Left ventricular assist device implantation with and without concomitant tricuspid valve surgery: a systematic review and meta-analysis

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ABSTRACT

Objectives

Moderate-to-severe tricuspid regurgitation is common in end-stage heart disease and is associated with an impaired survival after left ventricular assist device (LVAD) surgery. Controversy remains whether concomitant tricuspid valve surgery (TVS) during LVAD implantation is beneficial. We aimed to provide a contemporary overview of outcomes in patients who underwent LVAD surgery with or without concomitant TVS.

Methods

A systematic literature search was performed for articles published between January 2005 and March 2017. Studies comparing patients undergoing isolated LVAD implantation and LVAD + TVS were included. Early outcomes were pooled in risk ratios using random effects models, and late survival was visualized by a pooled Kaplan–Meier curve.

Results

Eight publications were included in the meta-analysis, including 562 undergoing isolated LVAD implantation and 303 patients with LVAD + TVS. Patients undergoing LVAD + TVS had a higher tricuspid regurgitation grade, central venous pressure and bilirubin levels at baseline and were more often female. We found no significant differences in early mortality and late mortality, early right ventricular failure and late right ventricular failure, acute kidney failure, early right ventricular assist device implantation or length of hospital stay. Cardiopulmonary bypass time was longer in patients undergoing additional TVS [mean difference +35 min 95% confidence interval (16–55), $P = 0.001$].

Conclusions

Adding TVS during LVAD implantation is not associated with worse outcome. Adding TVS, nevertheless, may be beneficial, as baseline characteristics of patients undergoing LVAD + TVS were suggestive of a more progressive underlying disease, but with comparable short-term outcome and long-term outcome with patients undergoing isolated LVAD.

INTRODUCTION

The favourable effects on survival of left ventricular assist devices (LVADs) as bridge-to-transplant and destination therapy for patients with end-stage heart failure are well established [1–3]. In approximately half of the patients undergoing LVAD implantation, moderate or severe tricuspid regurgitation (TR) is detected on echocardiography [2]. Usually, TR is secondary to changes in the right ventricular dimensions in response to a higher afterload due to left-sided heart disease [3].

Moderate-to-severe TR is associated with an impaired survival after LVAD surgery [2]. Significant TR has also been found to predict right ventricular failure (RVF) after LVAD implantation [2, 4], suggesting that concomitant treatment of the TR could be beneficial for these patients. However, spontaneous reduction in TR after LVAD implantation alone is also reported [5, 6]. Moreover, the sample size is small in most studies addressing this topic. Controversy remains whether TR should be surgically corrected at the time of LVAD implantation. Hence, some centres opt for an aggressive approach, whereas others are more conservative. Therefore, we conducted a systematic search of the literature to provide a comprehensive overview of outcomes in patients undergoing LVAD+ tricuspid valve surgery (TVS) when compared with patient undergoing isolated LVAD implantation using a meta-analysis.

METHODS

Search strategy

To establish an overview of reported outcome, a systematic literature search according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was conducted [7]. Search terms were developed in collaboration with the librarian in our centre. On 29 March 2017, Embase, MEDLINE, Web of Science, Cochrane and Google Scholar were searched for articles published after January 2005 (search terms are provided in Supplementary Material, Text S1). Inclusion and exclusion criteria were defined a priori. Randomized controlled trials and observational studies concerning adult patients undergoing LVAD implantation comparing patients with and without concomitant TVS were included. Studies with less than 20 patients or abstracts, poster and conference summaries were excluded. Reasons to exclude studies with less than 20 patients were that these studies were most likely early experiential series and do not reflect the general population and, in case of a small population, chances of zero events rise, resulting in a numerical problem in pooling the data. We did not include posters, abstracts, etc. because these formats did not undergo extensive peer reviewing. In the case of overlapping study populations, the study with the most patients-years of follow-up were selected. Exceptions were made for studies that reported on more outcomes of interest. Two researchers (M.E.A.K. and D.D.) independently reviewed abstracts and full texts in an unblinded

standardized manner. In case of disagreement to include a study, an agreement was negotiated. References in selected articles were independently cross-checked by 2 researchers (M.E.A.K. and D.D.) for other relevant studies.

Data extraction

Study design, year of surgery period and follow-up (patient-years and mean) were documented. If follow-up was not provided, patient-years were calculated by multiplying the number of patients with the mean follow-up (or median, if the mean is not provided). The following baseline characteristics were extracted: mean age at operation, gender, aetiology (ischaemic and non-ischaemic), TR grade (none, mild, moderate and severe), creatinine, central venous pressure (CVP), mean systolic pulmonary artery pressure, type of tricuspid valve repair (suture, ring), prosthesis type in case of tricuspid valve replacement and concomitant valvular procedures. In addition, the following outcomes were documented: early mortality (in-hospital or <30-day mortality), mean cardiopulmonary bypass (CPB) time, length of intensive care stay, hospital stay, early RVF, acute kidney failure, late mortality and late RVF. The individual study definitions were used to define the outcomes. Microsoft Office Excel 2011 (Microsoft Corp., Redmond, WA, USA) was used for data extraction. Data were independently extracted by 2 authors (M.E.A.K. and D.D.). The Newcastle–Ottawa scale was used to assess methodological quality of the studies [8], and the ROBINS-I tool was used to assess bias in the individual outcomes [9].

Statistical analyses

Log-transformed inverse variance weighted pooled baseline characteristics were calculated. Risk ratios (RRs) and mean differences (MDs) were used to compare baseline characteristics with the use of a fixed effects model, as our goal was to compute comparisons for the identified population and not to generalize to other populations and analyses of baseline characteristics similar in most cases [10]. A P-value <0.05 was considered statistically significant. Random effects models using the Der Simonian and Laird method were used to pool outcomes [11]. RRs were used for dichotomous data and MDs for continuous data. The Cochrane Q statistic and I^2 were used to assess heterogeneity. Microsoft Excel 2010 was used to calculate linearized occurrence rate and risk. Comprehensive Meta-Analysis (CMA) v2.2.064 (Biostat, Engelwood, NY, USA) was used to calculate the pooled outcomes and to generate forest and funnel plots.

Patient survival was visualized in a pooled Kaplan–Meier (KM) curve derived from the originally published KM curves using the method described by Guyot et al. [12]. The Engauge Digitizer v10.0 [13] was used to create a list of co-ordinates of the KM curve, and an algorithm written in the R language was employed (Version 3.3.3) to reconstruct the original patient data. Thereafter, GraphPad Prism version 7.00 for Windows (GraphPad Software, La Jolla, CA USA) was used to plot the pooled KM curve. The reconstructed data were used to obtain hazard ratios (HRs) of late mortality in TVS + LVAD group versus isolated LVAD implantation by univariate cox regression. Thereafter, the HRs were pooled using CMA.

RESULTS

The search of the literature resulted in 915 studies, of which 16 articles met the inclusion criteria. Eight articles had to be excluded due to overlapping data, resulting in 8 inclusions for the meta-analysis (Fig. 1). References are presented in Supplementary Material, Text S2 (References S1–S9). In 1 study, we made an exception of the general rule to include the study with the most patient-years. Piacentino et al. in 2012 (Supplementary Material, Reference S7) reported on more outcomes of interest when compared with Piacentino et al. in 2011 (Supplementary Material, Reference S8), hence we included Piacentino et al. (Supplementary Material, Reference S7). However, in the 2011 study Piacentino et al. (Supplementary Material, Reference S8) reported on the KM curves, and therefore, this study was included in the KM analyses. The meta-analysis included 562 patients in the LVAD group and 303 in the LVAD + TVS group, of which 392 patients in the LVAD group had reported late follow-up time encompassing 697 patient-years when compared with 247 in the LVAD + TVS group who had reported late follow-up time encompassing 351 patient-years. Baseline and procedural characteristics of all individual studies are shown in Table 1. All studies were observational. Most studies lost points on comparability using the Newcastle–Ottawa scale, and most outcomes are at serious risk of bias due to confounding according the ROBINS-I tool (Supplementary Material, Tables S1–S4).

Baseline characteristics

Pooled baseline and procedural characteristics are shown in Table 2. Patients who underwent LVAD + TVS were more often female, had a higher TR grade, and higher CVP and bilirubin levels. In patients who underwent TVS, the tricuspid valve was repaired in 93.2% of patients; a ring repair was performed in 87% and a suture repair in 13%. Tricuspid valve replacement—all biological prostheses—was conducted in 6.8% of patients.

Early outcomes

A forest plot containing the individual and pooled RRs for early mortality, RVF, acute kidney failure and RVAD implantation is presented in Fig. 2A–D. None of the pooled RRs were statistically significant between patients receiving LVAD + TVS and isolated LVAD. Three studies reported CPB time and length of hospital stay (Supplementary Material, References S3, S5 and S6). CPB time was longer in patients undergoing TVS [129 min, 95% confidence interval (CI) (114–126)] when compared with isolated LVAD surgery [91 min, 95% CI (81–101)] with a pooled MD of 35 min [95% CI (16–55), P =0.001] with I^2 = 83.0%, Q-value 11.734 and P-value 0.003 (Supplementary Material, Fig. S1). Length of hospital stay did not differ significantly between patients undergoing LVAD + TVS [35 days, 95% CI (20–49)] and isolated LVAD [41 days, 95% CI (20–61)] with a pooled MD of 4 days, 95% CI (-1 to 10), P = 0.126, with I^2 = 83.0%, Q-value 11.734 and P-value 0.003 (Supplementary Material, Fig. S2). Additionally, 2 other studies (Supplementary Material, References S4 and S7), which did not report data in extractable format, did not find

significant differences in hospital stay ($P < 0.05$). Funnel plots are presented in Supplementary Material, Figs S4–S9. Leave-one-out analysis did not change the significance of all outcomes.

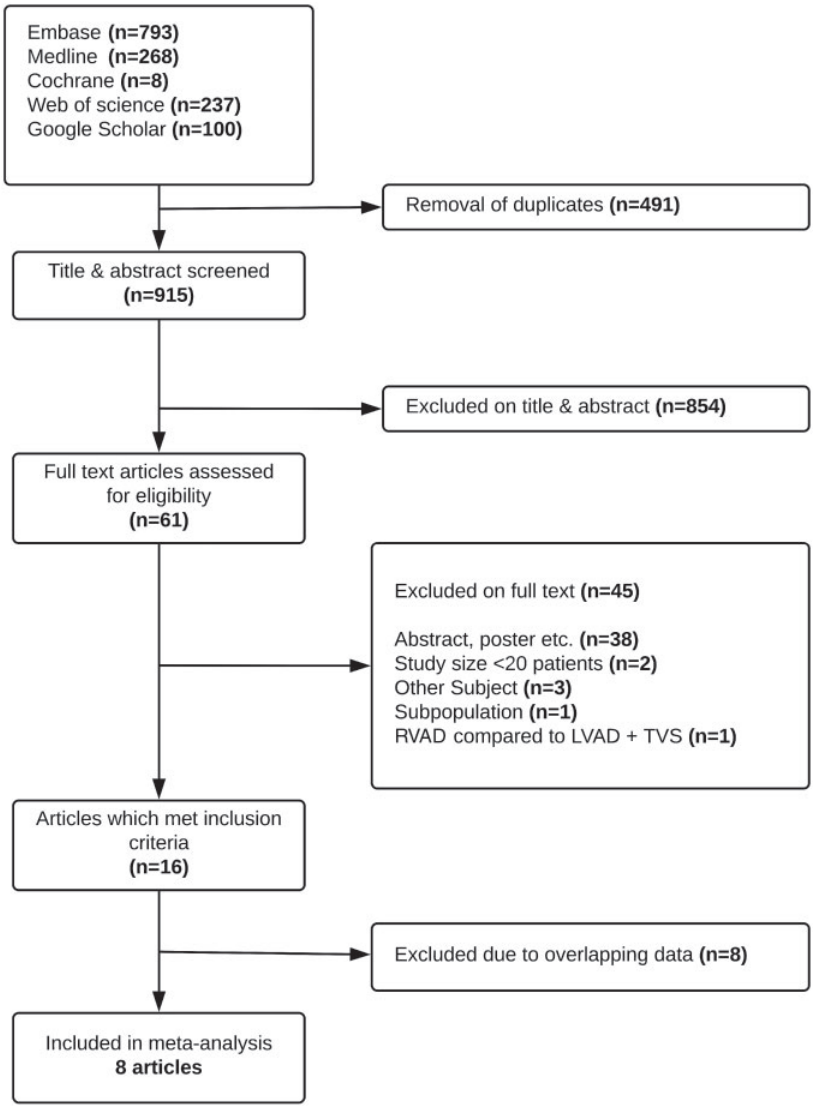

Figure 1: Flowchart of included studies in the meta-analysis. One of the 8 articles excluded due to overlapping contained a Kaplan–Meier curve which could be used in analysis, without including the article in other analysis. LVAD: left ventricular assist device; RVAD: right ventricular assist device; TVS: tricuspid valve surgery.

Table 1: Baseline characteristics of included studies

Publication	Design	Study characteristics							Newcastle–Ottawa scale		
		Group	Indication for TR surgery	*n* (% male)	Ischaemic aetiology (%)	TR severity	TV repair (%) (ring/suture)	TV replacement (%)	Selection	Comparability	Outcome
Brewer et al. (Supplementary Material, Reference S1)	Retrospective monocentre	LVAD		87 (74)	37				***	**	*
		LVAD + TVS	NR	14 (71)	14		100 (100/0)	0			
Fujita et al. Supplementary Material, Reference S2)	Retrospective monocentre	LVAD		72 (NR)	NR	Mean grade: 1.3 ± 0.8			***	–	***
		LVAD + TVS	>Moderate TR and >40 mm annulus dilatation	69 (NR)	NR	Mean grade: 2.6 ± 1.0	100 (70/30)	0			
Han et al. (Supplementary Material, Reference S3)	Retrospective monocentre	LVAD		252 (84)	43	≥Moderate 19%			***	**	***
		LVAD + TVS	≥Moderate TR	76 (76)	36	≥Moderate 99%	98 (95/3)	2			
Krishan et al. (Supplementary Material, Reference S4)	Retrospective monocentre	LVAD		14 (100)	36	≥Moderate 7%			***	–	***
		LVAD + TVS	>Moderate TR and >40 mm annulus dilatation	37 (84)	27	≥Moderate 60%	100 (100/0)	0			
Maltais et al. (Supplementary Material, Reference S5)	Retrospective multicentre	LVAD		49 (90)	52	TR VC 2.9 mm			***	*	***
		LVAD + TVS	NR	34 (71)	50	TR VC 5.6 mm	82 (12/70)	18			

Table 1: Baseline characteristics of included studies (continued)

Publication	Design	Study characteristics							Newcastle–Ottawa scale		
		Group	Indication for TR surgery	*n* (% male)	Ischaemic aetiology (%)	TR severity	TV repair (%) (ring/suture)	TV replacement (%)	Selection	Comparability	Outcome
Oezpeker et al. (Supplementary Material, Reference S6)	Retrospective monocentre	LVAD		26 (92)	58	>Moderate 100%			****	**	***
		LVAD + TVS	>Moderate TR	32 (88)	25	>Moderate 100%	100 (100/0)	0			
Piacentino et al.[b] (Supplementary Material, Reference S7)	Retrospective monocentre	LVAD		28 (54)	36	≥Moderate 100%			****	*	***
		LVAD + TVS	NR	33 (67)	56	≥Moderate 100%	88 (88/0)	12			
Piacentino et al.[a] (Supplementary Material, Reference S8)	Retrospective monocentre	LVAD		81 (79)	39	Severe 33%			****	*	***
		LVAD + TVS	NR	34 (65)	26	Severe 62%	75 (75/0)	15			
Saeed et al. (Supplementary Material, Reference S9)	Retrospective monocentre	LVAD		34 (74)	NR				***	–	**
		LVAD + TVS	>Moderate-to-severe (3) TR	8 (100)	NR		100 (37/63)	0			

*Only included in the Kaplan–Meier analysis.

**Only included in meta-analysis.

LVAD: left ventricular assist device; NR: not reported; TR: tricuspid regurgitation; TV: tricuspid valve; TVS: tricuspid valve surgery; VC: vena contracta.

Table 2: Pooled baseline and procedural characteristics

Characteristics	LVAD (*n* = 562)	95% CI	LVAD + TVS (*n* = 303)	95% CI	RR/MD	95% CI	*P*-value
Age (years)	56.0	54.8–57.2	56.9	55.1–58.7	-0.47	-2.8 to 1.9	0.693
Female (%)	24.0	20.4–28.8	40.8	34.1–48.7	0.71	0.52 to 0.94	0.020
Ischaemic heart disease (%)	44.0	39.6–48.8	41.0	34.8–48.2	1.15	0.93 to 1.4	0.195
Diabetes (%)	37.5	33.0–42.6	34.7	27.2–44.3	1.01	0.75 to 1.35	0.952
IABP (%)	41.6	36.6–47.2	47.6	41.1–55.1	0.92	0.76 to 1.20	0.407
Other valve procedure (%)	46.3	89.9–96.3	45.0	37.3–54.3	1.01	0.80 to 1.28	0.912
Moderate–severe TR (%)	93.1	89.9–96.3	97.5	95.2–99.9	0.93	0.89 to 0.97	<0.001
Severe TR (%)	17.7	11.8–26.4	57.4	49.9–66.6	0.47	0.28 to 0.80	0.006
CVP (mmHg)	10.8	10.3–11.3	12.9	12.0–13.8	-2.04	-3.08 to -0.99	<0.001
PCWP (mmHg)	23.3	22.5–24.1	23.4	22.4–24.4	-0.37	-1.69 to -0.95	0.672
Creatinine (mg/dl)	1.4	1.3–1.4	1.4	1.3–1.5	-0.07	-0.17 to 0.04	0.236
Bilirubin (mg/dl)	1.4	1.3–1.5	1.7	1.6–1.9	-0.21	-0.416 to -0.012	0.038
Continuous flow device (%)	99.7	99.2–100	98.8	97.3–100	1.00	0.998 to 1.02	0.602

CI: confidence interval; CVP: central venous pressure; IABP: intra-aortic balloon pump; LVAD: left ventricular assist device; MD: mean difference; PCWP: pulmonary capillary wedge pressure; RR: risk ratio; TR: tricuspid regurgitation; TVS: tricuspid valve surgery.

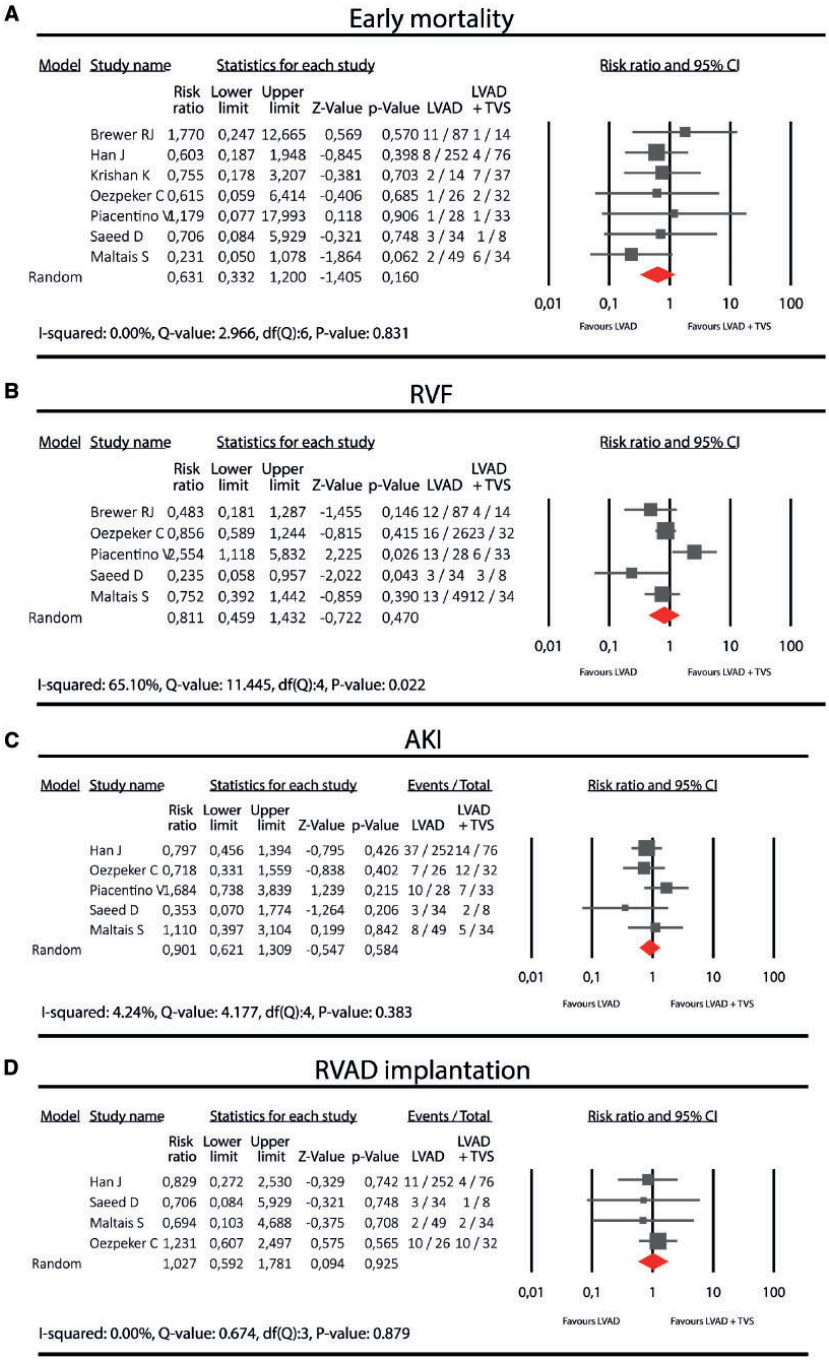

Figure 2: (A–D) Forest plots of early mortality (A), Right ventricular failure (RVF) (B), Acute kidney injury (AKI) (C) and Right ventricualr assist device (RVAD) implantation (D). CI: confidence interval; LVAD: left ventricular assist device; RR: risk ratio; TVS: tricuspid valve surgery.

Late outcomes

Seven studies (Supplementary Material, References S1–S3, S5, S6, S8 and S9) reported KM curves that could be pooled. The pooled KM curves showed comparable late survival in patients undergoing LVAD implantation with and without concomitant TVS (Fig. 3). The 1-, 2- and 3-year survival rates are 77.9 ± 3.0%, 71.8 ± 3.9% and 57.3 ± 6.0% in the LVAD+ TVS group and 82.2 ± 1.9%, 73.3 ± 2.6% and 58.1 ± 5.2% in the LVAD group, respectively. Pooled HR of concomitant TVS for late mortality is 1.13 [95% CI (0.68–1.90), *P*-value = 0.634] with I^2 = 47.1%, *Q*-value 11.344 and *P*-value 0.078 (Supplementary Material, Fig. S3). Additionally, 3 studies reported late mortality and follow-up (Supplementary Material, References S4, S6 and S7). The linearized occurrence rate of mortality in these studies was comparable in the group undergoing LVAD + TVS [43%/year, 95% CI (32–59)] compared with isolated LVAD implantation [36%/year, 95% CI (25–52)].

Data on late RVF are scarce; only 2 studies reported late RVF (Supplementary Material, References S3 and S6). Han et al. (Supplementary Material, Reference S3) found no significant differences in the cumulative readmission for RVF between patients with and without concomitant TVS during LVAD implantation (*P* = 0.95). Moreover, Oezpeker et al. (Supplementary Material, Reference S6) also found no differences in RVF at 1 year after LVAD implantation between patients receiving LVAD compared with LVAD +TVS [odds ratio 1.23 (0.18–8.44), *P* = 0.830].

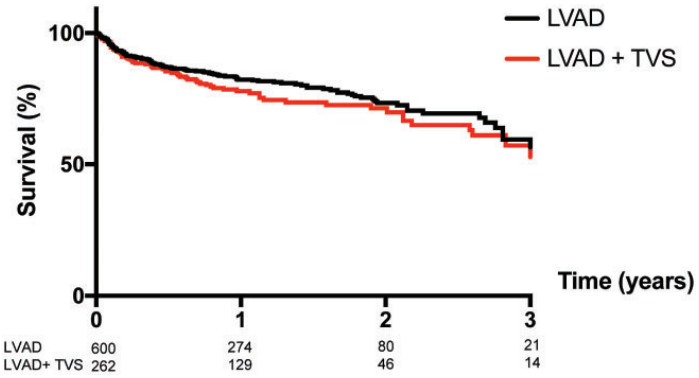

Figure 3: A pooled Kaplan–Meier curve of survival of patients undergoing LVAD implantation with or without TVS. Patients are censored at heart transplant. As Piacentino et al. (Supplementary Material, Reference S8) contained more patients than Piacentino et al. (Supplementary Material, Reference S7), more patients are included in the Kaplan–Meier analysis than in the meta-analysis. LVAD: left ventricular assist device; TVS: tricuspid valve surgery.

DISCUSSION

This meta-analysis showed that there are no significant differences in early mortality, RVF, acute kidney failure, hospital stay and RVAD implantation between patients receiving isolated LVAD implantation versus LVAD + TVS. Not surprisingly, CPB time was longer in patients receiv-

ing concomitant TVS. In addition, late mortality and late RVF were comparable for patients with and without TVS during LVAD implantation. To the best of our knowledge, this is the first systematic review that pools late survival using KM curves.

Our results can be interpreted two-fold. First, one could argue that despite the fact that patients receiving concomitant TVS are sicker at baseline, concomitant TVS results in comparable outcomes as isolated LVAD implantation, and thus, TVS during LVAD may be beneficial. Several authors have mentioned this reasoning (Supplementary Material, References S2, S4, S5 and S7). Second, one could argue that LVAD alone is also able to improve the loading conditions of the heart, and TVS does not have clinical relevance. It is difficult to discriminate between these 2 interpretations as the ideal control group (patients with severe TR and impaired RVF at baseline undergoing isolated LVAD implantation) is rarely compared with patients undergoing LVAD + TVS in the literature, as is also indicated by the differences in pooled baseline characteristics. Nevertheless, the pooled data show that additional TVS is not associated with worse outcomes. Therefore, we question the clinical impact of the pop-off valve hypothesis, which states that the tricuspid valve regurgitation serves as a 'pop-off', reducing right ventricular afterload (Supplementary Material, References S1 and S4). The results of this meta-analysis agree in this respect with a prior systematic review that focused on early outcomes [14].

Severe TR is associated with impaired right ventricle function [15], and RVF is uniformly recognized as a risk factor for adverse events and mortality following LVAD implantation [16]. These 2 observations raise important questions. Does TR impact outcomes by itself or is it merely a marker for the severity of the right ventricular dysfunction? If so, does TVS improve right ventricular function? Some data suggest that TVS improves right ventricular function in the setting of functional TR [17, 18], adding to the rationale that TVS may be beneficial. However, whether this is true in the setting of LVAD implantation remains unclear.

Complicating matters, significant TR can reduced to insignificant TR after optimizing loading conditions through diuretics use [3]. Therefore, baseline TR grade as sole operation criteria might not be sufficient. Dreyfus et al. [19] proposed that the decision of TVS should be based on annulus dilatation rather than TR grade in patients with functional TR. Some centres have adopted this approach in their decision-making process whether to operate on the TV during LVAD implantation (Supplementary Material, References S2 and S4). Current guidelines on management of TR recommend consideration of tricuspid valve repair if moderate or greater TR is present [20].

The data of the STS and the INTERMACS registries have been used to shed some light on routinely repairing the tricuspid valve if significant TR is present [21, 22]. Analysing the STS registry, Robertson et al. reported that patients undergoing TVS had a higher postoperative risk of renal failure, dialysis, reoperation, greater total transfusion requirement and a higher rate of hospital length of stay >21 days. They concluded that routinely operating on the tricuspid valve based on TR grade should be avoided [21]. Our recent article confirms also the increased risk of RVF if the CPB time is increased [23]. Increased CPB is a marker for a difficult situation,

subsequently requiring extended surgery, which may lead to RVF. We agree, therefore, with their suggestion to seek additional selection criteria for TVR. Nonetheless, their results should be interpreted with some caution, since they did not adjust for preoperative RVF, except for TR grade. Song et al. [22] showed comparable survival of patients undergoing TVS during LVAD implantation versus isolated LVAD implantation using the INTERMACS database. On the one hand, multicentre studies include more patients, increasing statistical power, and on the other hand, TR measurement and quantification remain challenging, and adding different centres with different operators results in less reliable data. This point was also raised by Shah [22, 24] commenting on the publication of the INTERMACS data. Furthermore, a limitation is that these multicentre studies were not designed to specifically address these research questions. Therefore, data on tricuspid valve function, time of assessment and reason for TVR are not collected uniformly or not available at all, which is expected to have resulted in significant bias. The study on the STS database attempted to adjust for baseline differences using a propensity score model. However, data on right heart function, except for TR grade in their model, were not included.

Additionally, the data from HeartMate II and ADVANCE trials have been retrospectively reviewed to assess the impact of TVS during LVAD implantation. Although patients undergoing TVS in the HeartMate II trial had worse baseline characteristics (higher CVP, higher CVP/PWCP ratio and lower right ventricular stroke work index) both early survival and late survival were comparable. The incidence of early RVAD implantation and early RVF was higher in the LVAD + TVS group [25]. However, the data from the ADVANCE trial showed that patients with moderate or severe TR receiving TVS have a lower incidence of late RVF when compared with patients with moderate or severe TR undergoing isolated LVAD implantation [26], suggesting that patients undergoing TVS may be at higher risk of early RVF, but this reverses during follow-up.

We speculate that TR is part of an interplay of RVF, pulmonary pressures, systemic volume status and kidney function. Subsequently, TVS may only be beneficial in patients who have not reached the point-of-no-return but are sick enough to require TVS. For example, patients with TR and risk factors for postoperative RVF, but not yet with full-blown RVF, may benefit more if TVS is able to improve right ventricular function or prevent further decrease in right ventricular function post-implantation. Therefore, identifying these patients should be a focus of further research, because clear insight in which subpopulation within the TR population may benefit from TVS remains yet to be elucidated. A randomized clinical trial including all patients with TR is not feasible, and multiple clinical trials in different subpopulations within the TR population would be a costly endeavour. However, newer innovative designs are rising that can possibly provide answers on this matter [27]. Currently, a clinical trial (NCT02537769) is being performed to assess the effect of TVS on patients with mild–moderate TR at baseline. This is already a subset of the general TR population; nevertheless it may be a subset which does not benefit from TVS. Therefore, it may still be elucidating to gain insights in the natural history of TR after LVAD implantation and to seek additional selection criteria for concomitant TVS.

Limitations

This study is a systematic review and meta-analysis of observational studies, which all are retrospective in nature. Therefore, the inherent limitations of meta-analysis and pooling retrospective data apply to this study [28]. Moreover, serious risk of bias due to confounding was found in most studies using the ROBINS-I tool. However, this bias mostly favours the LVAD group, further suggesting that there may be benefit of concomitant TVS that underlies our findings of comparable outcomes. Despite the inclusion of multiple studies, the sample size remains modest, possibly with too little power to show true differences. Funnel plots did not show clear evidence of publications bias. However, the small number of studies precludes unambiguous conclusions. Considerable heterogeneity was present in the RRs of early RVF, CBP and in the late mortality, including the pooled HRs. Unfortunately, exploring heterogeneity with meta-regression was not possible due to limited number of studies. The RVF heterogeneity may be explained by the fact that some studies included patients less prone to postoperative RVF in the LVAD group, resulting in different RRs. For example, Piacentino et al. (Supplementary Material, Reference S7) only included patients >moderate TR, and in the cohort of Maltais et al. (Supplementary Material, Reference S5), TR differed in groups, whereas TR is found to be a predictor of postoperative RVF after LVAD implant [29]. Additionally, CBP had significant heterogeneity, which can partly be explained by the fact that in the cohort of Maltais et al. (Supplementary Material, Reference S5), patients did not undergo other concomitant procedures (e.g. aortic valve procedure), whereas in the cohort of Han et al. (Supplementary Material, Reference S3), nearly half the population underwent concomitant procedures. Because of differences in postoperative care and censoring due to heart transplantation, the heterogeneity found in late mortality can be explained.

CONCLUSION

Concomitant TVS during LVAD implantation is not associated with worse outcome when compared with LVAD implantation, and some data indicate that it may be beneficial. However, current literature is unable to offer a definitive answer, as the majority the compares unmatched groups. Additional effort should be made to identify which patients will benefit most from adding TVS to LVAD implantation.

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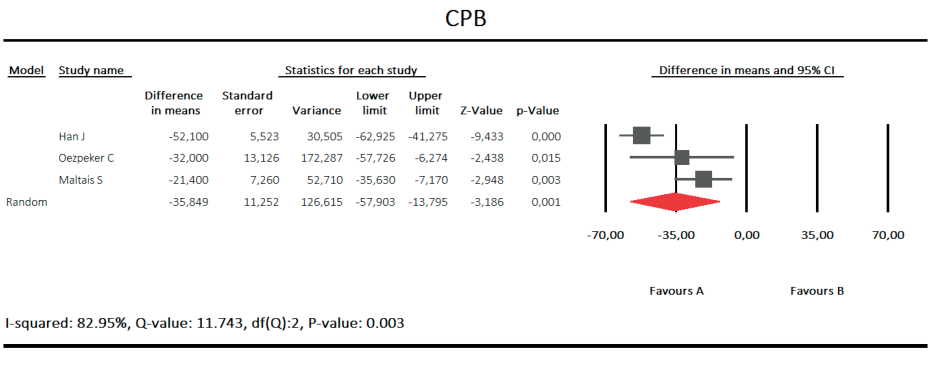
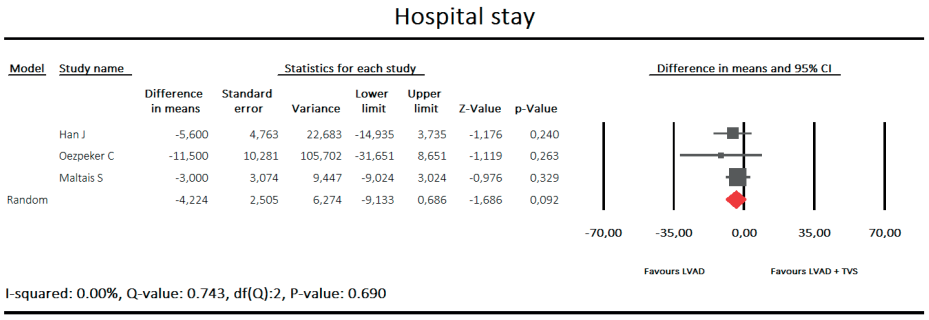
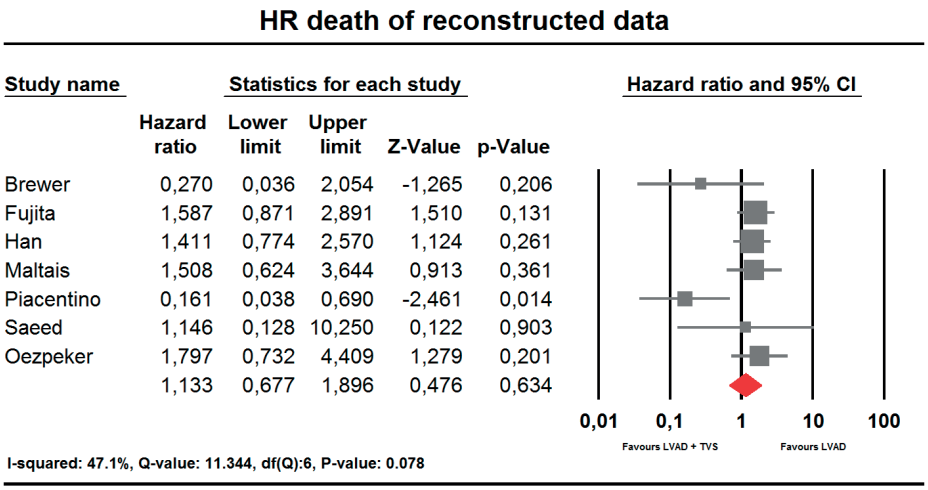
SUPPLEMENTARY MATERIAL



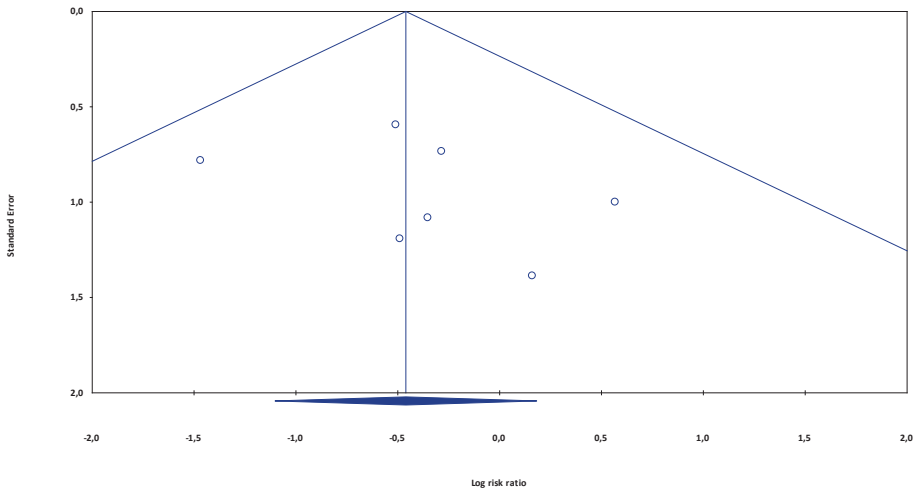
Supplementary Figure 1: Forest plot of cardiopulmonary bypass time.



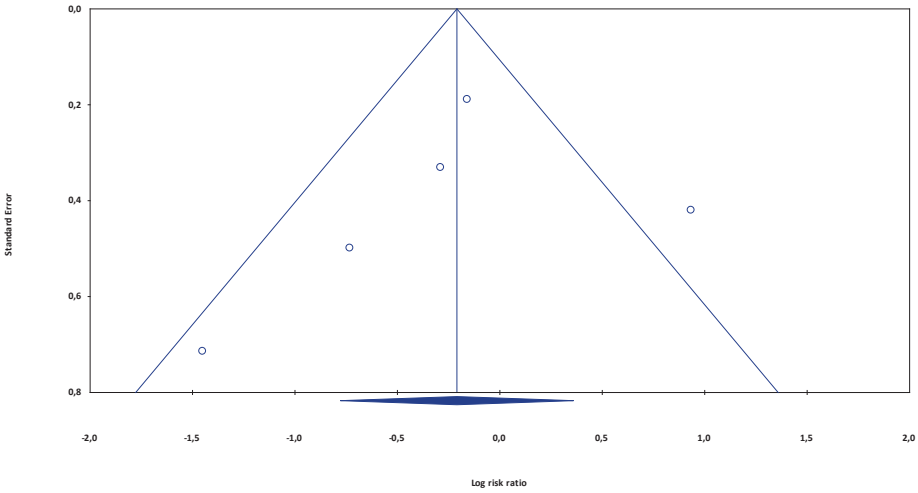
Supplementary Figure 2: Forest plot of length of hospital stay.



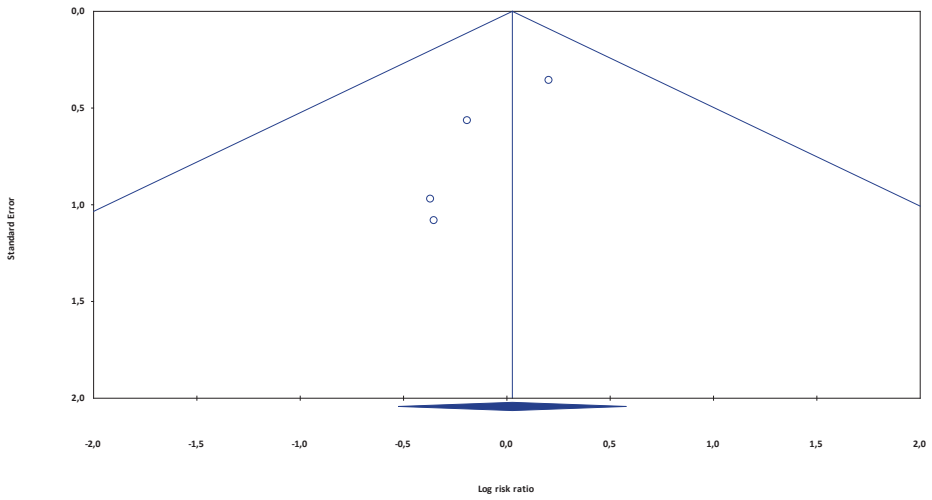
Supplementary Figure 3: Forest plot of constructed hazard ratio of late mortality of patients receiving isolated LVAD implant vs LVAD + TVS.



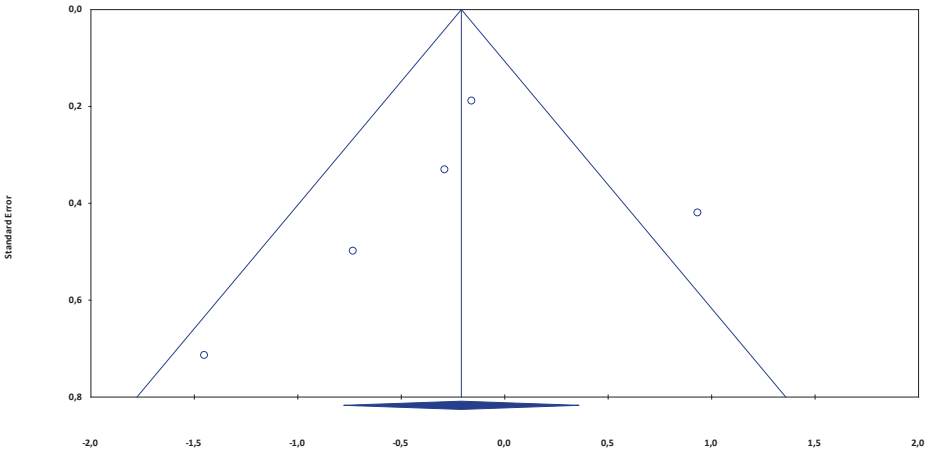
Supplementary Figure 4: Funnel plot of Early Mortality.



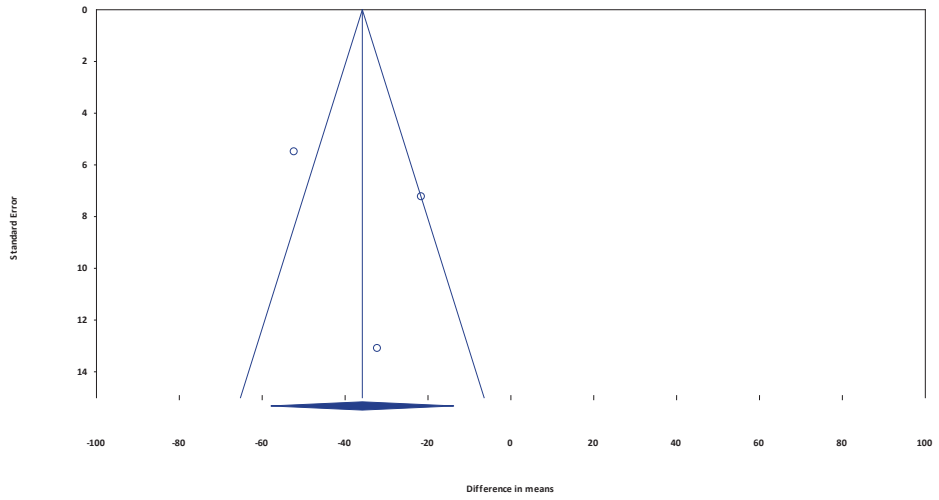
Supplementary Figure 5: Funnel plot of Acute Kidney Failure .



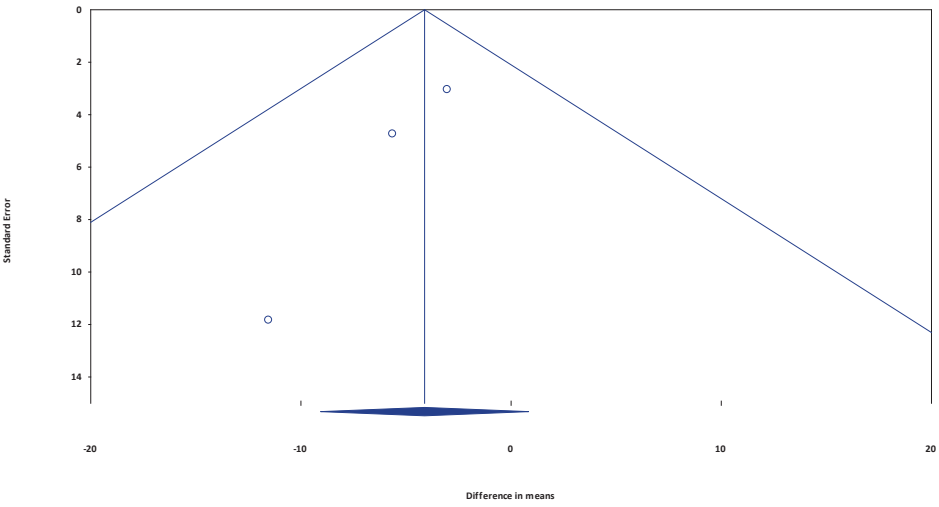
Supplementary Figure 6: Funnel plot of RVAD implantation.



Supplementary Figure 7: Funnel plot of right ventricular failure.



Supplementary Figure 8: Funnel plot of cardiopulmonary bypass time.



Supplementary Figure 9: Funnel plot of length of hospital stay.

Supplementary Table 1: ROBIN-I risk of bias judgements of the outcome Early mortality in all studies. LR: low risk, MR: moderate risk, SR: serious risk, CR:critical risk, NI: No information

Early mortality							
Study	**Brewer RJ**	**Han J**	**Krishan K**	**Oezpeker C**	**Piacentino V**	**Saeed D**	**Maltais S**
Bias due to confounding	**SR**	**MR**	**SR**	**MR**	**SR**	**SR**	**SR**
Bias due to participant selection	**LR**	**LR**	**LR**	**LR**	**LR**	**LR**	**LR**
Bias due to classification of interventions	**LR**	**LR**	**LR**	**LR**	**LR**	**LR**	**LR**
Bias due to deviations from intended interventions	**LR**	**LR**	**LR**	**LR**	**LR**	**LR**	**LR**
Bias due to missing data	**LR**	**LR**	**LR**	**LR**	**LR**	**LR**	**LR**
Bias in measurements of outcome	**LR**	**LR**	**LR**	**LR**	**LR**	**LR**	**LR**
Bias in selection of reported results	**SR**	**MR**	**MR**	**MR**	**MR**	**MR**	**MR**
Overall	**SR**	**MR**	**SR**	**MR**	**SR**	**SR**	**SR**

Supplementary Table 2: ROBIN-I risk of bias judgements of the outcome RVF in all studies. RVF: right ventricular failure. LR: low risk, MR: moderate risk, SR: serious risk, CR:critical risk, NI: No information

RVF					
Study	**Brewer RJ**	**Oezpeker C**	**Piacentino V**	**Saeed D**	**Maltais S**
Bias due to cofounding	**SR**	**MR**	**SR**	**SR**	**SR**
Bias due to participant selection	**LR**	**LR**	**LR**	**LR**	**LR**
Bias due to classification of interventions	**LR**	**LR**	**LR**	**LR**	**LR**
Bias due to deviations from intended interventions	**LR**	**LR**	**LR**	**LR**	**LR**
Bias due to missing data	**LR**	**LR**	**LR**	**LR**	**LR**
Bias in measurements of outcome	**MR**	**MR**	**MR**	**MR**	**MR**
Bias in selection of reported results	**SR**	**MR**	**MR**	**MR**	**MR**
Overall	**SR**	**MR**	**SR**	**SR**	**SR**

Supplementary Table 3: ROBIN-I risk of bias judgements of the outcome AKI in all studies. AKI: Acute kidney injury. LR: low risk, MR: moderate risk, SR: serious risk, CR:critical risk, NI: No information

AKI					
Study	**Han J**	**Oezpeker C**	**Piacentino V**	**Saeed D**	**Maltais S**
Bias due to cofounding	**MR**	**MR**	**SR**	**SR**	**SR**
Bias due to participant selection	**LR**	**LR**	**LR**	**LR**	**LR**
Bias due to classification of interventions	**LR**	**LR**	**LR**	**LR**	**LR**
Bias due to deviations from intended interventions	**LR**	**LR**	**LR**	**LR**	**LR**
Bias due to missing data	**LR**	**LR**	**LR**	**LR**	**LR**
Bias in measurements of outcome	**LR**	**LR**	**LR**	**LR**	**LR**
Bias in selection of reported results	**MR**	**MR**	**MR**	**MR**	**MR**
Overall	**MR**	**MR**	**SR**	**SR**	**SR**

Supplementary Table 4: ROBIN-I risk of bias judgements of the outcome RVAD implantation in all studies. RVAD: Right ventricular assist device. LR: low risk, MR: moderate risk, SR: serious risk, CR:critical risk, NI: No information

RVAD implantation				
Study	**Han J**	**Oezpeker C**	**Saeed D**	**Maltais S**
Bias due to cofounding	**MR**	**MR**	**SR**	**SR**
Bias due to participant selection	**LR**	**LR**	**LR**	**LR**
Bias due to classification of interventions	**LR**	**LR**	**LR**	**LR**
Bias due to deviations from intended interventions	**LR**	**LR**	**LR**	**LR**
Bias due to missing data	**LR**	**LR**	**LR**	**LR**
Bias in measurements of outcome	**LR**	**LR**	**LR**	**LR**
Bias in selection of reported results	**MR**	**MR**	**MR**	**MR**
Overall	**MR**	**MR**	**SR**	**SR**

SUPPLEMENTARY TEXT 1

Embase.com 793

('ventricular assist device'/exp OR 'heart assist device'/de OR (((ventricular OR lv OR assist*) NEAR/3 device*) OR lvad OR vad OR Heartware* OR HeartMate OR Levacor OR Novacor OR Ventrassist):ab,ti) AND ('tricuspid valve disease'/exp OR 'tricuspid valve repair'/de OR 'tricuspid valve'/de OR 'tricuspid annuloplasty'/de OR (tricuspid* OR (atrioventricular NEAR/3 (valve* OR right)) OR (functional* NEAR/3 regurgit*)):ab,ti)

Medline Ovid 268

("Heart-Assist Devices"/ OR (((ventricular OR lv OR assist*) ADJ3 device*) OR lvad OR vad OR Heartware* OR HeartMateOR Levacor OR Novacor OR Ventrassist).ab,ti,kf.) AND ("Tricuspid Valve Prolapse"/ OR "Tricuspid Valve Stenosis"/ OR "tricuspid valve"/ OR "Tricuspid Valve Insufficiency"/ OR (tricuspid* OR (atrioventricular ADJ3 (valve* OR right)) OR (functional* ADJ3 regurgit*)).ab,ti,kf.)

Web of science 237

TS=(((((ventricular OR lv OR assist*) NEAR/2 device*) OR lvad OR vad OR Heartware* OR HeartMateOR Levacor OR Novacor OR Ventrassist)) AND ((tricuspid* OR (atrioventricular NEAR/2 (valve* OR right)) OR (functional* NEAR/2 regurgit*))))

Cochrane CENTRAL 8

((((ventricular OR lv OR assist*) NEAR/3 device*) OR lvad OR vad OR Heartware* OR HeartMateOR Levacor OR Novacor OR Ventrassist):ab,ti) AND ((tricuspid* OR (atrioventricular NEAR/3 (valve* OR right)) OR (functional* NEAR/3 regurgit*)):ab,ti)

Google scholar 100

"ventricular|lv|assist device|devices"|lvad|vad|Heartware|HeartMate|Ventrassist tricuspid|"atrioventricular valve"|"functional regurgit"

SUPPLEMENTARY TEXT 2

S1. Brewer RJ, Cabrera R, El-Atrache M, Zafar A, Hrobowski TN, Nemeh HM, et al. Relationship of tricuspid repair at the time of left ventricular assist device implantation and survival. Int J Artif Organs. 2014;37(11):834-8.

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