobin concentration by 1 g/dl, an estimated decrease in haemoglobin will be calculated.

† “Overt” bleeding is defined by any of the following criteria being met: reoperation after closure of sternotomy for the purpose of controlling bleeding; chest tube output >2 l within any 24-hr period, >350 ml within the first postoperative hour, ≥250 ml within the second postoperative hour, or >150 ml within the third postoperative hour; or visible bleeding from the vascular system either at or remote from the access/surgical site.

‡ Adjusted for the number of units of blood transfused (1 U packed red blood cells or whole blood is equivalent to 1 g/dl haemoglobin).