Biatrial vs Bicaval Orthotopic Heart Transplantation: A Systematic Review and Meta-Analysis

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Background

Orthotopic heart transplantation (OHT) is the gold standard treatment in end-stage heart disease. Controversy remains whether bicaval OHT is superior to biatrial OHT in both early and late outcomes. This study aimedto provide an overviewof the early andlate outcomes in patients who underwent a bicaval or biatrial OHT.

Methods

A systematic literature search was performed for articles published before December 2017. Studies comparing adult patients undergoing biatrial OHT and bicaval OHT were included. Early outcomes were pooled in odds ratios and late outcomes were pooled in rate ratios. Late survival was visualized by a pooled Kaplan- Meier curve.

Results

A total of 36 publications were included in the meta-analysis, counting 3555 patients undergoing biatrial OHT and 3208 patients undergoing bicaval OHT. Early outcomes in mortality, tricuspid regurgitation, mitral regurgitation, and permanent pacemaker implantation differed significantly in favor of the bicaval OHT patients. Long-term survival was significantly better in patients undergoing bicaval vs biatrial OHT (hazard ratio, 1.32; 95% confidence interval, 1.1-1.6; *P* = .008). Also, late tricuspid regurgitation was less frequently seen in the bicaval OHT patients (rate ratio, 2.14; 95% CI, 1.17- 3.94; *P* = .014).

Conclusions

This systematic review with metaanalysis shows that bicaval OHT results in more favorable early and late outcomes for patients undergoing a bicaval OHT compared with a biatrial OHT. Therefore, bicaval OHT should be considered as preferable technique for OHT.

INTRODUCTION

Orthotopic heart transplantation (OHT) remains the gold standard for patients with end-stage heart failure.[1] The standard biatrial OHT technique was introduced by Lower and Shumway in 1960[2] and is still widely used because of its relative simplicity. This technique only requires 2 anastomoses to the atria of the recipient. Yacoub and colleagues[3] introduced the bicaval OHT technique in 1989, and it has gained popularity since. The bicaval technique requires a single left atrial anastomosis and separate caval suture lines. However, controversy regarding the preferred surgical OHT technique remains. There is a broad variety of studies that describe potential differences in outcome between the 2 surgical techniques. The biatrial technique tends to be less technical challenging for cardiac implantation, which results in a reduced ischemic time of the allograft.[4,5] However, the biatrial technique is known for worse hemodynamics because of the redundant atrial tissue and an increased risk of atrial arrhythmias in the postoperative period. The bicaval technique is more complicated and, therefore, might require a longer operation times. However, the bicaval technique leads to improved hemodynamics and a lower incidence of atrial arrhythmias in the postoperative period.[6,7] Unfortunately, most reported studies are insufficiently powered to detect important differences. Therefore, a systematic review and meta-analysis was conducted to assess the possible advantages in early and late posttransplantation outcomes in patients who underwent biatrial OHT compared with bicaval OHT.

MATERIAL AND METHODS

Search Strategy

To establish an overview of reported outcome, a systematic literature search, according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines, was conducted (Supplemental Text 1).[8] Search terms were developed in collaboration with a dedicated librarian in our center. On December 15, 2017, Embase, MEDLINE, Cochrane, Web of Science, and Google Scholar were searched (search terms are provided in Supplemental Text 2). Inclusion and exclusion criteria were defined a priori. Randomized controlled trials and observational studies concerning adult patients undergoing OHT comparing the standard biatrial OHT and the bicaval OHT were included. Studies with less than 20 patients, poster publications, abstracts, and conference summaries were excluded. Studies with less than 20 patients were excluded because these studies were most likely early experiential series and do not reflect the general population. Posters and abstracts were not included because these formats did not undergo extensive peer reviewing. In the case of overlapping study populations, the study with the most patient-years of follow-up were selected. Exceptions were made for studies that reported on more outcomes of interest. Furthermore, non-English studies were excluded. Two

researchers (C.F.Z. and K.M.V.) independently reviewed abstracts and full texts in an unblinded standardized manner. In case of disagreement to include a study, an agreement was negotiated.

Data Extraction

Study design, year of surgery, 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 was not provided). The baseline characteristics extracted from the individual studies are displayed in Supplemental Table 1. In addition, the following procedural characteristics were extracted: cardiopulmonary bypass time, aortic cross-clamp time, length of hospital stay, and ischemic time. The following post-transplantation outcomes were extracted and documented as early (in-hospital or <30 day[s]) or late (out-of-hospital or >30 days): mortality, tricuspid regurgitation, mitral regurgitation, and pacemaker implantation. The length of hospital stay was defined as the day the patient received the OHT till the day the patient was dismissed from the hospital after the transplant. The individual study definitions were used to define the outcomes. Data were independently extracted by 2 authors (C.F.Z. and T.S.). The Newcastle–Ottawa Scale was used to assess the methodological quality of the studies.[9]

Statistical Analyses

Log-transformed inverse variance–weighted pooled baseline characteristics were calculated. To compare baseline and procedural characteristics, in cases of descriptive data, odds ratios (ORs) were used, and in cases of categorical data, mean differences were used. The ORs and mean differences were calculated with the use of a fixed-effects model, as the goal was to compute comparisons for the identified population, and not to generalize to other populations, and an assessment of baseline characteristics similar in most cases.[10] A *P* value less than .05 was considered statistically significant and a 95% confidence interval (CI) was calculated. Continuous data were presented as mean with 95% CI and discrete variables were presented as percentage with 95% CI. Random-effects models using the DerSimonian-Laird method were used to pool outcomes.[11] ORs were used for dichotomous data for early outcomes, and rate ratios (RRs) were used for dichotomous data for late outcomes. The Cochrane Q statistic and I^2 were used to assess heterogeneity. Egger's test and funnel plots were used to assess the risk of publication bias.[12] Comprehensive Meta-Analysis v2.2.064 (Biostat, Engelwood, NJ) 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 and colleagues.[13] The Engauge Digitizer v10.0[14] was used to create a list of coordinates of the KM curve, and an algorithm written in R (version 3.3.3; R Foundation for Statistical Computing, Vienna, Austria) was employed to reconstruct the original patient data. Thereafter, GraphPad Prism version 7.00 for Windows (GraphPad Software, San Diego, CA) was used to plot the pooled KM curve. The reconstructed data were used to

obtain hazard ratios (HRs) of late mortality in the biatrial and bicaval groups by univariable Cox regression. Thereafter, the HRs were pooled using Comprehensive Meta-Analysis. In order to evaluate whether studies before the year 2000 yielded different conclusions compared with contemporary studies, a subgroup analysis was performed.

RESULTS

The literature search resulted in 3648 studies, of which 45 articles met the inclusion criteria. Owing to overlapping data, 9 studies had to be excluded, resulting in 36 inclusions for the meta-analysis (Figure 1). References are represented together with the baseline characteristics of all individual studies in Supplemental Table 1 (References S1-S36). The meta-analysis included 6763 patients who had underwent OHT, of whom 3555 (52.6%) received a biatrial OHT and 3208 (47.4%) received a bicaval OHT. The median year of operation in the biatrial group was 1996 (range, 1988-2005) and in the bicaval group was 1998 (range: 1990-2005). Of the 36 studies, 32 were observational studies and 4 studies were randomized (References S1, S4, S14, and S17 in Supplemental Table 1). The biatrial group contained 1911 patients who had reported a mean follow-up time of 6.2 ± 8.8 years, encompassing 11,833 patient-years. The bicaval group contained 1935 patients who had reported a mean follow-up time of 6.5 ± 10.2

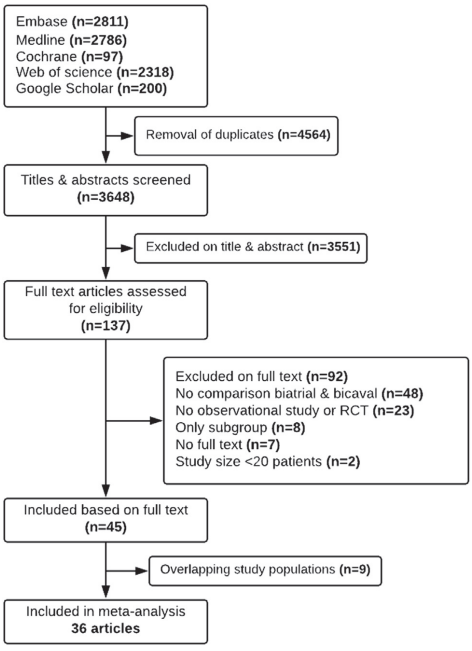

Figure 1. Flowchart of included studies in the meta-analysis.

years, encompassing 12,601 patient-years. All studies scored between 5 and 9 points on the Newcastle–Ottawa Scale and most studies lost points on comparability (Supplemental Table 1).

Baseline and Procedural Characteristics

Pooled baseline and procedural characteristics of the 6763 patients included in the meta-analysis are shown in Table 1.

Table 1. Pooled Baseline and Procedural Characteristics of Included Studies

Variable	Biatrial (n = 3555)	Bicaval (n = 3208)	OR/MD (95% CI)	*P* Value	Studies Reported	I^2 (%)
Age, y[a]	50.5 (50.0-51.0)	50.3 (49.8-50.8)	–0.63 (–1.42 to 0.16)	.118	23	54.0
Male, %[b]	82.6 (81.0-84.2)	77.6 (75.6-79.5)	1.31 (1.12 to 1.55)	.002	27	47.8
Systolic PAP, mm Hg[a]	40.7 (38.8-42.6)	41.7 (39.6-43.8)	–1.64 (–4.55 to 1.28)	.272	6	48.0
CVP, mm Hg[a]	5.37 (5.10-5.63)	3.48 (3.22-3.75)	1.01 (0.62 to 1.41)	<.001	9	76.6
Ischemic etiology, %[b]	39.5 (37.1-41.9)	36.8 (34.2-39.5)	1.10 (0.94 to 1.28)	.245	19	0.0
Diabetes, %[b]	29.6 (25.5-34.1)	26.6 (22.2-31.6)	1.10 (0.79 to 1.52)	.573	5	52.9
CPB, min[a]	116.5 (103.3-129.6)	126.8 (111.0-142.5)	–9.90 (–21.7 to 1.9)	.099	11	90.2
Aortic cross-clamp time, min[a]	64.7 (53.3-76.1)	75.0 (58.5-91.6)	–10.15 (–20.8 to 0.5)	.062	6	93.4
Ischemia time, min[a]	164.7 (162.8-166.6)	174.8 (165.8-183.9)	–16.7 (–27.7 to –4.3)	.007	25	93.8
Length of hospital stay, d[a]	26.2 (19.3-33.2)	25.1 (17.4-32.9)	1.07 (–2.82 to 4.95)	.590	7	70.0

[a]MD [b]OR

Values are median (interquartile range).

CI, confidence interval; CPB, cardiopulmonary bypass time; CVP, central venous pressure; MD, mean difference; OR, odds ratio; PAP, pulmonary artery pressure.

Early Outcomes

A forest plot containing the individual and pooled ORs for the early outcomes of mortality, tricuspid regurgitation, mitral regurgitation, and pacemaker implantation is presented in Figures 2A to 2D. The pooled early mortality in the biatrial group was 12.5% (95% CI, 8.3%-18.4%) and in the bicaval group was 8.8% (95% CI, 4.8%-15.5%), with an OR of 1.47 (95% CI, 1.0-2.2; *P* = .048). Furthermore, early moderate-to-severe tricuspid regurgitation, early moderate-to-severe mitral regurgitation, and need of early pacemaker implantation were observed more frequently in the biatrial OHT group (Table 2).

Table 2. Pooled Early and Late Outcomes

Outcome	Variable	Biatrial (n = 3555)	Bicaval (n = 3208)	OR/RR (95% CI)	*P* Value	Studies Reported	I^2 (%)
Early	Mortality	12.5 (8.30 to 18.4)	8.80 (4.8 to 15.5)	1.47 (1.0 to 2.2)[a]	.048	10	4.7
	Tricuspid regurgitation	42.8 (30.8 to 55.7)	28.5 (20.2 to 38.6)	1.92 (1.4 to 2.7)[a]	<.001	13	52.6
	Mitral regurgitation	11.1 (3.6 to 29.7)	6.9 (2.4 to 17.9)	2.13 (1.3 to 3.5)[a]	.002	6	12.1
	Pacemaker implantation	19.2 (12.2 to 28.7)	8.6 (4.8 to 15.0)	2.49 (1.5 to 4.2)[a]	.001	14	34.8
Late	Mortality	4.9 (1.1 to 8.7)	4.1 (0.3 to 7.8)	1.77 (1.2 to 2.6)[b]	.004	4	0
	Tricuspid regurgitation	6.3 (3.9 to 8.6)	1.2 (0.5 to 2.0)	2.14 (1.2 to 3.9)[b]	.014	8	79.5
	Mitral regurgitation	0.4 (–0.4 to 1.3)	0.4 (–0.3 to 1.0)	1.23 (0.6 to 2.4)[b]	.528	6	0
	Pacemaker implantation	3.3 (1.3 to 5.4)	1.4 (2.0 to 2.5)	1.93 (0.9 to 4.1)[b]	.083	8	41.5

[a]OR; [b]RR.

Values are % (95% CI) for early outcomes and linearized occurrence rate as percentage per patient year (95% CI) for late outcomes. CI, confidence interval; OR, odds ratio; RR; rate ratio.

Late Outcomes

The meta-analyses contained 10 studies (References S13, S14, S18, S21, S22, S26, S27, S32, S33, and S36 in Supplemental Table 1) that reported KM curves that could be pooled. The KM curves showed differences in late mortality between the biatrial and bicaval groups (Figure 3). The 2-year, 5-year, and 10-year survival rates were 80.0% ± 0.1%, 71.0% ± 0.1%, and 60.1% ± 0.2% in the biatrial group and 84.3% ± 0.01%, 76.8% ± 0.1%, and 71.2% ± 0.2% in the bicaval group, respectively. Pooled HR for late mortality showed a significantly higher risk in the biatrial group, with an HR of 1.32 (95% CI, 1.1-1.6; *P* = .008) and an I^2 of 38.0%. The linearized occurrence rates of late outcomes of the individual transplant groups are presented in Table 2. Data on late tricuspid regurgitation were reported in 8 studies and showed a significant difference in favor of the bicaval group, with a linearized occurrence RR of 2.14 (95% CI, 1.17-3.94; *P* = .014) (Supplemental Figure 1A). Late mitral regurgitation was reported in 6 studies, with a linearized occurrence RR of 1.23 (95% CI, 0.64-2.37; *P* = .528) (Supplemental Figure 1B). Late pacemaker implantation was reported in 8 studies and had a linearized occurrence RR of 1.93 (95% CI, 0.92-4.10; *P* = .083) (Supplemental Figure 1C).

Subgroup Analysis

Subgroup analysis of the 4 randomized controlled trials was only possible for early permanent pacemaker implantation, as other outcomes were reported in less than 3 individual studies and no pooling attempt was made. Early permanent pacemaker implantation was comparable

in these 3 studies. Subgroup analysis of the observational studies did not lead to a change in significance in any of the outcomes. Subgroup analyses of studies published before and after year 2000 did not lead in changes in significance in any of the outcomes.

Publication Bias and Sensitivity Analysis

Early and late outcomes did not show publication bias according to Egger's test. Funnel plots are presented in Supplemental Figures 2A to 2D for early outcomes and Supplemental Figures 3A to 3C for late outcomes. Leave-one-out sensitivity analysis did not change the significance of all outcomes.

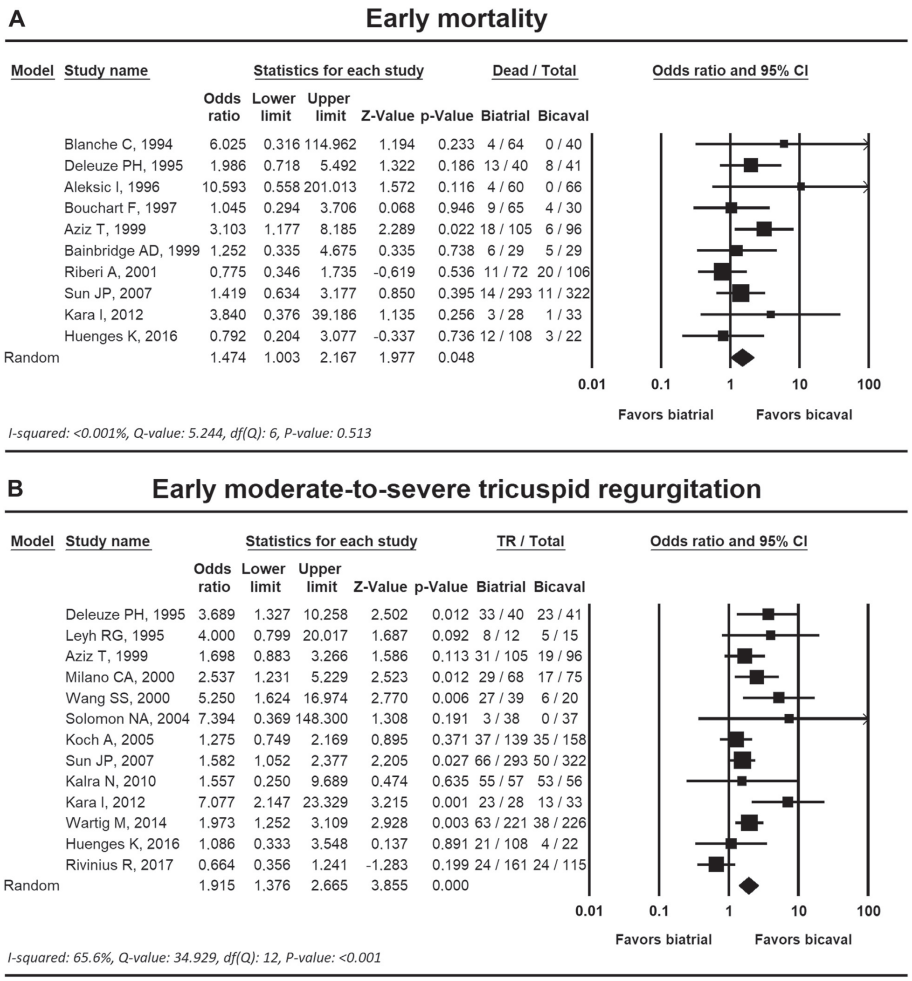

Figure 2. Forest plots of (A) early mortality, (B) moderate-to-severe tricuspid regurgitation (TR), (C) moderate-to-severe mitral regurgitation (MR), and (D) permanent pacemaker (PM) implantation. CI, confidence interval.

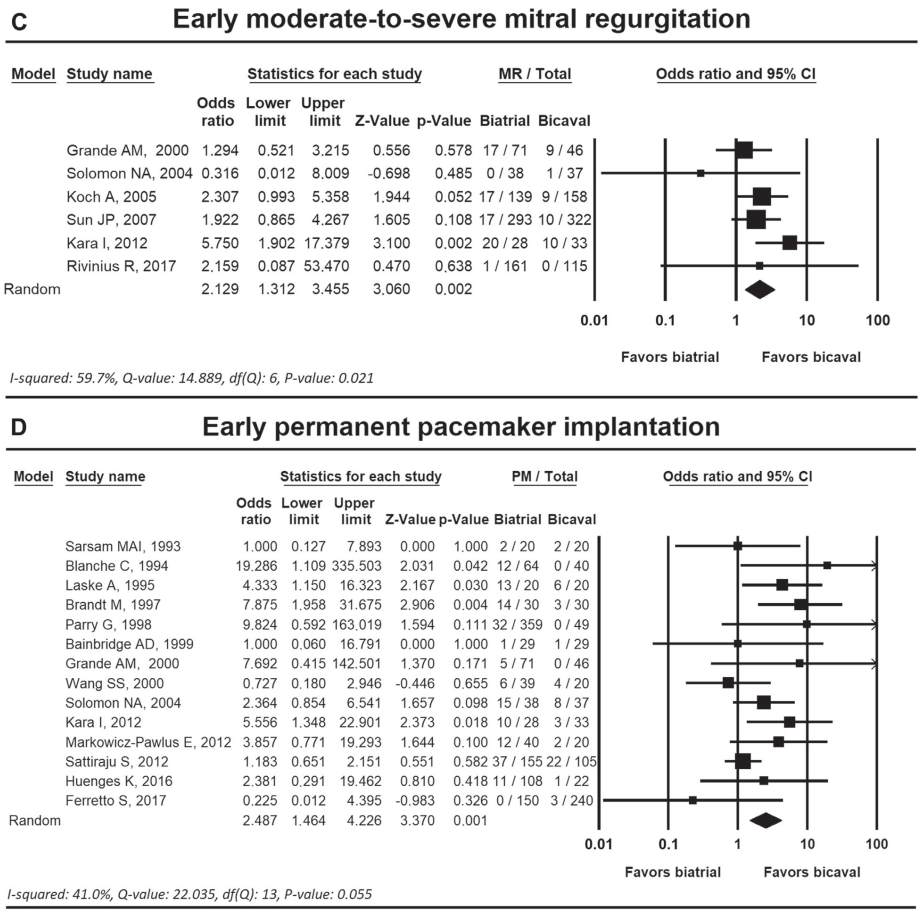

Figure 2. (continued).

COMMENT

This systematic review and meta-analysis shows that the bicaval technique is associated with superior early and late survival, less early and late tricuspid regurgitation, less early mitral regurgitation, and reduced early need of permanent pacemaker implantation.

Although bicaval OHT can be considered the preferable technique to perform an OHT, there are still many centers worldwide where the biatrial approach is preferred.[15] More than a decade ago, Schnoor and colleagues[6] performed a meta-analysis and concluded that early outcomes in the bicaval technique have beneficial effects in comparison with the biatrial technique. More recent overviews of the literature have presented similar conclusions.[16,17] However, little is known about the difference between these 2 techniques with regard to late outcomes.[6] Our meta-analysis confirms the association of the bicaval technique with better outcomes in the

short term. Moreover, this meta-analysis, with novel contemporary statistics, shows clinically relevant beneficial effects of the bicaval technique in the long term as well.

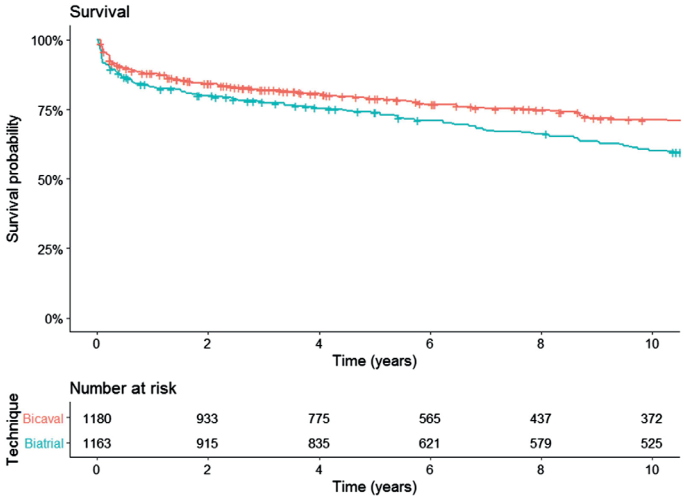

Figure 3. Pooled Kaplan-Meier curve of patient survival after bicaval (red) or biatrial (green) heart transplantation.

Ischemia Time

There was a significant difference in the ischemia time between the 2 transplanted groups. Although statistically different, the absolute time difference was only 10 minutes. Cardiopulmonary bypass time and aortic cross-clamp time did not differ significantly. The prolonged ischemia time could be explained by the duration of transport or waiting time before or during the operation. In a retrospective study, Russo and colleagues[18] reviewed ischemia time in 33,640 OHT recipients in the United Network for Organ Sharing (UNOS) database performed between 1987 and 2004 and found no difference in long-term survival (10 years) between prolonged ischemia time (3.50-5.49 hours) and limited ischemia time (0.00-3.49 hours). Taking these observations into account, it seems implausible that a 10-minute difference would lead to major changes in postoperative outcomes. Nevertheless, as in some selected cases, such as in reoperative heart transplantation or abnormal caval veins, a biatrial approach may still be preferred.

Mortality

A significant difference was found in both early mortality and late survival between the 2 transplanted groups in favor of the bicaval group. Davies and colleagues[19] reviewed the UNOS database data between 1997 and 2007 and reported a higher survival rate in the bicaval vs biatrial group after 10 years (57.4% vs 51.1%). The survival rate in the present meta-analysis is

higher when compared with Davies and colleagues (71.2% vs 60.1%).[19] This could be due to the fact that Davies and colleagues[19] used the UNOS database, whereas the individual studies in this meta-analysis mostly reviewed their own patients. Thereby, a strong improvement of the posttransplant care has been seen in the last decade, which has resulted in increased long-term survival.[20] However, both our meta-analysis and the registry study provide a higher survival rate in the bicaval group after 10 years of follow-up.

Tricuspid Regurgitation

This study shows a significant difference in early and late tricuspid regurgitation in favor of the bicaval group. Moderate-to-severe tricuspid regurgitation is usually caused by donor-recipient size mismatch, right ventricular failure due to pretransplant pulmonary hypertension, and right ventricular dysfunction due to donor heart rejections.[21] The cause of donor-recipient size mismatch is mainly a problem of the atria, and the biatrial technique may induce tricuspid regurgitation due to changes in atrial geometry. The bicaval technique only uses the left atrium and both caval veins to perform the anastomosis and, therefore, the technique may prevent tricuspid regurgitation.[3] Moreover, moderate-to-severe tricuspid regurgitation after OHT could also been caused by torn leaflets and ruptured chordae due to surveillance endomyocardial biopsies in the years after transplantation.[22,23] It has been shown that patients with no or mild tricuspid regurgitation have better survival than do those with moderate or severe tricuspid regurgitation.[24] Moderate-to-severe tricuspid regurgitation was, as confirmed byour analysis, reportedmore often in the biatrial group and therefore could have contributed to a higher mortality rate in this group.[25-27] However, the optimal treatment of posttransplant severe tricuspid regurgitation is very cumbersome and still not well defined. Generally, because severe tricuspid regurgitation remains asymptomatic for a long time, it is not unusual that conservative treatment is preferred to surgical treatment, probably missing the optimal timing of tricuspid surgery.[28] Therefore, reduction of occurrence of tricuspid regurgitation by bicaval OHT might be a suitable approach for this post-OHT problem.

Mitral Regurgitation

Mitral regurgitation post OHT is still not well studied. Mitral regurgitation could be caused by a mismatch in size between the donor heart and native heart, early allograft rejection, left ventricular failure after OHT, and a dilated left atrium.[29-31] In our study, early mitral regurgitation occurred more frequently in the biatrial transplant group (Figure 2D). However, in late outcomes, no mitral regurgitation was observed. The treatment of mitral regurgitation depends on the severity and symptoms of the patients. Symptomatic severe mitral regurgitation is associated with excess mortality and frequent heart failure.[32,33] Despite these poor outcomes, only a minority of the affected patients undergo some kind of treatment.[32]

Permanent Pacemaker Implantation

Early after OHT, sinus node dysfunction and atrioventricular conduction abnormalities are frequently encountered, with some cases in need of permanent pacemaker implantation.[34] Increased ischemic time, a higher donor age, frequent episodes of rejection, and the anatomy of the blood supply to the sinoatrial node are denoted as causes of sinus node and atrioventricular conduction abnormalities after OHT.[35-39] However, the most commonly stated cause is surgical trauma at time of transplantation.[40] Our systematic review and meta-analysis confirms this hypothesis, showing a significant decrease in requirement of early permanent pacemaker implantation in the bicaval group. This is in line with the retrospective study of Davies and colleagues[19] that showed a higher early pacemaker implantation risk in patients who underwent the biatrial OHT vs bicaval OHT after discharge from the hospital (5.1%vs. 1.9%). Although Davies and colleagues[19] also found a higher rate of late pacemaker implantation in the biatrial group, this could not be confirmed in the present study. This may be explained by the fact that only a few studies reported late permanent pacemaker implantation, resulting in insufficient power to show a difference. Another explanation could be that the differences in pacemaker implantation are only presented in the early postoperative period and become comparable with a longer follow-up period. This was also observed by Herre and colleagues,[34] who noted comparable findings to this meta-analysis.

Strengths and Limitations

The majority of studies were retrospective in nature, which made them prone to selection bias.[41] This was confirmed by the fact that most studies scored 6 points on the Newcastle–Ottawa Scale and no points on comparability. Publication bias may have led to an underestimation of the pooled estimates when studies with relatively poor outcomes are not published. However, funnel plots and the Egger's test found no indication for the presence of publication bias. Notwithstanding, some publication bias may be present based on visual inspection of the funnel plots. There was moderate-to-substantial heterogeneity between studies in most outcomes, which may potentially have led to inaccurate results. Another limitation was caused by the limited availability of posttransplant clinical data about the number and severity of rejections and cardiac transplant vasculopathy in the 2 groups, as these factors are known to influence the long-term prognosis. Furthermore, studies over a large time span were included in the meta-analysis. Nevertheless, subgroup analyses yielded comparable outcomes of both older and contemporary studies.

Conclusion

This systematic review with meta-analysis provides ample evidence that bicaval OHT is associated with better early and late clinical outcomes, including early and late survival, prevention of tricuspid regurgitation, and need of permanent pacing.

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SUPPLEMENTARY MATERIAL

CONTENT

Supplementary Text 1, Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist:

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	X
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	21/22
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5

Supplementary Text 1, Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist: (continued)

Section/topic	#	Checklist item	Reported on page #
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	22/23/24
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	25/26/27
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	15/16/24/25
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	16/17
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	16/17
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

SUPPLEMENTARY TEXT 2, SEARCH OF THE LITERATURE:

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('heart transplantation'/exp OR 'cardiac graft rejection'/de OR 'cardiac allograft vasculopathy'/de OR (((heart* OR cardiac) NEXT/1 (transplant* OR allotransplant* OR homotransplant* OR graft* OR homograft* OR allograft*))):ab,ti,kw) AND ('biatrial heart transplantation'/de OR 'bicaval heart transplantation'/de OR 'orthotopic transplantation'/de OR (('intermethod comparison'/de OR 'heart atrium'/exp OR 'cava vein'/exp) AND 'surgical technique'/de) OR (biatrial* OR bicaval* OR orthotopic* OR intermethod* OR ((surgical* OR operat*) NEAR/6 (method* OR technique* OR approach*) NEAR/6 compar*) OR (technique* NEAR/6 compar*) OR (left NEAR/3 right NEAR/3 (atrium OR atria)) OR (inferior* NEAR/3 superior*)):ab,ti,kw) NOT ([animals]/lim NOT [humans]/lim) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) AND [english]/lim

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(Heart Transplantation/ OR (((heart* OR cardiac) ADJ (transplant* OR allotransplant* OR homotransplant* OR graft* OR homograft* OR allograft*))).ab,ti,kw.) AND (((Methods/ OR Methods.fs.) AND (exp Heart Atria/ OR exp Venae Cavae/)) OR (biatrial* OR bicaval* OR orthotopic* OR intermethod* OR ((surgical* OR operat*) ADJ6 (method* OR technique* OR approach*) ADJ6 compar*) OR (technique* ADJ6 compar*)).ab,ti,kw.) NOT (exp animals/ NOT humans/) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt. AND english.la.

Cochrane CENTRAL 97

((((heart* OR cardiac) NEXT/1 (transplant* OR allotransplant* OR homotransplant* OR graft* OR homograft* OR allograft*))):ab,ti,kw) AND ((biatrial* OR bicaval* OR orthotopic* OR intermethod* OR ((surgical* OR operat*) NEAR/6 (method* OR technique* OR approach*) NEAR/6 compar*) OR (technique* NEAR/6 compar*) OR (left NEAR/3 right NEAR/3 (atrium OR atria)) OR (inferior* NEAR/3 superior*)):ab,ti,kw)

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TS=(((((heart* OR cardiac) NEAR/1 (transplant* OR allotransplant* OR homotransplant* OR graft* OR homograft* OR allograft*)))) AND ((biatrial* OR bicaval* OR orthotopic* OR intermethod* OR ((surgical* OR operat*) NEAR/5 (method* OR technique* OR approach*) NEAR/5 compar*) OR (technique* NEAR/5 compar*) OR (left NEAR/2 right NEAR/2 (atrium OR atria)) OR (inferior* NEAR/2 superior*))) NOT ((animal* OR rat OR rats OR mouse OR mice OR murine OR dog OR dogs OR canine OR cat OR cats OR feline OR rabbit OR cow OR cows OR bovine OR rodent* OR sheep OR ovine OR pig OR swine OR porcine OR veterinar* OR chick* OR zebrafish* OR baboon* OR nonhuman* OR primate* OR cattle* OR goose OR geese OR duck OR macaque* OR avian* OR bird*) NOT (human* OR patient*))) AND DT=(article) AND LA=(english)

Google scholar

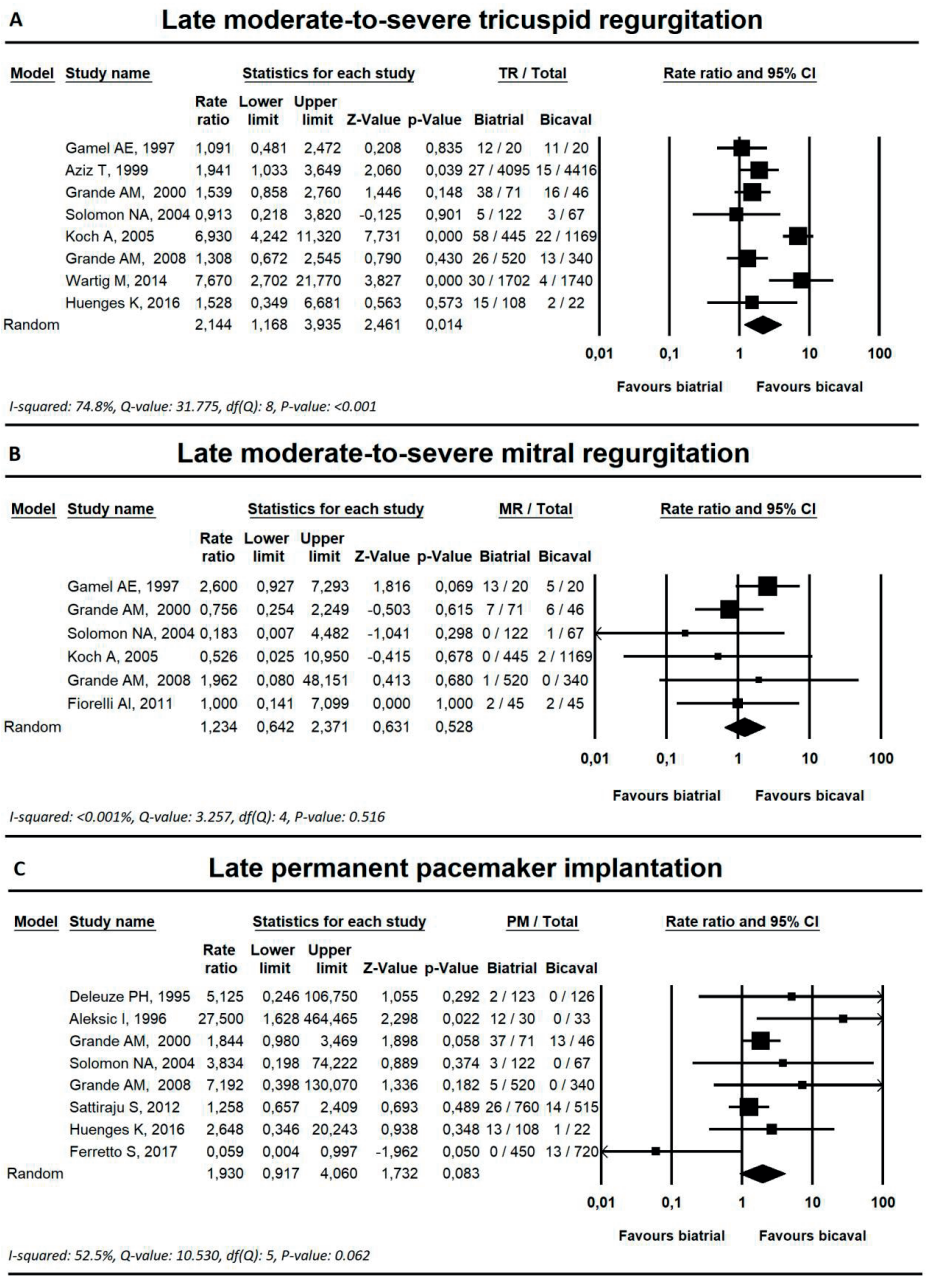
"heart|cardiac transplantation|allotransplantation|homotransplantation|graft|homograft|allograft" biatrial|bicaval -pig -animal -nonhuman -canine

Supplementary Table 1: Baseline characteristics of the individual studies including study references (S1-S36).

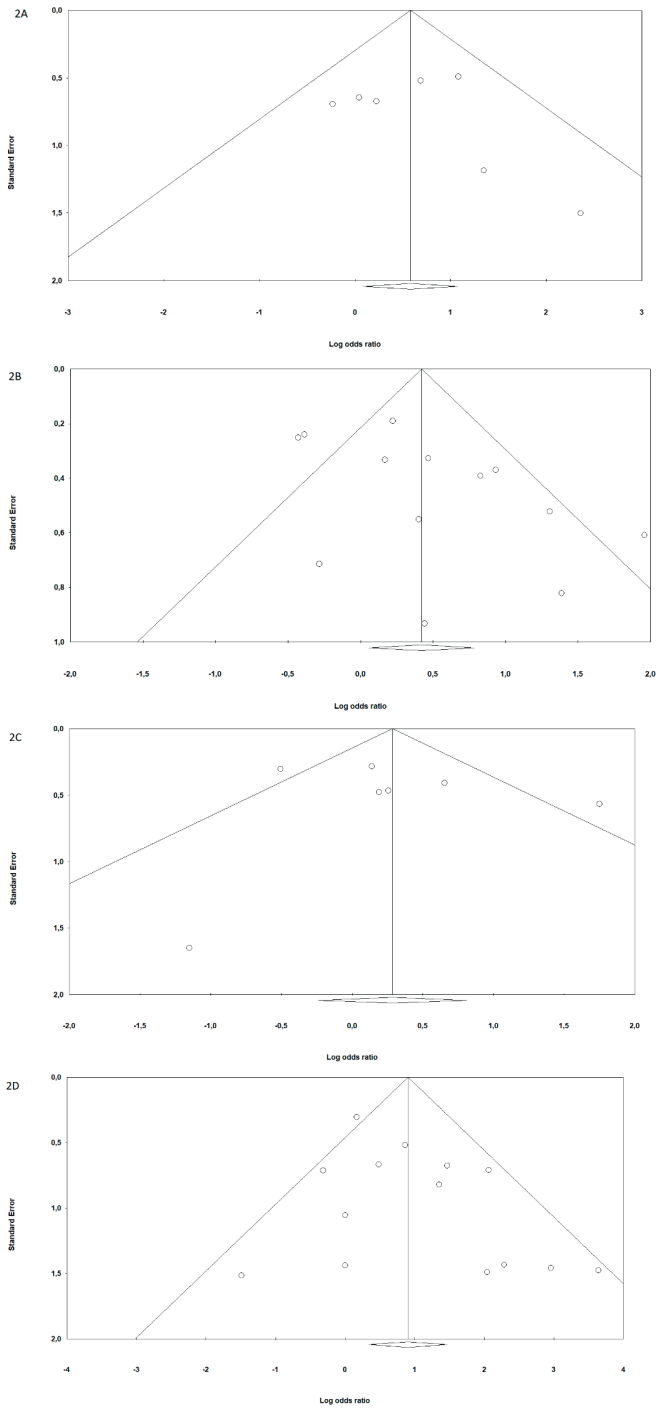
Publication, Supplementary Material Reference (S)	Year	Design	Group size, n (biatrial/ bicaval)	Male % (biatrial/ bicaval)	Ischemic aetiology % (biatrial /bicaval)	Follow-up, years (biatrial/ bicaval)	Median year of operation (biatrial /bicaval)	Points in Newcastle-Ottawa-Scale (Selection/ Comparability/ Outcome)
Sarsam M.A.I. et al., S1	1993	Prospective randomized	20 / 20					4 / 0 / 2
Bizouarn P. et al., 1994, S2	1994	Retrospective cohort	11 / 9	91 / 100	73 / 56	0.0055 / 0.0055	1991.5 / 1991.5	4 / 0 / 2
Blanche C. et al., S3	1994	Retrospective cohort	64 / 40	83 / 93	59 / 65		1989.5 / 1992	4 / 0 / 2
Deleuze P.H. et al., S4	1995	Prospective randomized	40 / 41	80 / 83	38 / 39	3.08 / 3.08	1992 / 1992	4 / 0 / 3
Laske A. et al., S5	1995	Prospective cohort	20 / 20	90 / 80	35 / 40			4 / 0 / 1
Leyh R.G. et al., S6	1995	Retrospective cohort	12 / 15	83 / 93				4 / 0 / 2
Aleksic I. et al., S7	1996	Retrospective cohort	60 / 66	82 / 92		0.5 / 0.5	1990 / 1992.5	4 / 0 / 2
Gamel A.E. et al., S8	1997	Retrospective cohort	20 / 20	65 / 75	55 / 45	1 / 1	1993.5 / 1993.5	4 / 0 / 2
Beniaminovitz A. et al., S9	1997	Retrospective cohort	10 / 10					4 / 0 / 1
Bouchart F. et al., S10	1997	Retrospective cohort	65 / 30		32 / 23		1990.5 / 1990.5	4 / 0 / 1
Brandt M. et al., S11	1997	Retrospective cohort	30 / 30	87 / 90		0.75 / 0.75	1992.5 / 1992.5	4 / 0 / 3
Parry G. et al., S12	1998	Retrospective cohort	359 / 49	84 / 84				4 / 0 / 2
Aziz T et al., S13	1999	Retrospective cohort	105 / 96	84 / 88	56 / 66	39 / 46	1993.5 / 1993.5	4 / 0 / 3
Bainbridge A.D. et al., S14	1999	Prospective randomized	29 / 29	86 / 86				4 / 0 / 2
Grande A.M. et al., S15	2000	Retrospective cohort	71 / 46	80 / 80	35 / 30	1 / 1		4 / 0 / 3
Milano C.A. et al., S16	2000	Retrospective cohort	68 / 75	76 / 75	46 / 53		1993 / 1997	4 / 0 / 1
Wang S.S. et al., S17	2000	Prospective randomized	39 / 20	72 / 75	28 / 35		1998 / 1998	4 / 0 / 1

Supplementary Table 1: Baseline characteristics of the individual studies including study references (S1-S36). (continued)

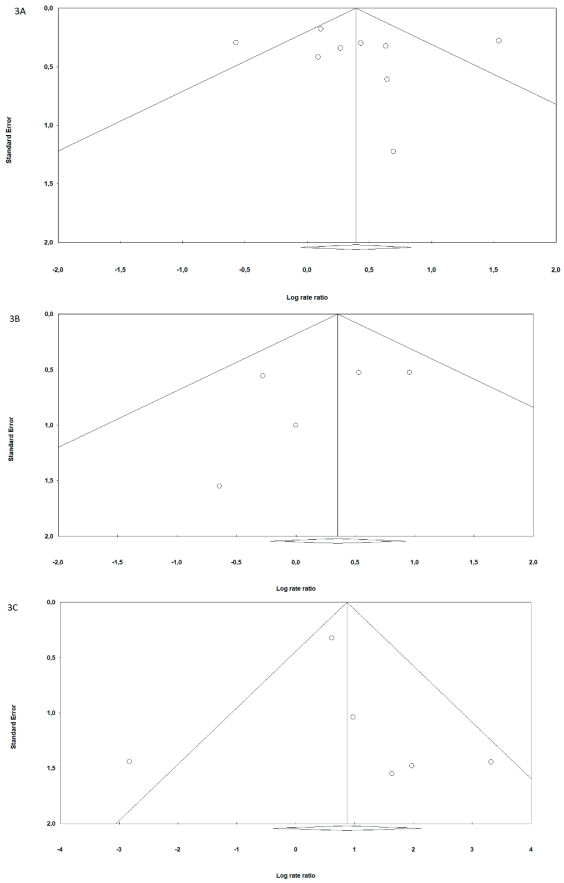
Publication, Supplementary Material Reference (S)	Year	Design	Group size, n (biatrial/ bicaval)	Male % (biatrial/ bicaval)	Ischemic aetiology % (biatrial /bicaval)	Follow-up, years (biatrial/ bicaval)	Median year of operation (biatrial /bicaval)	Points in Newcastle-Ottawa-Scale (Selection/ Comparability/ Outcome)
Riberi A. et al., S18	2001	Retrospective cohort	72 / 106			8.7 / 5.9	1992 / 1992	4 / 0 / 3
Solomon N.A. et al., S19	2004	Retrospective cohort	38 / 37	76 / 81	32 / 30	3.2 / 1.8	1998.5 / 1998.5	4 / 0 / 3
Koch A. et al., S20	2005	Retrospective cohort	139 / 158		30 / 27	3.2 / 7.4	1996 / 1996	4 / 0 / 3
Park K.Y. et al., S21	2005	Retrospective cohort	13 / 25	77 / 68	8 / 12		1995 / 1999.5	4 / 0 / 3
Sun J.P. et al., S22	2007	Retrospective cohort	293 / 322	92 / 73	38 / 33	3.8 / 3.8	1998.5 / 1998	4 / 2 / 3
Grande A.M. et al., S23	2008	Retrospective cohort	52 / 34	83 / 82		10 / 10	1996 / 1996	4 / 0 / 3
Kalra N. et al., S24	2010	Retrospective cohort	57 / 56	70 / 73				4 / 0 / 2
Fiorelli A.I. et al., S25	2011	Retrospective cohort	15 / 15	87 / 60	40 / 20	3 / 3	1992 / 2004.5	4 / 0 / 3
Jung S.H. et al., S26	2011	Retrospective cohort	53 / 148			6.4 / 6.4	2000 / 2000	4 / 0 / 3
Dell'Aquila A.M. et al., S27	2012	Retrospective cohort	117 / 99	89 / 93	50 / 58	10.5 / 5.2	1998.5 / 1998.5	4 / 0 / 3
Kara I. et al., S28	2012	Retrospective cohort	28 / 33	86 / 79			1998.5 / 1998.5	4 / 0 / 2
Markowicz-Pawlus E. et al., S29	2012	Retrospective cohort	40 / 20					4 / 0 / 1
Sattiraju S. et al., S30	2012	Retrospective cohort	155 / 105	79 / 75		4.9 / 4.9	2002 / 2002	4 / 2 / 3
Kim G.S. et al., S31	2014	Retrospective cohort	53 / 148				2000 / 2000	4 / 0 / 3
Wartig M. et al., S32	2014	Retrospective cohort	221 / 226	80 / 73	33 / 23	7.7 / 7.7	1996.5 / 1996.5	4 / 2 / 3
Huenges K et al., S33	2016	Retrospective cohort	108 / 22	82 / 95	45 / 41	1 / 1	2005 / 2005	4 / 0 / 3
Ferretto S. et al., S34	2017	Retrospective cohort	150 / 240	87 / 80		3 / 3	1999 / 1999	4 / 0 / 2
Mallidi H.R. et al., S35	2017	Retrospective cohort	767 / 683				1998 / 1998	4 / 0 / 2
Rivinius R. et al., S36	2017	Retrospective cohort	161 / 115	81 / 72	32 / 32	0.08 / 0.08	2000.5 / 2000.5	4 / 2 / 3



Supplementary Figure 1: (A-C) Forest plots of late moderate-to-severe tricuspid regurgitation (A), moderate-to-severe mitral regurgitation (B) and permanent pacemaker implantation (C). CI: confidence interval; TR: tricuspid regurgitation; MR: mitral regurgitation; PM: permanent pacemaker implantation.



Supplementary Figure 2: (A-D) Funnel plots of early mortality (A), early tricuspid regurgitation (B), early mitral regurgitation (C) and early permanent pacemaker implantation (D).



Supplementary Figure 3: (A-C) Funnel plots of late tricuspid regurgitation (A), late mitral regurgitation (B) and late permanent pacemaker implantation (C).

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