Bicaval versus standard technique in orthotopic heart transplantation: A systematic review and meta-analysis

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Supplemental material is available online.

Objective: We aimed to evaluate and compare the efficacy of the bicaval and the biatrial standard techniques in orthotopic heart transplantation.

Methods: A systematic review with meta-analysis was performed. As data sources, we used the electronic databases EMBASE and Medline (1966–August 2006), hand searching in 4 journals, expert consultation, and reference lists of reviews. Observational and randomized and prospective and retrospective controlled trials that reported outcomes on the 2 techniques of heart transplantation were considered.

Results: A total of 23 retrospective and 18 prospective studies were included. Meta-analyses of prospective trials including between 228 and 472 patients revealed significant superiority of the bicaval technique in comparison with the biatrial procedure for early atrial pressure (weighted mean difference, −3.95; 95% confidence interval, −6.50 to −1.40), perioperative mortality (odds ratio, 0.41; 95% confidence interval, 0.17 to 0.98), tricuspid valve regurgitation (odds ratio, 0.23; 95% confidence interval, 0.15 to 0.36), and sinus rhythm (odds ratio, 7.01; 95% confidence interval, 2.57 to 19.13). The latter also showed a significant difference in the analysis of retrospective studies (odds ratio, 2.69; 95% confidence interval, 1.55 to 4.66).

Conclusion: In summary, this systematic review and meta-analysis provides evidence of clinically relevant beneficial effects of the bicaval technique in comparison with those of the standard technique. Nevertheless, the longer-term beneficial effects of the bicaval technique remain to be evaluated.

Since the first reported case in 1967,[1] heart transplantation has become the treatment of choice for patients with end-stage heart failure. Today, more than 3000 heart transplantations are performed yearly worldwide.[2] During several decades, the biatrial or standard technique for orthotopic cardiac transplantation, based on the description of Cass and Brock[3] and Lower and Shumway,[4] has been used successfully. This technique requires, to some extent, the excision of the posterior part of the donor left atrium and incision of the right atrium from the inferior vena cava toward the right atrial appendage to avoid injury of the sinus node. The atrial anastomoses can be performed straightforward, reducing from 8 possible single-vessel anastomoses for complete transplantation to 4. However, there are theoretic disadvantages with this standard technique, including enlarged, figure-of-eight configured right and left atria probably interfering with their contractile and electrophysiologic, as well as tricuspid and mitral valve, functions.[5] Two alternative techniques of orthotropic heart transplantation were developed and introduced into clinical practice around 1990 to overcome these potential imperfections. In 1989, Banner and colleagues,[6] from the Harefield Group, introduced the total transplantation technique that preserves the integrity of both the donor atria by anastomosing pulmonary veins as a cuff on each side of the heart and also the vena cava separately. Sievers and co-workers,[7] in 1991, and the Wythenshawe group,[8] in 1993, introduced into clinical practice the bicaval transplantation technique, which is characterized by 2 arterial, 1 left atrial, and 2 caval anasto-

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Abbreviation and Acronym
CI = confidence interval

moses, preserving the right atrium intact and leaving only a small posterior part of recipient left atrial tissue between both pulmonary veins.

There are several studies comparing these 3 different techniques of orthotopic heart transplantation that have also been summarized in recent reviews.[9-11] It is essential to summarize and appraise the available studies under the rigorous methods of evidence-based medicine to help in the decision making on what technique should be preferred. This has not been done thus far.

We therefore aimed to compare the more recent bicaval heart transplantation techniques (Figure 1),[6,7] both combined under the term "bicaval techniques," with the standard procedure (Figure 1) for clinically relevant outcomes and, by implementing the methods of a systemic review and meta-analysis, to achieve the best available level of evidence for that subject.

Materials and Methods

Data Collection

To obtain the most comprehensive evidence base, we implemented 4 independent literature search strategies: a search in electronic databases, hand searching, consultation of an experienced cardiovascular surgeon (HHS), and reference lists of recent reviews.

We conducted a literature search in PubMed and the database of the German Institute of Medical Documentation and Information, including EMBASE and Medline, from 1966 through August 2006 using the following search strategy: [("heart transplantation") OR ("cardiac transplantation") AND bicaval]. In addition, the Cochrane library of systematic reviews was visited.

For a hand search, the 4 journals (*The Annals of Thoracic Surgery, The European Journal of Cardiothoracic Surgery, The Journal of Heart and Lung Transplantation*, and *The Journal of Thoracic and Cardiovascular Surgery*) that provided the most

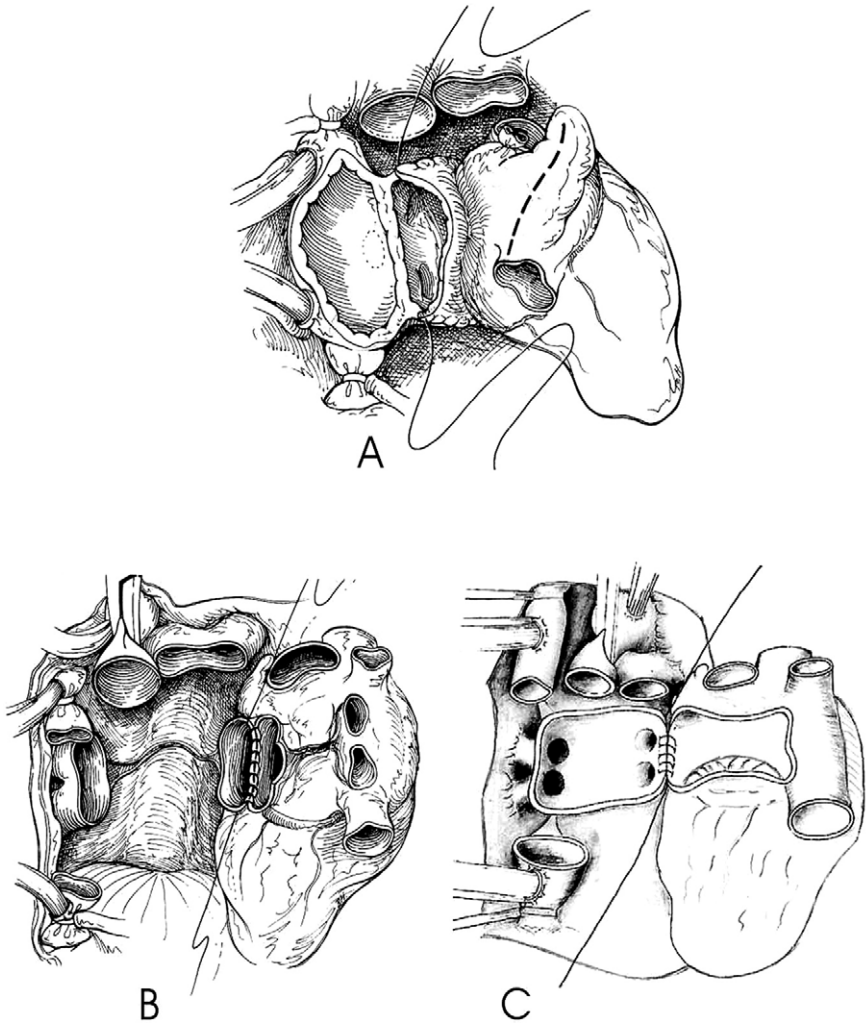

Figure 1. Schematic drawings of the standard biatrial heart transplantation technique (A)[6] and the 2 bicaval techniques (B[6] and C[7]), both preserving the right atrium intact.

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studies on the use of the bicaval technique thus far were identified. A hand search was then performed for the period from 1999 through June 2005.

In addition, HHS was asked to give hints on further literature and research groups that were not covered by the achieved studies. Furthermore, the reference lists of recent reviews were checked for relevant literature. Studies had to evaluate orthotopic heart transplantation by using the bicaval technique to be eligible for inclusion.[6,7] We included only studies in the English or German languages. The search was not limited to randomized controlled trials. Observational controlled and uncontrolled, prospective and retrospective studies were included. The search was not age restricted. We excluded letters, comments, case reports and series, and nonhuman studies.

A 2-stage filter process applying the eligibility criteria was implemented by screening titles and abstracts first and then full texts. Both stages of the filter process were performed independently by 2 investigators (DL, TS). Results were then compared and showed identical results.

Data Extraction and Critical Appraisal

The data extraction and critical methodologic appraisal of the included studies was undertaken by MS. Levels of evidence were assigned to each study according to the Oxford Centre of Evidence-based Medicine. For the detailed methodologic assessment, a standardized form, which was developed on the basis of the Scottish Intercollegiate Guideline Network checklist, and an evaluation sheet of the German Institute for Quality and Efficiency in Health Care were used. Both are standardized instruments for the quality assessment of randomized controlled trails. The extracted information included lead author, publication year, intervention and observation period, study group characteristics (number, sex, and age), indication, criteria of inclusion and exclusion, techniques of the operation, statistical methods, outcomes, and adverse events. Quantitative results, either as means and standard deviations or rates, were summarized in tables.

With respect to the methodologic quality of the study, we further appraised the randomization process (sequence generation and allocation concealment), blinding, statistical methods, baseline characteristics of both groups, and handling of losses to follow-up.

Outcome Measures

All reported outcomes were retrieved and could be divided into 3 groups. The first group included clinically relevant outcomes, which were assessed in more than 2 studies in a comparable way and on which a meta-analysis could be performed. This group included intraoperative ischemic time of transplantation, permanent pacemaker insertion, early mortality (30-day mortality), 1-year survival, 3-year survival, duration of hospital stay, and atrial pressure in the early postoperative period. Furthermore, tricuspid valve regurgitation and sinus rhythm after cardiopulmonary bypass, although measured at different time points in prospective studies (Table E1), were considered.

A second group included outcome parameters that were determined in few studies only or at different time points: pulmonary vascular resistance, hemodynamic parameters (eg, pulmonary artery pressure, systolic blood pressure, right atrial pressure, cardiac index, and cardiac output), tricuspid valve regurgitation examined in retrospective studies, mitral valve regurgitation, need for a temporary pacemaker, and duration of intensive care unit stay.

The last group included outcomes that were determined only in single studies, such as the hemodynamic vasomotor responses to lower body negative pressure. These results were not considered in our review.

Statistical Analyses

We reported and summarized descriptive results as either means or rates according to the original publications. Meta-analyses were performed for outcomes as mentioned above for prospective and retrospective controlled trials separately. The software RevMan 4.2 (Cochrane Collaboration, http://www.cc-ins.net/RevMan/) was used for these analyses. Odds ratios or weighted differences of the means and corresponding 95% confidence intervals (CIs) were reported as measures of association and stability. Heterogeneity among studies for every outcome was assessed by using the Cochrane Q test. Fixed-effect models were chosen in case no significant heterogeneity among studies was observed. Otherwise, random-effect models are presented. Sensitivity analyses were performed by comparing random and fixed-effect models, evaluating the effect of omitting influential studies, presenting funnel blots for parameters in which fixed-effect models were used with more than 3 included studies, and omitting studies with overlapping patient samples.

Results

Literature Search

PubMed revealed 90 and EMBASE and Medline revealed 95 potentially relevant studies. Duplicates were excluded, and a total of 95 references remained. In addition, 9 studies were provided by HHS, and 5 studies were identified by hand searching. Overall, 109 publications were retrieved. In the 2 screening processes 38 and 30 studies were excluded for reasons that are given in detail in Figure 2. Finally, we included 41 studies in our review.[E1-E41]

Description of the Studies

The descriptive characteristics of the included 23 retrospective and 18 prospective studies, as well as the levels of evidence, are given in Tables 1 and 2, respectively. Four retrospective and 2 prospective trials were studies without a control group. The transplantation techniques could be divided into the standard technique described by Cass and Brock[3] and Lower and Shumway[4] and the bicaval technique introduced by Sievers and colleagues[7] (n = 30) or Banner and associates[6] (n = 9). In 2 studies the bicaval technique was not explained in detail.[E1,E2] Overall, the retrospective studies included 753 patients undergoing heart transplantation by means of the standard technique, 203 patients undergoing heart transplantation according to the method of Banner and associates,[6] and 517 patients undergoing heart transplantation according to the method of Sievers and colleagues.[7] The prospective studies included 318 patients with the standard technique and 305

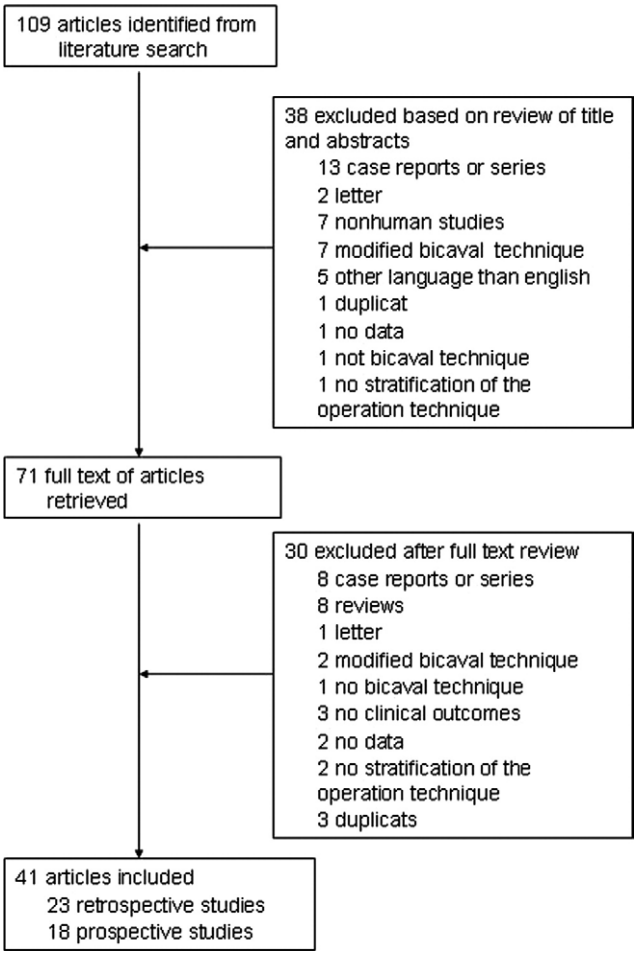


Figure 2. Flow chart of study selection.

patients with the bicaval technique.[7] One study included 10 patients receiving the bicaval technique but did not specify the transplantation technique. Several studies were carried out in the same setting and investigated in part the same study population but different outcomes. Five of the retrospective studies[E3-E7] were conducted in the Cedars-Sinai Medical Centre, Los Angeles, California. One of the prospective[E8] and one of the retrospective[E9] studies were conducted at the University of Pavia, Italy. We included 4 prospective studies of the Whythenshawe Hospital in Manchester, United Kingdom.[E10-E13] Two prospective studies[E14,E15] were performed at the Temple University Hospital in Philadelphia, Pennsylvania, but at different times, and 3 studies were performed at the University of Kiel, Germany.[12,E16-E18] Because of overlapping study periods, only the study with the longest study period was considered.

The mean age of the population of the included studies ranged between 14.8 and 58.0 years, and the proportion of men was about 80%. The most frequent indications for receiving orthotopic heart transplantation were ischemic or dilated cardiomyopathy and valvular heart diseases.

Methodologic Quality

Prospective studies. Most of the studies had potential or obvious methodologic limitations. Two of the included 18 prospective studies were uncontrolled trails. In 9 studies the study population was randomized to the operation technique, in most of them (n = 8) on an alternate basis. The latter cannot be considered as adequate because the allocation was foreseeable. One study did not describe the randomization technique at all. The study population consisted of less than 20 patients per group in 8 studies. Two studies failed to give information about inclusion or exclusion criteria. The time between transplantation and observation was shorter in the bicaval group compared with the standard group in 4 studies. For 2 studies the observation time point is unknown. Another 2 studies did not give information on the indication for transplantation. In all but 2 controlled studies,[E14,E19] the study groups (bicaval and standard) were comparable regarding age, sex and preoperative parameters. One study[E14] showed a significant age difference between study groups, and the other study[E19] reported a significant difference in the preoperative right atrial pressure.

Retrospective studies. We included 23 retrospective studies in our review. Four of the studies were not controlled by a patient group undergoing heart transplantation by means of the standard technique. In 9 studies the allocation to a study group occurred by pseudorandomization (time intervals). Some centers compared the time periods before and after the introduction of the bicaval technique. In 3 studies the observation period was shorter for the bicaval group than for the standard group. Four studies reported no exact observation period. In 4 studies the sample size was small (<20 patients per group). Inclusion and exclusion criteria were given in 15 studies, and the indication for heart transplantation was given in another 15 studies.

Outcomes

Meta-analyses. The results of the meta-analyses are displayed in Figure 3 for prospective and Figure E1 for retrospective studies.

The intraoperative ischemic time was longer in patients undergoing bicaval techniques. For prospective studies, a nonsignificant weighted mean difference of 3.7 minutes was obtained (Figure 3, *A*). The 7 included retrospective studies showed heterogeneity and resulted in a nonsignificant difference of 15.8 minutes (Figure E1, *A*).

The summary of 3 prospective studies each proved a significantly reduced early atrial pressure of 4.0 mm Hg (Figure 3, *B*) and a significantly reduced perioperative mortality of 59% (relative risk reduction; Figure 3, *C*) by means of the bicaval technique. The proportion of patients with

TABLE 1. Basic characteristics of included retrospective studies

No.	Author	Publication year	Country	Operative technique	No. of cases	Age	Sex (male)	Level of evidence
1	Grande and coworkers[E9]	2000	Italy	Standard	71	50.4 ± 13.4 y	79%	2b
				Bicaval (S)	46	50.9 ± 10.8 y	80%	
2	Wang and coworkers[E1]	2003	Canada	Standard	48	51.1 y	82%	2b
				Bicaval	57	(18.51-79.56)	overall	
3	Solomon and coworkers[E30]	2004	New Zealand	Standard	100	43 ± 13.3 y	82%	2b
				Bicaval (S)	37	(overall)	overall	
4	Milano and coworkers[E24]	2000	United States	Standard	68	50.0 ± 9 y	76%	2b
				Bicaval (S)	75	50.0 ± 11 y		
5	Meyer and coworkers[E31]	2005	Canada	Standard	48	55.2 ± 12.0 y	85%	2b
				Bicaval (S)	57	56.0 ± 10.4 y	77%	
6	Parry and coworkers[E2]	1998	United Kingdom	Standard	17	51.6 y	83%	2b
				Bicaval (S)	46	Overall	overall	
7	Cui and coworkers[E32]	2001	United States	Standard	419	NI	72%	3b
				Bicaval	415		overall	
8	Brandt and coworkers[E33]	1997	Germany	Standard	30	51.6 ± 10.3 y	90%	2b
				Bicaval (S)	30	52.8 ± 10.9 y	87%	
9	Riberi and coworkers[E27]	2001	France	Standard	72	44.0 y	81%	2b
				Bicaval (S)	106	48.0 y	overall	
10	Laske and coworkers[E20]	1996	Switzerland	Standard	20	45.0 ± 10 y	90%	2b
				Bicaval (S)	20	48.0 ± 10 y	80%	
11	Aleksic and coworkers[E3]	1997	United States	Standard	14	54.0 ± 10 y	73%	2b
				Bicaval (B)	17	57.0 ± 10 y	89%	
13	Freimark and coworkers[E4]	1995	United States	Standard	15	56.4 ± 8.2 y	67%	4
				Bicaval (B)	13	53.2 ± 8.5 y	92%	
14	Blanche and coworkers[E6]	1994	United States	Standard	64	53.1 ± 11.5 y	83%	2b
				Bicaval (B)	40	55.8 ± 9.7 y	92%	
15	Blanche and coworkers[E7]	1997	United States	Standard	56	53.1 ± 11.5 y	83%	2b
				Bicaval (B)	101	57.2 ± 11.0 y*	92%*	
16	Koch and coworkers[E25]	2005	Germany	Standard	94	50.6 ± 10.7 y	77%	2b
				Bicaval (B)	72	49.1 ± 14.9 y	overall	
17	Bouchart and coworkers[E28]	1997	France	Standard	65	50.0 ± 11 y	NI	2b
				Bicaval (B)	30	47.0 ± 10 y		
18	Wang and coworkers[E34]	2000	Taiwan	Standard	39	49.0 ± 12 y	75%	2b
				Bicaval (S)	20	46.0 ± 14 y	72%	
19	Park and coworkers[E26]	2005	South Korea	Standard	15	33.1 ± 11.8 y	77%	2b
				Bicaval (S)	28	43.6 ± 11.0 y	68%	
20	Forni and coworkers[E35]	1995	Italy	Bicaval (S)	23	56.3 ± 10.8 y	91%	2b
21	Forni and coworkers[E36]	1996	Italy	Bicaval (S)	28	52.3 ± 10.5 y	93%	2b
22	Trento and coworkers[E37]	1996	United States	Bicaval (B)	93	57.0 ± 11.1 y	92%	2b
23	Luciani and coworkers[E38]	1997	Italy	Bicaval (S)	69	55 y	83%	2b

Study groups: Grande and Traversi; Aleksic, Blanche, Trento, and Freimark; Forni and Luciani. See the online-only reference list for further information. *B*, Banner and colleagues[6]; *S*, Sievers and associates[7]; *NI*, no information. *$P < .05$.

tricuspid valve regurgitation was reduced significantly by 77% in the bicaval group according to the summarized results of 7 prospective studies (Figure 3, *D*). In case the assessment of tricuspid valve regurgitation was graded, only moderate and severe cases were considered, and in case multiple observation points were given, results of the latest observation were included. According to 2 prospective studies, a sinus rhythm was achieved significantly more frequently with the bicaval technique (Figure 3, *D*). It turned out that the meta-analyses of prospective studies only included those that implemented the bicaval transplantation technique according to Sievers and associates,[7] with the exemption of the study of Beniaminowitz and coworkers,[E19] in which both bicaval techniques were used.[6,7]

The summary of 4 retrospective studies showed a nonsignificant reduction in hospital stay of 1 day in the bicaval group (Figure E1, *B*). Patients undergoing the bicaval technique also had a nonsignificant 88% risk reduction for a

TABLE 2. Basis characteristics of the included prospective studies

No.	Author	Publication	Country	Operative technique	No. of cases	Age	Sex (male)	Level of evidence
1	Pahl and coworkers[E39]	2003	United States	Standard	14	14.8 ± 3.4 y	NI	4
				Bicaval (S)	5	17.7 ± 3.2 y		
2	Sievers and coworkers[E16]	1994	Germany	Standard	10	49.7 ± 13.1 y	70%	2b
				Bicaval (S)	8	56.3 ± 9.3 y	75%	
3	Leyh and coworkers[E17]	1995	Germany	Standard	12	50.3 ± 10.4 y	83%	2b
				Bicaval (S)	15	52.2 ± 10.3 y	93%	
4	Aziz and coworkers[E21]	1999	United Kingdom	Standard	161	NI	NI	2b
				Bicaval (S)	88			
5	Aziz and coworkers[E22]	1999a	United Kingdom	Standard	105	49.0 ± 9.9 y	84%	2b
				Bicaval (S)	96	47.0 ± 11.2 y	88%	
6	Sarsam and coworkers[E40]	1993	United Kingdom	Standard	20	NI	NI	2b
				Bicaval (S)	20			
7	Traversi and coworkers[E8]	1996	Italy	Standard	27	45.0 ± 10 y	93%	2b
				Bicaval (S)	22	50.0 ± 12 y	73%	
8	McDowell and coworkers[E41]	2000	United Kingdom	Standard	7	44.7 y	100%	2b
				Bicaval (S)	10	45.0 y	100%	
9	Beniaminowitz and coworkers[E19]	1997	United States	Standard	10	NI	NI	4
				Bicaval (S and B)	10			
10	Grant and coworkers[E10]	1995	United Kingdom	Standard	35	49.2 y	89%	2b
				Bicaval (S)	31	44.1 y	81%	
11	El Gamel and coworkers[E12]	1996	United Kingdom	Standard	13	52.0 ± 8.5 y	77%	2b
				Bicaval (S)	24	49.0 ± 9.0 y	71%	
12	El Gamel and coworkers[E11]	1995	United Kingdom	Standard	35	50 y	80%	2b
				Bicaval (S)	40	53 y	78%	
13	El Gamel and coworkers[E13]	1997	United Kingdom	Standard	20	49.0 ± 6.1 y	65%	2b
				Bicaval (S)	20	52.0 ± 4.2 y	75%	
14	Rothman and coworkers[E14]	1996	United States	Standard	33	56.0 ± 8.0 y	73%	2b
				Bicaval (S)	37	49.0 ± 13.0 y*	76%	
15	Weisbrod and coworkers[E29]	2004	Australia	Standard	6	58.0 ± 3.0 y	67%	2b
				Bicaval (S)	9	49.0 ± 4.0 y	67%	
16	Deleuze and coworkers[E23]	1995	France	Standard	40	49.8 ± 8.0 y	80%	2b
				Bicaval (S)	41	45.6 ± 11.0 y	80%	
17	Jahnke and coworkers[E18]	1995	Germany	Bicaval (S)	9	43.0 ± 5.9 y	NI	2b
18	Jeevanandam and coworkers[E15]	2004	United States	Bicaval (S)	60	52 y	63%	2b

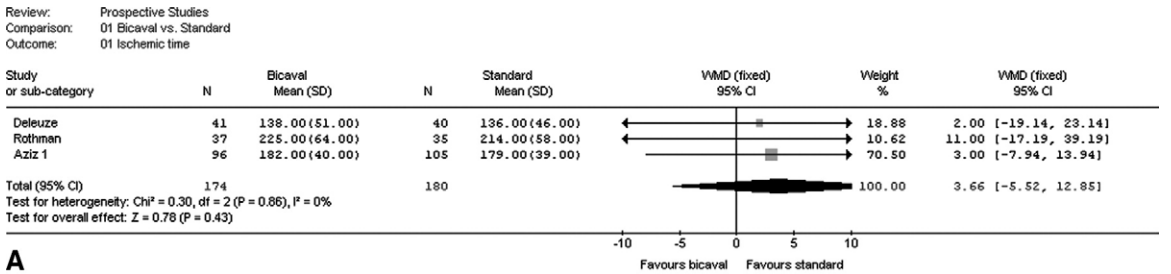
Study groups: Sievers, Leyh, and Jahnke; Aziz, Sarsam, Grant, and El Gamel; Rothman and Jeevandam. See the online-only reference list for further information. *B*, Banner and colleagues[6]; *S*, Sievers and associates[7]; *NI*, no information. *$P < .05$.

permanent pacemaker implantation (Figure E1, *C*). Furthermore, 1-year and 3-year mortality was reduced in patients who underwent the bicaval technique by 40% and 36%, respectively (nonsignificant; Figure E1, *D* and *E*). The summary of retrospective studies also indicated a significantly higher proportion of patients achieving sinus rhythm with the bicaval technique (Figure E1, *F*).

Outcomes not included in the meta-analyses. The quantitative results of the outcome measurements not included in the meta-analysis are shown in Table E1. In summary, superiority of the bicaval technique introduced by Sievers and associates[7] is indicated for the outcomes "need for temporary pacemaker,"[E9-E11,E20] "right atrial pressure 12 months after transplantation,"[E3,E7,E21] "pulmonary artery pressure after 1 year,"[E7,E22] "cardiac index at first postoperative day,"[E22-E24] "mitral valve regurgitation,"[E7,E11] "tricuspid valve regurgitation,"[E7,E20,E24-E26] and "left atrial thrombosis."[E27,E28] No differences were seen for "pulmonary vascular resistance,"[E3,E9] "systolic blood pressure,"[E5,E29] "cardiac output,"[E7,E9,E25] and intensive care unit stay.[E5,E22]

Sensitivity analysis. A comparison of the results of fixed- and random-effect models is displayed in Table E2. Overall, the effect estimates did not differ substantially by either model. As expected, the higher variability under the random-effect assumption led to loss of statistical significance in some cases (perioperative mortality in prospective studies and permanent pacemaker in retrospective studies).

We excluded influential studies in some models and compared the results as given in Table E3. The superi-



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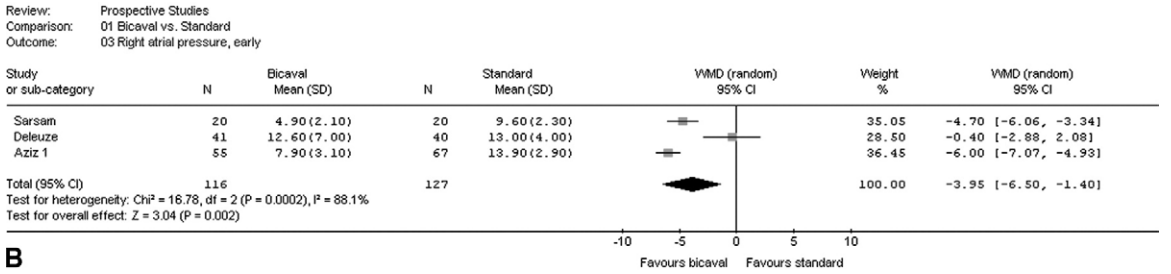

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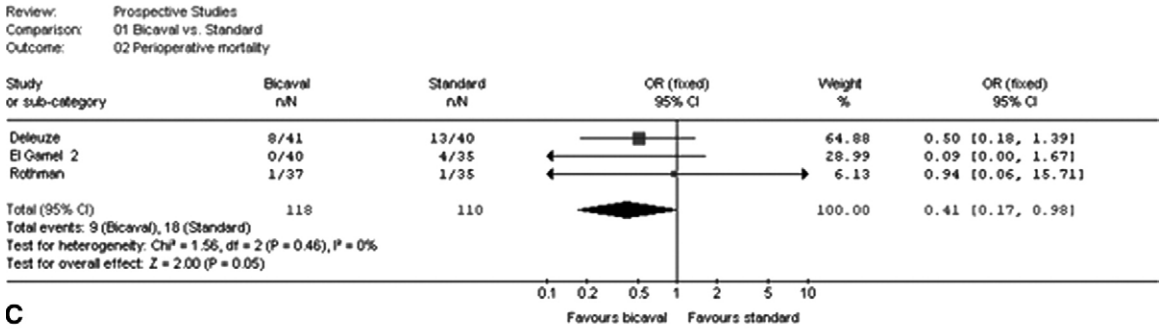

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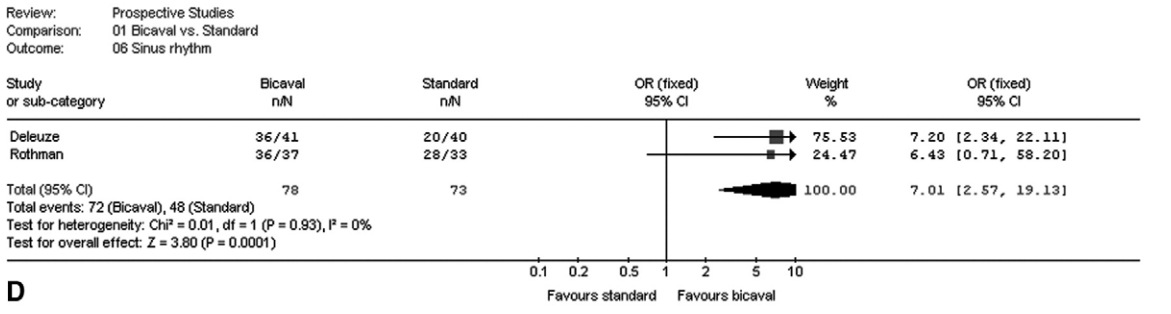

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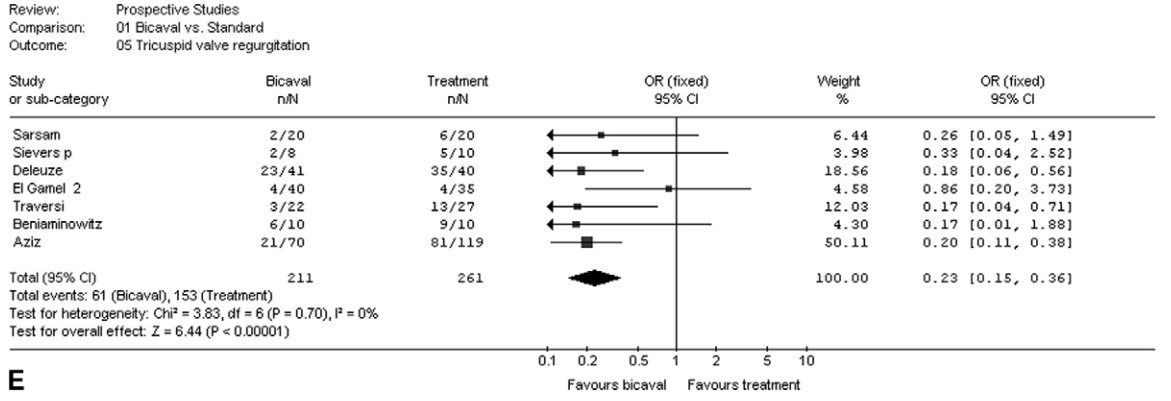

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Figure 3. Meta-analyses of prospective studies. A, Ischemic time. B, Early atrial pressure. C, Perioperative mortality. D, Sinus rhythm. E, Tricuspid valve regurgitation. *OR*, Odds ratio.

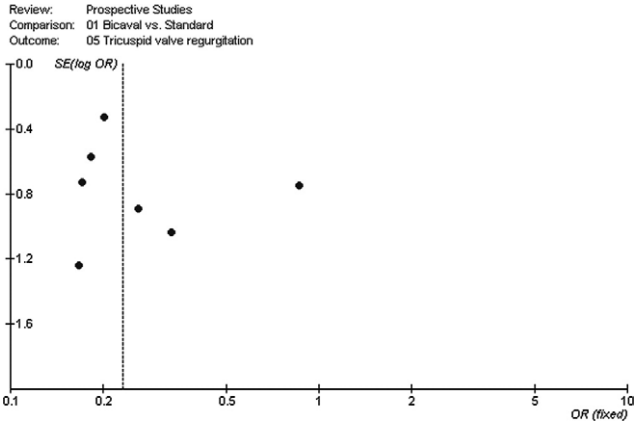

Figure 4. Funnel blot for prospective studies on tricuspid valve regurgitation. *OR*, Odds ratio.

ority of the bicaval technique was enhanced for the outcomes "early atrial pressure" in prospective studies and "1-year survival" in retrospective studies. For the outcomes "permanent pacemaker" and "3-year survival," as obtained in retrospective studies, the results gained statistical significance. Hospital stay seems to be longer with the bicaval technique rather than reduced when omitting an influential study.

The funnel blot of prospective studies on tricuspid valve regurgitation does not indicate a substantial effect of publication bias (Figure 4).

To exclude overlapping, the analyses on "early right atrial pressure" and "tricuspid valve regurgitation" in prospective studies were repeated by omitting the studies of Sarsam,[E40] El Gamel,[E12] and Aziz,[E21] respectively. The early right atrial pressure was still reduced by 3.32 mm Hg in the bicaval group, but statistical significance was no longer reached (−8.80; 2.17). Tricuspid valve regurgitation was significantly reduced to the same degree in the bicaval group (odds ratio, 0.20; 95% CI, 0.12–0.32). In retrospective studies the analyses on "ischemic time," "permanent pacemaker," and "3-year survival" were repeated by omitting the studies of Freimark,[E5] and Aleksic,[E3] respectively. The ischemic time was longer (13.7 minutes) and the need for permanent pacemakers (odds ratio, 0.14; 95% CI, 0.0–11.1) and 3-year survival were reduced (odds ratio, 0.81; 95% CI, 0.29–2.25) in the bicaval group. As before, none of these results reached statistical significance.

Discussion

This systematic review and meta-analysis demonstrated the significant superiority of the bicaval technique of orthotopic heart transplantation compared with the standard technique for some clinically relevant parameters, particularly right atrial pressure, perioperative mortality, tricuspid regurgitation, and sinus rhythm, according to prospective studies. For pediatric orthotopic heart transplantation, comparably excellent results have been reported with the standard biatrial technique.[13] In addition, the biatrial technique might be preferred in certain cases of caval size mismatches, reoperation, or complex anatomy.

Heart transplantation in its most anatomic form would require 8 circumferential anastomoses of 4 pulmonary veins, 2 venae cavae, and 2 arteries. This technique, however, has several shortcomings, such as prolonged ischemic time, potentially difficult accessible suture lines in case of bleeding, anastomotic stenoses, and surgical complexity. Therefore, different transplantation techniques were developed experimentally to reduce the number of anastomoses. Berman and coworkers in 1957[14] sutured the donor left atrium to cuffs around the pulmonary veins of the recipient on each side, reducing the number of anastomoses to 6. Berman and associates[14] left the posterior cuff of the recipient left atrium in place, reducing the number of anastomoses to 5. Cass and Brock,[3] in 1959, and Lower and Shumway,[4] in 1960, introduced the concept of 2 atrial and 2 arterial anastomoses, reducing the number of anastomoses to 4.

This latter technique has been the standard clinical procedure since 1967, when the first human heart transplantation was performed by Barnard.[1] Major parts of the recipient right and left atria are left in situ, the donor left atrium is partially excised, and the donor right atrium is incised from the inferior vena cava to the right atrial appendage. Postoperatively, the atria are acutely enlarged, showing a figure-of-eight configuration.[5]

Theoretically, these morphologic alterations might interfere with hemodynamic, electrophysiologic, innervative, and valvular function of the donor heart. Therefore former experimental alternative surgical principles were introduced into clinical practice recently. In 1989, Banner and associates[6] first used the total transplantation technique, leaving the left and right atria completely intact. In 1991, Sievers and colleagues[7] introduced clinically the bicaval technique, preserving the right atrium intact, only using 2 vena caval anastomoses, and leaving a small bridge of recipient left atrial tissue in place for simple left atrial anastomosis similar to those of the standard technique. During the last 15 years, the bicaval technique has become the most commonly used procedure for orthotopic heart transplantation.[15] Different refinements of the principal technique have been used, such as interrupted sutures for the caval anastomosis with absorbable or unabsorbable material, and performed during the ischemic state or even leaving some right atrial bridge between the superior and inferior vena cava.[16,17]

This meta-analysis provides evidence that the expected theoretic advantages of bicaval transplantation in

comparison with the standard technique have come true in clinical practice. In prospective trials, a reduction in right atrial pressure was found. The absolute difference in right atrial pressure is probably of no clinical relevance at rest. Conclusions with respect to clinical relevance under exercise with increased tricuspid regurgitation cannot be drawn.[E17]

The higher rate of sinus rhythm after transplantation, the significant reduced rate of tricuspid valve regurgitation, the prevention of contraction abnormalities by the acute atrial enlargement with the standard technique, and the asynchrony of recipient and donor atrial innervation probably have contributed to the beneficial hemodynamic effects after bicaval transplantation.[18-20] The enlargement and distension of the atria after the standard technique might not only induce impairment of electrical impulse initiation and conduction, as well as trigger arrhythmias,[21,22] but also promote atrial thrombus formation most likely avoided by the bicaval technique.[23,E27] There was a trend toward reduced permanent pacemaker requirement for the bicaval groups.[E3,E7,E10,E11,E23] However, also with the standard technique, the incidence of permanent pacemaker implantation can be kept comparably low when sinus node area is protected.[E30,E33,E34]

Furthermore, Bernardi[24] found that the bicaval technique leads to an increased parasympathetic reinnervation compared with the standard technique, which might be of clinical relevance because an increase in control of blood pressure by larger reflex changes in heart rate might improve adaptation to various stimuli and to physical exercise.

Potential shortcomings of the bicaval technique include the marginally prolonged ischemic transplantation time of some minutes, which is likely of no clinical relevance, as well as some kind of stenosis at the level of the venous anastomoses. Both problems, however, can be neutralized by refined surgical techniques, such as performing anastomoses with the unclamped aorta and partially interrupted caval sutures. Furthermore, it can be discussed whether the longer hospital stay (when omitting an influential study) in the bicaval group is related to the particular surgical technique or the patient's clinical conditions.

This review has limitations. Although we implemented several strategies to obtain all relevant studies, including searches in electronic databases, hand searching, contact with experts, and screening of actual reference lists, it cannot be excluded that we have missed some information.

The quality of the review is reflected by the quality of the included single studies. Well-performed single studies can provide valid information and bear the potential advantage of a low variability in important parameters, such as myocardial protection, reperfusion techniques, or immunosuppression. The majority of studies were retrospective in nature. These rather observational retrospective cohort studies have not implemented a rigorous randomization principle, which makes these studies prone to several biases, including selection and information bias (Level of evidence 2b). Furthermore, in 2 studies it is not always ascertained that the outcomes were obtained in a standardized and comparable way, which downgraded these studies to level of evidence 4 (poor-quality cohort studies). We identified 7 prospective randomized trials. All studies did not describe the randomization technique in detail or the randomization was on alternate basis, which downgraded these studies to level of evidence 2b (low-quality randomized controlled trial). Overall, the study quality was limited mainly because of a small sample size, lack of randomization, and blinding. Blinding should be possible for the patient, and an independent outcome assessment should be introduced.

Some reports were based on overlapping patient samples. We therefore performed meta-analyses with results from different centers only. The results changed only marginally. The estimate on early right atrial pressure in prospective studies lost its statistical significance.

Another potential limitation of meta-analysis is that different studies assessed outcomes in different ways and at different time points. We included in the meta-analysis studies assessing tricuspid valve regurgitation at different time points. This could bias our results and should be considered in the interpretation. The different time points could influence the pacemaker implantation, as well as the tricuspid valve insufficiency. Especially the latter might be impaired by biopsy and rejection. In addition, differences in the protocols of the practical performances of the outcome assessments cannot be ruled out, which might have affected comparability. There might also be a time trend in survival because of changing conditions in heart transplantation, which is not related to a particular transplantation technique.

A consequence for future studies should be the use of a minimum set of clinically relevant outcomes, which must be measured in a standardized and comparable way.

In summary, this systematic review and meta-analysis proves evidence of clinically relevant beneficial effects of the bicaval technique in comparison with the standard technique of orthotopic heart transplantation, which warrants careful consideration for further decision making. As a result of this analysis, the perioperative mortality seems to be reduced significantly in subjects after bicaval transplantation. Nevertheless, the longer-term beneficial effects of the bicaval technique remain to be evaluated, especially with regard to exercise capacity[E16] and patient-oriented outcomes, such as health-related quality of life (Short Form–36).

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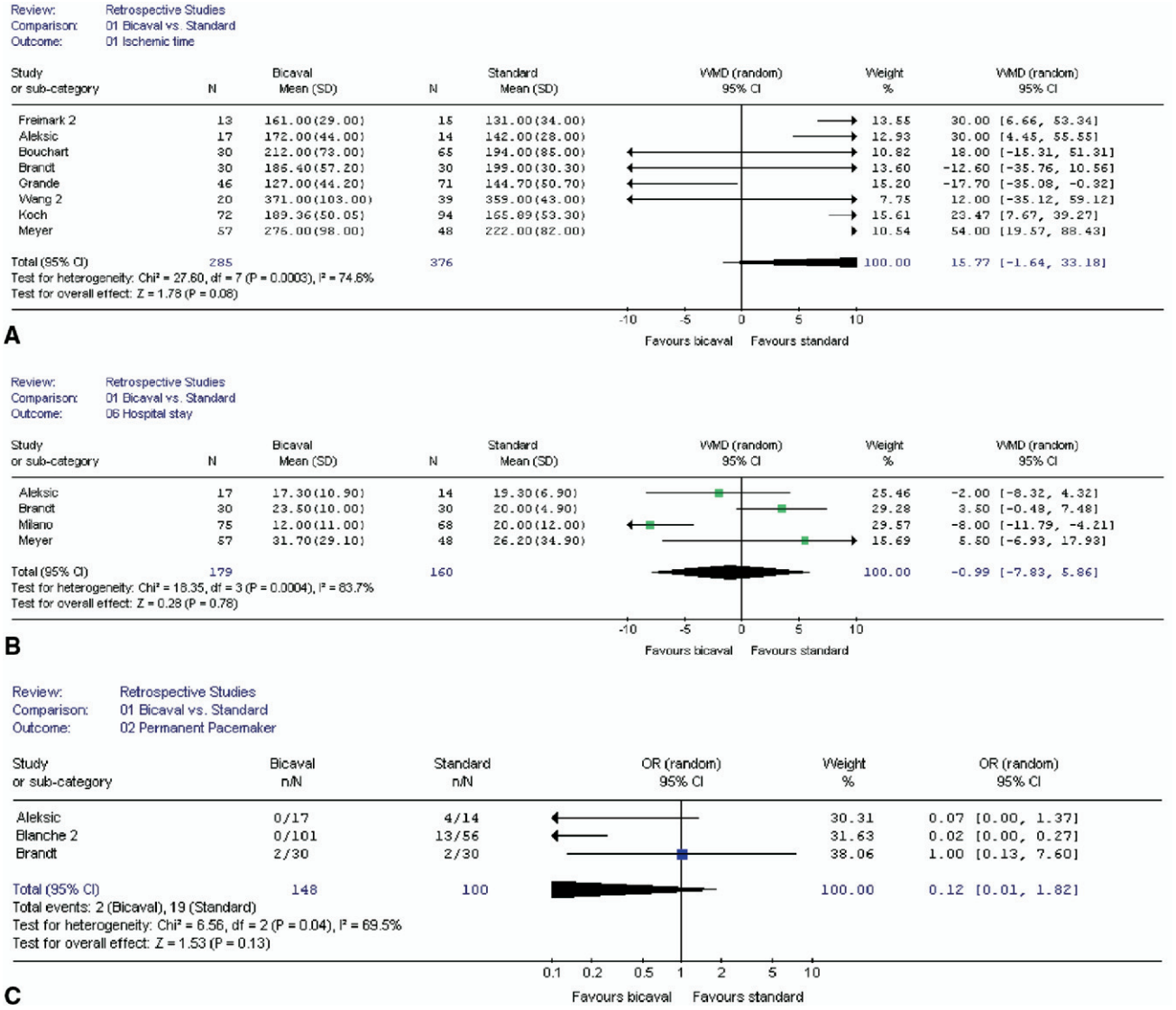

Figure E1. Meta-analyses of retrospective studies. A, Ischemic time. B, Hospital stay. C, Permanent pacemaker. D, One-year survival. E, Three-year survival. F, Sinus rhythm. *SD*, Standard deviation; *WMD*, weighted mean difference; *CI*, confidence interval; *OR*, odds ratio.

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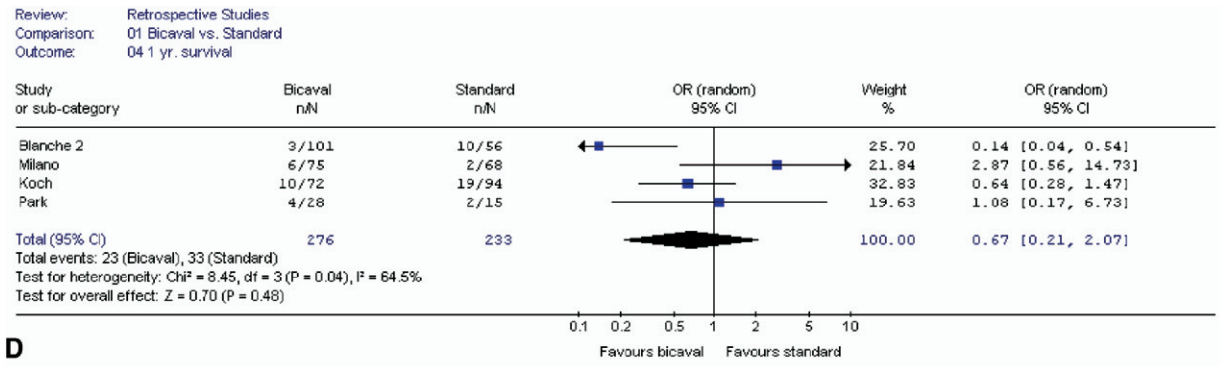

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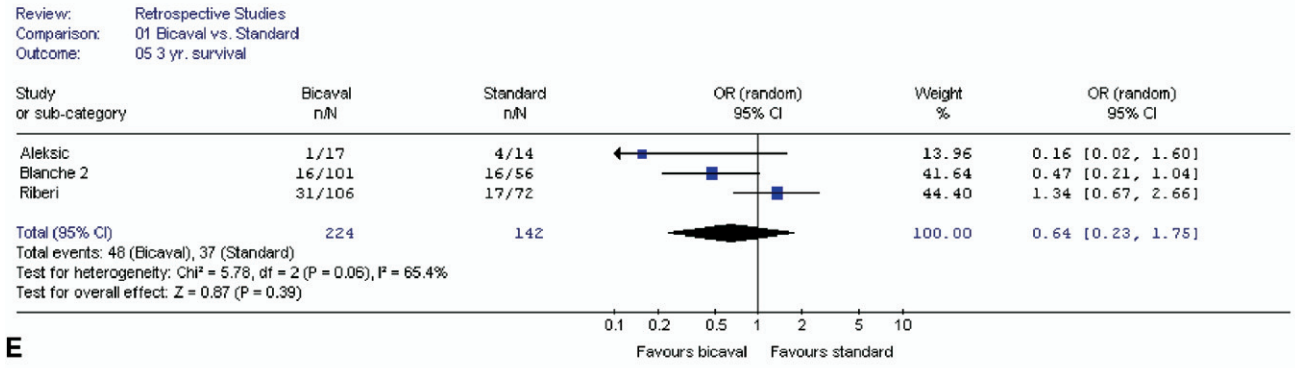

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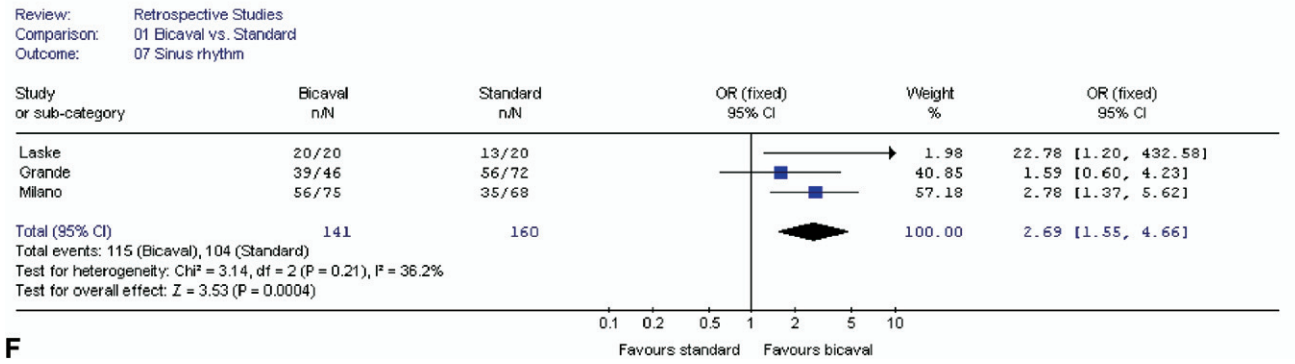

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Figure E1. Continued

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TABLE E1. Results of the comparison of the outcomes between heart transplantation with the bicaval technique and the standard technique

Outcome parameter	Design	Technique		*P* value
		Bicaval	Standard	
Temporary pacemaker				
Grande and coworkers, 2000[E9]	R	28%	44%	NS
Laske and coworkers, 1996[E20]	R	30%	65%	<.05
Wang and coworkers, 2000[E34]	R	20%	15%	NS
El Gamel and coworkers, 1995[E11]	P	26%	49%	<.05
Grant and coworkers, 1995[E10]	P	32.3%	45.7%	NS
Sarsam, 1993[E40]	P	10%	10%	NS
Pulmonary vascular resistance 12 mo after transplantation (Wood units)				
Grande and coworkers, 2000[E9]	R	1.3 ± 0.6	1.4 ± 0.6	NS
Aleksic and coworkers, 1997[E3]	R	2.7 ± 1.7	1.7 ± 0.7	NS
Right atrial pressure 12 mo after transplantation (mm Hg)				
Aleksic and coworkers, 1997[E3]	R	5 ± 2	7 ± 3	.07
Blanche and coworkers, 1997[E7]	R	4	6	.006
Aziz and coworkers, 1999[E22]	P	5	11	NI
Cardiac index at first day ($L \cdot min^{-1} \cdot m^{-2}$)				
Milano and coworkers, 2000[E24]	R	3.1 ± 0.7	2.7 ± 0.5	<.05
Deleuze and coworkers, 1995[E23]	R	4.1 ± 0.9	3.8 ± 0.7	.04
Aziz and coworkers, 1999a[E21]	P			
First period		3.7 ± 1.1	2.6 ± 0.2	.02
Second period		3.9 ± 0.5	2.5 ± 0.6	.03
Cardiac index at least 15 mo ($L \cdot min^{-1} \cdot m^{-2}$)				
Freimark and coworkers, 1995[E4]		2.8 ± 0.7	2.7 ± 0.6	NS
Leyh and coworkers, 1995[E17]		3.2 ± 0.5	2.9 ± 0.6	NS
Sinus rhythm at end of cardiopulmonary bypass				
Laske and coworkers, 1996[E20]	R	100%	65%	<.005
Deleuze and coworkers, 1995[E23]	P	88%	50%	<.001
Sinus rhythm at 1 wk				
Milano and coworkers, 2000[E24]	R	74%	50.7%	<.05
Rothman and coworkers, 1996[E16]	P	95%	58%	<.05
Sinus rhythm at 1 mo				
Grande and coworkers, 2000[E9]	R	85%	78%	NS
Cardiac output (L/min) postoperatively				
Koch and coworkers, 2005[E25]	R	5.5	5.0	NS
Cardiac output (L/min) at 12 mo after transplantation				
Grande and coworkers, 2000[E9]	R	4.7 ± 1.1	5.2 ± 1.4	NS
Blanche and coworkers, 1997[E7]	R	5.6	5.3	NS
Koch and coworkers, 2005[E25]	R	5.8	5.3	NS
Pulmonary artery pressure (mm Hg) at 12 mo after transplantation				
Blanche and coworkers, 1997[E7]	R	18.7 (95% CI, 17.5–20.0)	21.0 (95% CI, 19.4–21.8)	.03
Koch and coworkers, 2005[E25]	R	18.5	18.5	NS
Aziz and coworkers, 1999a[E21]	P			
First period		17.6 ± 4.3	22.8 ± 5.1	.01
Second period		17.4 ± 5.8	21.9 ± 5.8	.008
Systolic pressure (mm Hg) at least 15 mo after transplantation				
Freimark and coworkers, 1995[E5]	R	133 ± 20	125 ± 11	NS
Weisbrod and coworkers, 2004[E29]	P	138 ± 4	122 ± 7	NS

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TABLE E1. Continued

Outcome parameter	Design	Technique		*P* value
		Bicaval	Standard	
Mitral valve regurgitation				
Blanche and coworkers, 1997[E7]; 6–19 mo after regurgitation	R			
None		72%	50%	.35
Mild		17%	39%	
Moderate		4%	7%	
Severe		0%	4%	
Koch and coworkers, 2005[E25]; at 5 y after transplantation	R			
None		100%	98%	<.05
Mild		0%	0%	NS
Moderate		0%	2%	NS
Severe		0%	0%	NS
El Gamel and coworkers, 1995[E11]; 3 mo after transplantation	P			
None		85%	60%	<.05
Mild		15%	34%	
Moderate		0%	0%	
Severe		0%	6%	
Moderate or severe tricuspid valve regurgitation				
Milano and coworkers, 2000[E24]	R			
Month after transplantation		22%	45%	<.05
Laske and coworkers, 1996[E20]	R			
1-3 mo after transplantation		0%	10%	NS
Blanche and coworkers, 1997[E7]	R			
6-19 mo after transplantation		9%	43%	<.001
Park and coworkers, 2005[E26]	R			
1 y after transplantation		32%	69%	.029
Koch and coworkers, 2005[E25]	R			
5 y after transplantation		14%	43%	<.05
El Gamel and coworkers, 1995[E11]	P			
3 mo after transplantation		10%	12%	NS
Aziz and coworkers, 1999a[E21]	P			
2 y after transplantation		16%	32%	.031
Left atrial thrombosis at least 6 mo after transplantation				
Riberi and coworkers, 2001[E27]	R	0%	12.5%	.04
Bouchart and coworkers, 1997[E28]	R	0%	26.1%	.01
Peripheral atrial embolism at least 6 mo after transplantation				
Bouchart and coworkers, 1997[E28]	R	0%	13.8%	NS
Intensive care unit stay (d)				
Freimark and coworkers, 1995[E5]	R	6.0 ± 3.6	5.8 ± 2.3	NS
Aziz and coworkers, 1999a[E21]	P			
First period		5.6 ± 2.0	3.5 ± 2.5	.007
Second period		4.5 ± 2.5	3.2 ± 1.9	.02

R, Retrospective; *NS*, nonsignificant; *P*, prospective; *NI*, no information; *CI*, confidence interval.

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TABLE E2. Sensitivity analysis: Comparison of random- and fixed-effect models

Parameter	Fixed-effect model WMD or OR (95% CI)	Random-effect model WMD or OR (95% CI)
Prospective studies		
Ischemic time	3.66 (−5.52 to 12.85)	3.56 (−5.52 to 12.83)
Early atrial pressure	−4.97 (−5.77 to −4.17)	−3.95 (−6.50 to −1.40)
Perioperative mortality	0.41 (0.17 to 0.98)	0.46 (0.18 to 1.13)
Tricuspid valve regurgitation	0.23 (0.15 to 0.36)	0.23 (0.15 to 0.36)
Sinus rhythm	7.01 (2.57 to 19.13)	7.03 (2.59 to 19.12)
Retrospective studies		
Ischemic time	12.22 (3.99 to 20.46)	15.77 (−1.64 to 33.18)
Hospital stay	−2.14 (−4.61 to 0.32)	−0.99 (−7.83 to 5.06)
Permanent pacemaker	0.10 (0.03 to 0.33)	0.12 (0.01 to 1.02)
1-y Survival	0.57 (0.31 to 1.04)	0.60 (0.14 to 2.53)
3-y Survival	0.78 (0.48 to 1.28)	0.64 (0.23 to 1.75)
Sinus rhythm	2.69 (1.55 to 4.66)	2.59 (1.15 to 5.84)

WMD, Weighted mean difference; *OR*, odds ratio; *CI*, confidence interval.

TABLE E3. Sensitivity analysis: Exclusion of influential studies

Parameter	Original model WMD or OR (95% CI)*	Exclusion of study	Model after exclusion WMD or OR (95% CI)*
Prospective studies			
Early atrial pressure	−3.95 (−6.50 to −1.40)	Deleuze[E23]	−5.42 (−6.69 to −4.15)
Perioperative mortality	0.41 (0.17 to 0.98)	Rothman[E14]	0.37 (0.15 to 0.95)
Tricuspid valve regurgitation	0.23 (0.15 to 0.36)	El Gamel 2[E12]	0.20 (0.13 to 0.32)
Retrospective studies			
Hospital stay	−0.99 (−7.83 to 5.06)	Milano[E24]	2.01 (−1.82 to 5.84)
Permanent pacemaker	0.12 (0.01 to 1.02)	Brandt[E33]	0.03 (0 to 0.25)
1-y Survival	0.60 (0.14 to 2.53)	Milano[E24]	0.33 (0.08 to 1.43)
3-y Survival	0.64 (0.23 to 1.75)	Riberi[E27]	0.42 (0.20 to 0.89)

WMD, Weighted mean difference; *OR*, odds ratio; *CI*, confidence interval. *All random effect model if not specified otherwise.