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REVIEW

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Contemporary outcomes after surgical aortic valve replacement with bioprostheses and allografts: a systematic review and meta-analysis†

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Summary

Many observational studies have reported outcomes after surgical aortic valve replacement (AVR), but there are no recent systematic reviews and meta-analyses including all available bioprostheses and allografts. The objective of this study is to provide a comprehensive and up-to-date overview of the outcomes after AVR with bioprostheses and allografts reported in the last 15 years. We conducted a systematic literature review (PROSPERO register: CRD42015017041) of studies published between 2000–15. Inclusion criteria were observational studies or randomized controlled trials reporting on outcomes of AVR with bioprostheses (stented or stentless) or allografts, with or without coronary artery bypass grafting (CABG) or valve repair procedure, with study population size $n \geq 30$ and mean follow-up length ≥5 years. Fifty-four bioprosthesis studies and 14 allograft studies were included, encompassing 55 712 and 3872 patients and 349 840 and 32 419 patient-years, respectively. We pooled early mortality risk and linearized occurrence rates of valve-related events, reintervention and late mortality in a random-effects model. Sensitivity, meta-regression and subgroup analyses were performed to investigate the influence of outliers on the pooled estimates and to explore sources of heterogeneity. Funnel plots were used to investigate publication bias. Pooled early mortality risks for bioprostheses and allografts were 4.99% (95% confidence interval [CI], 4.44–5.62) and 5.03% (95% CI, 3.61–7.01), respectively. The late mortality rate was 5.70%/patient-year (95% CI, 4.99–5.62) for bioprostheses and 1.68%/patient-year (95% CI, 1.23–2.28) for allografts. Pooled reintervention rates for bioprostheses and allografts were 0.75%/patient-year (95% CI, 0.61–0.91) and 1.87%/patient-year (95% CI, 1.52–2.31), respectively. There was substantial heterogeneity in most outcomes. Meta-regression analyses identified covariates that could explain the heterogeneity: implantation period, valve type, patient age, gender, pre-intervention New York Heart Association class III/IV, concomitant CABG, study design and follow-up length. There is possible publication bias in all outcomes. This comprehensive systematic review and meta-analysis provides an overview of the outcomes after AVR with bioprostheses and allografts reported during the last 15 years. The results of this study can support patients and doctors in the prosthetic valve choice and can be used in microsimulation models to predict patient outcomes and estimate the cost-effectiveness of AVR with bioprostheses or allografts compared with current and future heart valve prostheses.

Keywords: Aortic valve replacement • Bioprostheses • Allografts • Homografts • Systematic review • Meta-analysis

INTRODUCTION

Heart valve substitutes available for surgical aortic valve replacement (AVR) can be broadly divided into mechanical and biological valves. Biological valves have the advantages that there is no need for lifelong anticoagulation medication and that the ticking sound of mechanical valves is absent. However, disadvantages of biological valves are a limited durability and a subsequent risk of reoperation. The use of biological valves for AVR in the USA increased from 37.7% of all implanted valves during 1998–2001 to 63.6% during 2007–2011 [1].

Biological valves can be divided into bioprostheses (stented or stentless), allografts and autografts. Stented bioprostheses are the most frequently implanted biological valves [2]. Stentless bioprostheses are presumed to have better haemodynamics than stented bioprostheses and therefore might prevent prosthesis–patient mismatch and improve durability [3]. However, long-term outcomes indicated that the durability was not better than

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expected [3]. Allografts were hypothesized to have improved durability compared with bioprostheses because they are obtained from human donors. However, several studies have shown that the risk of reoperation for structural valve deterioration (SVD) is comparable or even higher than in bioprostheses [4, 5]. Therefore, bioprostheses that are readily available might be preferred. Currently, allografts are predominantly implanted in patients with acute infective endocarditis with perivalvular lesions [6].

Many observational studies reported the long-term mortality and occurrence of valve-related events after AVR with biological valve prostheses. Grunkemeier *et al.* [7] reviewed the long-term clinical results of various options for heart valve replacement, based on publications between 1989 and 1999. There are also several systematic reviews and meta-analyses that analysed the outcomes of implantation with specific bioprostheses across several publications [8, 9]. However, to our knowledge, there are no recent systematic reviews and meta-analyses that include all available bioprostheses and allografts. The objective of this study is to provide up-to-date estimates of reported outcomes after surgical AVR (especially long-term mortality, valve-related events and reinterventions) with bioprostheses and allografts reported during the last 15 years.

METHODS

Search strategy and selection of studies

This systematic review was conducted according to the PRISMA guidelines [10] and registered in the PROSPERO register (CRD42015017041; see Supplementary Material for the PRISMA checklist). On 17 February 2015, the Embase, Medline, Cochrane, Pubmed publisher and Google Scholar databases were searched using keywords regarding aortic heart valve bioprostheses or allografts and outcomes (search terms are provided in Supplementary Material). We limited our search to studies that were conducted in humans and published in the last 15 years (1 January 2000–17 February 2015). This time frame was selected to reflect recent outcomes of AVR. Two researchers (Simone A. Huygens and Mostafa M. Mokhles) independently reviewed the results on titles and abstracts to determine whether the study met the inclusion criteria. In case of disagreement, an agreement was negotiated. The inclusion criteria were observational studies or randomized controlled trials (RCTs) reporting on the outcomes of AVR with bioprostheses or allografts with or without coronary artery bypass grafting (CABG) or any other valve repair procedure, but excluding other valve replacements (a maximum of 10% multiple valve replacements in the study population was allowed) with a minimum study population size $n \geq 30$ and a minimum mean follow-up length of 5 years. Studies were excluded if they only reported results of a propensity-matched population (because of less generalizability of the study population), if the mean or median follow-up length was not reported, or when they only reported early mortality risk and no event occurrence, reoperation or late mortality (because the main aim of this study was to report long-term outcomes after AVR). In case of multiple publications on the same patient population, the publication with most follow-up patient-years was generally included. Exceptions were studies that had less follow-up patient-years but reported more relevant data than the overlapping study. Two researchers (Simone A. Huygens and Mostafa M. Mokhles) jointly decided whether the exception was justified. References of selected papers were cross-checked for other relevant studies.

Data extraction

Microsoft Office Excel 2010 (Microsoft Corp., Redmond, WA, USA) was used for data extraction. Data extraction of all included studies was performed independently by two researchers (Simone A. Huygens and Mostafa M. Mokhles). In case of disagreement about extracted data, an agreement was negotiated. Study design, valve implantation period (in calendar years) and follow-up duration (mean and total patient-years) were documented. The following patient characteristics were registered: mean patient age at the time of surgery, proportion of male patients, concomitant procedures, pre- and post-intervention New York Heart Association (NYHA) class, subcoronary allograft valve replacement and endocarditis as indication for surgery. If the total number of patient-years was not provided, mean (or if mean was not reported, median) follow-up was multiplied by the reported number of patients. Occurrence of valve-related events, reintervention and mortality was registered according to the '2008 AATS/EACTS/STS guideline for reporting morbidity and mortality after cardiac valvular operations' [11]. The following valve-related events were registered: early mortality (≤30 days postoperatively or in-hospital), late mortality (>30 days postoperatively, divided into sudden unexpected unexplained death [SUUD], cardiac and valve-related mortality), reintervention (with the reasons for reintervention), early event occurrence (≤30 days postoperatively or in-hospital) and late event occurrence (>30 days postoperatively). The included valve-related events were SVD, non-structural valve dysfunction (NSD), valve thrombosis, thromboembolism, bleeding and endocarditis. In case, an event was reported not to occur, for pooling purposes it was assumed that 0.5 patient experienced the event. When the occurrence of valve-related events was only reported as a linearized occurrence rate (LOR), the number of events that occurred in the study population was calculated by multiplying the LOR with the total follow-up patient-years. In studies where the results were reported separately for subgroups (such as pericardial/porcine or stented/stentless valve prostheses), the weighted mean of covariates for the total population was calculated and occurrence rates were summed. Authors were contacted when full text was not available or to request additional information when follow-up length and total follow-up patient-years or the proportion of multiple valve replacements were not reported.

Statistical analyses

Early risks of mortality and valve-related events and late LORs of valve-related events, reintervention and mortality were calculated for each individual study and pooled on a logarithmic scale with the use of the inverse variance method in a random-effects model. In the random-effects model, the Der Simonian and Laird method was used for estimating the between-studies variance [12]. The choice to use a logarithmic scale was verified by performing Shapiro–Wilk tests on aggregated data on the study level to test the normality of the distributions in our meta-analysis (i.e. we did not test the normality of the distributions of the underlying individual patient data). Leave-one-out sensitivity analyses were performed to assess the influence of outliers in the early mortality risk, late mortality and reintervention rates. The Cochrane Q statistic and I^2 statistic were used to assess heterogeneity between studies. The causes of heterogeneity were explored by performing univariable meta-regression in the main outcome measures: early mortality, late mortality, SVD, NSD, valve thrombosis,

thromboembolism, bleeding, endocarditis and reintervention. The covariates that were explored for both bioprostheses and allografts were the start and end of the valve implantation period, study design, mean follow-up, mean patient age, proportion of male patients, proportion of patients undergoing concomitant procedures, proportion of patients undergoing concomitant CABG and proportion of patients in NYHA class III/IV before surgery. In addition, valve type (stented or stentless and porcine or pericardial) was explored in the bioprostheses review, and the proportion of patients undergoing subcoronary valve replacement (instead of total root replacement) and endocarditis as indication for surgery were explored in the allografts review. Subsequently, we have performed subgroup analyses for stented versus stentless bioprostheses, retrospective versus prospective study design (including RCT) and studies including AVR with concomitant CABG versus studies that only included AVR without concomitant CABG to investigate the differences in the outcome measures between these subgroups. Finally, funnel plots were used to investigate publication bias.

The meta-analysis, heterogeneity tests, subgroup analysis and funnel plots were performed in Microsoft Office Excel 2010, Shapiro–Wilk tests using SPSS and leave-one-out sensitivity and univariable meta-regression analyses using open-source meta-analysis software that uses R as the underlying statistical engine [13].

RESULTS

Literature search

The literature search resulted in 5756 studies on bioprostheses and 2291 studies on allografts. After applying inclusion and exclusion criteria, 54 studies on bioprostheses and 14 studies on allografts were included in the systematic review (references provided in Supplementary Material). The study selection processes are illustrated in the flowchart in Fig. 1. We made one exception on the general rule to include the publication with the most follow-up patient-years in case of overlapping study populations: Ashikhmina *et al.* [14] reported more relevant outcome measures (early mortality, late SVD and late mortality); therefore, this study was included instead of Said *et al.* [15] where more follow-up patient-years were included.

Study characteristics

Tables 1 and 2 provide an overview of studies included in the present study. In the bioprosthesis group, 55 712 patients were included, resulting in 349 840 follow-up patient-years. The allograft group included 3872 patients with 32 419 follow-up patient-years. The pooled mean follow-up length was 6.7 years for bioprostheses and 8.5 years for allografts. The pooled mean patient age was 71.8 years for bioprostheses and 48.8 years for allografts. Concomitant procedures were performed in 51.9% of the patients in studies on bioprostheses and 28.0% of the patients in studies on allografts. A common concomitant procedure is CABG, performed in 40.0% of the patients in studies on bioprostheses and 11.9% of the patients in studies on allografts.

Study outcomes

The Shapiro–Wilk tests showed that the aggregated data on study level of the majority of the outcome measures had a normal distribution after log transformation (note that the distribution of the underlying individual patient data has not been tested). Table 3 gives the pooled estimates of early mortality and early valve-related events, late mortality, late valve-related events and reintervention for bioprostheses and allografts. Estimates of the outcome measures for individual studies are provided in Supplementary Tables 1–8.

Sensitivity analyses

The forest plots of the leave-one-out sensitivity analysis showed that there were no outliers in the meta-analysis of early mortality risk, late mortality and reintervention rate in studies on bioprostheses. There was more variation in the outcome measures in studies on allografts. Figure 2 shows the forest plot of early mortality risk in studies on allografts. The other forest plots can be found in Supplementary Material.

Heterogeneity

There was substantial heterogeneity according to the Cochrane Q and I^2 statistics in most outcome measures (Table 3), except for early valve thrombosis, early endocarditis, late valve thrombosis and reintervention for valve thrombosis between studies on bioprostheses and late cardiac mortality, late bleeding, late endocarditis and reintervention for valve thrombosis and endocarditis between studies on allografts. The results of the univariable meta-regression analyses in the outcome measures with substantial heterogeneity between studies are described below and reported in Supplementary Tables 9–16.

Early mortality. Studies on bioprostheses with a more recent end of implantation period or studies with a high proportion of males reported lower early mortality risks. Studies on allografts with a more recent start of the implantation period report higher early mortality risks.

Late mortality. Studies on bioprostheses with a relatively old study population reported higher late mortality rates. In addition, studies on stentless bioprostheses reported lower late mortality rates compared with those on stented bioprostheses. Studies on allografts with a more recent start of implantation period, prospective studies, studies with a large proportion of concomitant procedures or studies with a large proportion of patients with pre-intervention NYHA class III/IV reported lower late mortality rates.

Late valve-related events. Studies on stentless bioprostheses reported higher SVD rates compared with those that report on stented bioprostheses. Prospective studies reported lower SVD rates compared with retrospective studies as did studies with a higher mean patient age. Studies on allografts with more recent start or end dates of the implantation period reported lower rates of SVD. Furthermore, studies with high mean follow-up duration, high proportion of patients with pre-intervention NYHA class III/IV or high proportion of patients undergoing subcoronary valve replacement reported relatively high SVD rates.

Relatively low NSD rates were reported in studies on bioprostheses with a more recent end of implantation period or a high proportion of males.

None of the covariates can explain the heterogeneity in thromboembolism, bleeding and endocarditis rates between studies on bioprostheses. Studies on allografts with more recent start or end dates of the implantation period reported lower thromboembolism

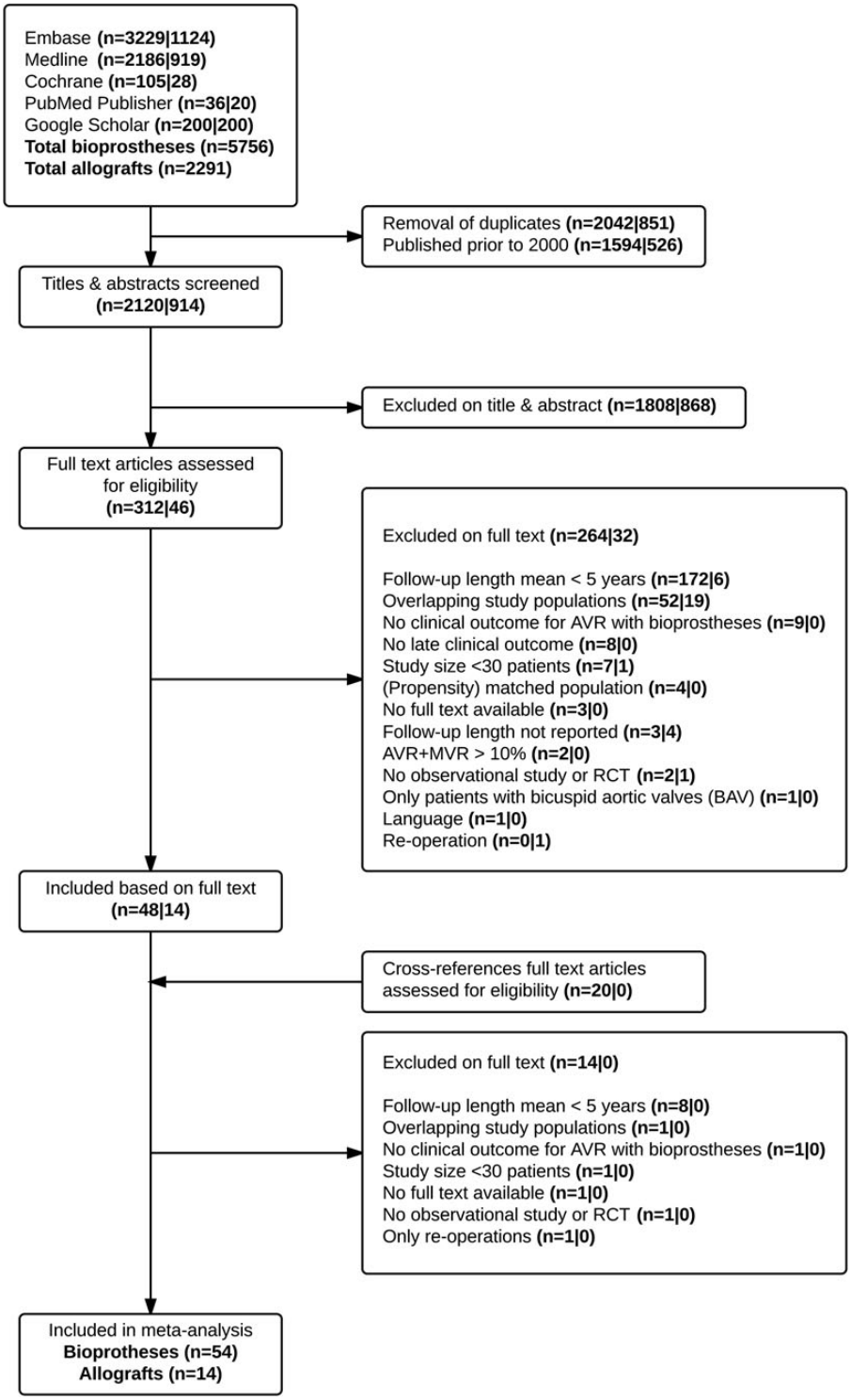

Figure 1: Flowchart of study selection (*n* = bioprostheses|allografts). AVR: aortic valve replacement; MVR: mitral valve replacement; RCT: randomized controlled trial.

rates. Furthermore, studies with a high proportion of patients undergoing concomitant CABG, with pre-intervention NYHA class III/IV or subcoronary valve replacements reported higher thromboembolism rates.

Reintervention. Studies on bioprostheses with a high mean patient age reported lower rates for reintervention. In addition, studies on stentless bioprostheses reported higher reintervention rates compared with those on stented bioprostheses. Prospective studies on allografts reported lower reintervention rates compared with retrospective studies.

Subgroup analyses

Table 4 summarizes the pooled estimates of patient and study characteristics and outcome measures in the subgroups of studies with stented ($n = 37$) and stentless ($n = 13$) bioprostheses. Noticeable are the differences in the percentage of male patients

Table 1: Overview of included publications on bioprostheses

First author[a]	Year of publication	Implantation period	No. of patients	Type of valve		Study type	Mean follow-up (years)	Mean age, years (range)	Concomitant CABG, *n* (%)
Akins	2002	1984–97	469	Stented	Porcine + pericardial	Retrospective	5.1	75.0 (–)	469 (100)
Albert	2010	1996–2006	815	Stentless	Porcine	Retrospective	7.7	73.0 (–)	–
Amabile	2014	1997–2004	500	Stentless	Porcine	Prospective	5.9	74.5 (26–91)	120 (24)
Anselmi	2014	1994–2004	1005	Stented	Porcine	Retrospective	8.5	74.7 (26–93)	147 (15)
Ashikhmina	2011	1993–2007	2658	Stented	Porcine + pericardial	Prospective	5.0	78.0 (–)	1409 (53)
Benetis	2014	1997–2012	167	Stentless	Porcine + pericardial	Prospective	5.0	72.5 (48–86)	53 (32)
Benhameid	2008	1982–92	161	Stented	Pericardial	Retrospective	8.6	69.5 (60–94)	39 (24)
Biglioli	2004	1984–2000	327	Stented	Pericardial	Retrospective	6.0	67.2 (19–83)	75 (23)
Birla	2013	2001–05	403	Stented	Porcine + pericardial	RCT	6.0	74.9 (40–91)	200 (50)
Bottio	2004	1992–2001	258	Stented	Porcine	Prospective	5.0	75.0 (45–91)	56 (22)
Bottio	2005	1970–84	192	Stented	Porcine	Retrospective	12.3	48.5 (18–70)	13 (7)
Bourguignon	2015	1984–2008	2758	Stented	Pericardial	Prospective	6.7	70.7 (16–91)	637 (23)
Celiento	2012	1995–2008	178	Stented	Porcine	Retrospective	5.7	74.0 (–)	25 (14)
Chan	2006	1992–98	2195	Stented	Porcine + pericardial	Retrospective	7.5	– (–)	955 (44)
Chan	2011	1976–2010	3152	Stented	Porcine + pericardial	Prospective	5.8[b]	– (–)	1631 (52)
Chiang	2014	1997–2004	1466	Unknown	Porcine + pericardial	Retrospective	10.6[c]	62.3 (50–69)	0 (0)
David	2008	1991–2004	357	Stentless	Porcine	Retrospective[d]	7.7	65.0 (22–84)	114 (32)
David	2010	1982–2004	1134	Stented	Porcine	Prospective	12.4	67.0 (19–94)	572 (50)
de la Fuente	2003	1988–2000	215	Stented	Porcine + pericardial	Prospective	6.0	68.5 (24–81)	0 (0)
Dellgren	2002a	1984–95	254	Stented	Pericardial	Retrospective	5.0	71.3 (25–87)	130 (51)
Dellgren	2002b	1990–2000	112	Stentless	Porcine	Prospective	5.5	78.5 (61–89)	35 (31)
Desai	2004	1992–2000	200	Stentless	Porcine	Retrospective	5.8	64.6 (33–82)	69 (35)
Eichinger	2008	1985–96	455	Stented	Porcine	Retrospective	8.2	72.5 (–)	171 (38)
Flameng	2014	1991–2005	648	Stented + stentless	Porcine + pericardial	Retrospective	7.5	73.8 (–)	318 (49)
Forcillo	2013	1981–2011	2405	Stented	Pericardial	Retrospective	6.0	71.0 (18–90)	1010 (42)
Franzen	2001	1989–96	90	Stented	Pericardial	Retrospective	5.0	78.0 (58–84)	37 (41)
Frapier	2002	1986–90	90	Stented	Porcine	Retrospective	6.6	72.6 (36–86)	18 (20)
Gansera	2014	1993–2007	272	Stented	Porcine	Retrospective	6.1	76.8[c] (31–91)	0 (0)
Glaser	2014	2002–10	1219	Stented	Porcine + pericardial	Retrospective	5.0	73.6 (–)	–
Grocott-Mason	2000	1969–93	47	Stented	Porcine	Retrospective	5.2	70.2 (43–85)	20 (43)
Grunkemeier	2012	1974–2010	2955	Stented	–	Prospective	5.3	73.1 (–)	1377 (47)
Jamieson	2001	1986–96	836	Stented	Porcine	Retrospective	6.2	67.0 (9–91)[e]	–
Jamieson	2006	1984–2001	1430	Stented	Pericardial[f]	Retrospective	5.4	69.5 (16–90)	257 (18)
Jamieson	2011	1994–2000	797	Stented	Porcine	Prospective	7.5	69.0 (21–88)	362 (45)
Johnston	2015	1982–2011	12 569	Stented	Pericardial	Prospective	6.5	71.0 (18–91)	6033 (48)
Kurlansky	2007	1976–99	438[g]	Stented	Porcine	Retrospective	5.3	77.0 (65–91)	0 (0)
Le Tourneau	2007	1989–93	222	Unknown	Unknown	Retrospective	7.3	73.0 (–)	32 (14)
Lehmann	2011	1996–99	225	Stented + stentless	Porcine	Prospective	8.5	72.3 (–)	0 (0)
Luciani	2001	1992–96	106	Stentless	Porcine	Retrospective	5.8	70.0 (26–83)	27 (25)
McClure	2010	1991–2002	1000	Stented	Pericardial	Retrospective	6.0	74.1 (19–95)	443 (44)
Merie	2012	1997–2009	4075	Unknown	Unknown	Retrospective	6.6[c]	74.6 (18–95)	1858 (46)
Minakata	2014	1986–2001	574	Stented	Pericardial	Retrospective	8.2	71.9 (21–89)	114 (20)
Minami	2005	1985–2004	1516	Stented	Pericardial	Retrospective	5.5	75.6 (16–92)	811 (54)
Mohammedi	2014	1993–2013	531	Stentless	Porcine	Prospective	10.3	67.6 (–)	174 (33)
Myken	2009	1983–2003	1518	Unknown	Porcine	Retrospective	6.0	70.8 (16–88)	638 (42)
Pavoni	2007	1994–2004	185	Stentless	Porcine	Retrospective	5.4	72.0 (–)	52 (28)
Polvani	2005	1992–94	67	Stentless	Porcine	Retrospective	9.8	67.9 (22–83)	2 (3)

Continued

Table 1: Continued

First author[a]	Year of publication	Implantation period	No. of patients	Type of valve		Study type	Mean follow-up (years)	Mean age, years (range)	Concomitant CABG, *n* (%)
Rizzoli	2006	1983–2002	809	Stented	Porcine	Retrospective	6.4	68.0 (–)	238 (29)
Ruggieri	2012	1983–94	1002	Stented	Pericardial	Prospective	13.7	74.3 (–)	151 (15)
Sakamoto	2006	1991–2002	53	Stented	Pericardial	Retrospective	7.1	68.8 (–)	4 (8)
Sansone	2014	1996–2004	138	Stented + stentless	Porcine + pericardial	Retrospective	10.4	62.0 (–)	0 (0)
Silberman	2008	1993–2004	163	Stented + stentless	–	Retrospective	5.1	71.0 (25–87)	73 (45)
Sjögren	2006	1990–93	152	Stented	Pericardial	Retrospective	6.2	79.5 (75–91)	74 (49)
Stanger	2014	2005–09	149	Stentless	Pericardial	Retrospective	5.5	73.6 (47–87)	79 (53)
Pooled			55 712				6.7	71.8	21 115 (40)

CABG: coronary artery bypass grafting; RCT: randomized controlled trial; AVR: aortic valve replacement; MVR: mitral valve replacement; '–': variable not reported.
[a]The full references of the included studies are provided in Supplementary Material.
[b]Mean follow-up of total population, including MVR patients.
[c]Median.
[d]First 174 patients were prospectively followed, the remaining patients retrospectively.
[e]Mean and range age of the total population, including MVR patients.
[f]Only the subgroup of patients who received a Carpentier-Edwards Perimount pericardial valve was included. The subgroup of patients who received a Carpentier-Edwards supra-annular porcine valve was excluded because of overlap with the patient population from another included study.
[g]Only the subgroup of patients with isolated AVR (without concomitant CABG) was included.

(61.9 vs 55.0% in studies on stented versus stentless bioprostheses, respectively) and the percentage of concomitant CABG procedures (41.5 vs 28.9% in studies on stented versus stentless bioprostheses, respectively). The early mortality risk and late mortality rate are higher in studies on stented bioprostheses, whereas the SVD and reintervention rates are higher in studies on stentless bioprostheses.

The results of the subgroup analyses comparing studies with retrospective versus prospective designs are reported in Supplementary Tables 17 and 18. There were no large differences in outcome measures between retrospective and prospective studies; therefore, we can safely combine the outcomes of both types of studies in our meta-analysis.

Supplementary Table 19 presents the results of the subgroup analysis of studies on bioprostheses without concomitant CABG ($n = 6$) versus with concomitant CABG ($n = 45$). The mean patient age was higher in the AVR with concomitant CABG group (72.1 vs 67.4 years in AVR with CABG versus AVR without CABG, respectively). The late mortality rate is higher in the studies including concomitant CABG (5.83%/patient-year) than in those including only isolated AVR (4.81%/patient-year). In addition, the rates of late SVD, bleeding, endocarditis and reintervention are higher in studies on AVR with CABG than those on AVR without CABG. This subgroup analysis could not be performed for the studies on allografts because none of the studies reported outcomes of AVR without CABG.

Publication bias

The funnel plots showed evidence of possible publication bias in all outcome measures. Smaller studies with relatively high event rate estimates seemed to be less likely to be published. Figure 3 shows the funnel plot of reintervention rate in studies on bioprostheses. The other funnel plots can be found in Supplementary Material.

DISCUSSION

This is the first comprehensive systematic review and meta-analysis of the outcomes after surgical AVR with bioprostheses and allografts reflecting an overview of reported outcome after biological AVR in the past 15 years. In this study, we have screened over 8000 studies and included almost 70 studies from which we extracted data on the outcomes after AVR. The results of this study can inform patients and doctors about the expected outcomes after AVR with bioprostheses or allografts and thereby support prosthetic valve selection. Furthermore, we will use the results of this study in microsimulation models to predict individual patient outcomes and estimate the cost-effectiveness of AVR with bioprostheses or allografts. Finally, the results can be used as a benchmark for the performance of new alternative interventions for conventional surgical AVR, such as sutureless valves, transcatheter aortic valve implantation (TAVI) and, in the future, potentially *in situ* tissue-engineered heart valves.

Patient and study characteristics

There are several differences in the patient and study characteristics between the studies on bioprostheses and allografts. Patients in studies on bioprostheses are older (mean age: 71.8 vs 48.8 years in studies on bioprostheses versus allografts), they have more concomitant CABG (40.0 vs 11.9% in studies on bioprostheses versus

Table 2: Overview of included publications on allografts

First author[a]	Year of publication	Implantation period	No. of patients	Surgical technique, %		Study design	Mean follow-up (years)	Mean age, years (range)	Endocarditis as indication for surgery, *n* (%)	Concomitant CABG, *n* (%)
				Subcoronary	Root replacement					
Ali	2010	1991–2001	217	60	40	Retrospective	6.4	62.0 (–)	–	43 (20)
Ganguly	2004	1990–98	58[b]	83	17	Retrospective	5.5	63.0 (22–88)	8 (14)	12 (21)
Grocott-Mason	2000	1969–93	381	92	8	Retrospective	9.8	53.8 (15–84)	–	60 (16)
Hickey	2007	1973–83	200	100	0	Retrospective	15.8	– (–)	5 (3)	4 (2)
Kaya	2005	1989–2003	213	0	100	Retrospective	5.8	51.3 (14–79)	125 (59)	17 (8)
Killian	2010	1992–?	351	21	79	Prospective	15.2	51.6 (12–84)	62 (18)	42 (12)
Kitamura	2011	1990–?	40	58	43	Retrospective	9.9	50.4 (16–73)	18 (45)	5 (12.5)
Mokhles	2014	1987–2010	356	26	74	Prospective	10.8	44.4 (16–83)	–	34 (10)
O'Brien	2001	1969–98	1022	66[c]	34	Retrospective	7.3	46.6 (1–80)	–	110 (11)
Ruzmetov	2012	1990–2011	44	0	100	Retrospective	7.4	18.8 (0–40)	12 (27)	–
Smedira	2006	1987–2000	744	3	97	Retrospective	5.6	49.0 (18–44)	186 (25)	112 (15)
Talwar	2005	1994–2003	154	71	29[d]	Prospective	5.2	28.8 (5–68)	4 (3)	6 (4)
Vuran	2012	?–?	40	0	100	Retrospective	5.6	40.0[e] (0–79)	20 (50)	–
Wasywich	2003	1980–89	52	–	–	Retrospective	6.8	73.0[e] (70–80)	–	–
Pooled			3872	45	55		8.5	48.8	23.9	445 (12)

CABG: coronary artery bypass grafting; '–': variable not reported.
[a]The full references of the included studies are provided in Supplementary Material.
[b]Including pulmonary homografts ($n = 11$).
[c]Including intraluminal cylinder implant ($n = 35$).
[d]Including conduits replacing the aortic valve and ascending aorta ($n = 6$).
[e]Median.

Table 3: Pooled estimates of outcomes after AVR with bioprostheses and allografts

	Bioprostheses	Reported in no. of studies	I^2, % (χ^2 *P*-value)	Allografts	Reported in no. of studies	I^2, % (χ^2 *P*-value)
Study characteristics						
No. of studies	54			14		
No. of patients	55 712			3872		
Mean follow-up, years ± SD	6.7 ± 4.7	54		8.5 ± 3.0	14	
Mean age, years ± SD	71.8 ± 9.3	52		48.8 ± 13.0	13	
Male (%)	61.0	48		69.4	13	
Concomitant CABG (%)	40.0	51		11.9	11	
Early mortality						
Early mortality, %	4.99 (4.44–5.62)	48	81 (0.000)	5.03 (3.61–7.01)	14	73 (0.000)
Early valve-related events						
SVD, %	0.58 (0.01–25.32)	3	91 (0.000)		0	
NSD, %		2			0	
Valve thrombosis, %	0.34 (0.15–0.79)	3	0 (0.488)		0	
Thromboembolism, %	2.95 (1.55–5.60)	7	92 (0.000)		0	
Re-exploration for bleeding, %	4.06 (2.93–5.63)	14	92 (0.000)		1	
Endocarditis, %	0.22 (0.07–0.70)	4	36 (0.194)		1	
Late mortality						
Late mortality, %/year	5.70 (4.99–6.53)	47	99 (0.000)	1.68 (1.23–2.28)	10	86 (0.000)
Cardiac late mortality %/year	2.49 (1.95–3.18)	29	98 (0.000)	1.03 (0.88–1.19)	8	0 (0.760)
Valve-related late mortality, %/year	0.92 (0.74–1.15)	33	94 (0.000)	0.41 (0.29–0.58)	9	51 (0.037)
SUUD, %/year	0.15 (0.09–0.26)	21	90 (0.000)		2	
Late valve-related events						
SVD, %/year	0.60 (0.47–0.76)	37	93 (0.000)	2.26 (1.02–4.97)	3	90 (0.000)
NSD, %/year	0.20 (0.13–0.32)	20	88 (0.000)		1	
Valve thrombosis, %/year	0.04 (0.03–0.07)	13	0 (0.651)		0	
Thromboembolism, %/year	1.10 (0.83–1.47)	36	97 (0.000)	0.46 (0.20–1.08)	5	93 (0.000)
Bleeding, %/year	0.44 (0.30–0.65)	31	96 (0.000)	0.15 (0.09–0.25)	3	0 (0.548)
Endocarditis, %/year	0.38 (0.32–0.44)	35	57 (0.000)	0.42 (0.31–0.58)	5	28 (0.236)
Reinterventions						
Total, %/year	0.75 (0.61–0.91)	47	95 (0.000)	1.87 (1.52–2.31)	13	80 (0.000)
Valve-related, %/year	0.72 (0.60–0.86)	45	94 (0.000)	1.85 (1.49–2.29)	13	81 (0.000)
SVD, %/year	0.42 (0.33–0.54)	37	92 (0.000)	1.15 (0.77–1.70)	8	90 (0.000)
NSD, %/year	0.11 (0.07–0.17)	28	74 (0.000)	0.13 (0.05–0.32)	7	73 (0.001)
Valve thrombosis, %/year	0.03 (0.02–0.05)	25	0 (0.642)	0.02 (0.01–0.06)	8	0 (0.655)
Endocarditis, %/year	0.19 (0.16–0.23)	31	46 (0.004)	0.27 (0.19–0.38)	9	36 (0.128)

95% CIs of the pooled estimates are provided in parentheses.
Pooled estimates are only reported when ≥3 studies reported the outcome measure.
Total numbers of early and late valve-related events are not reported because few studies reported all valve-related events.
SVD: structural valve deterioration; NSD: non-structural valve dysfunction; SUUD: sudden unexpected unexplained death; CABG: coronary artery bypass grafting.

allografts) and the mean follow-up duration of studies on bioprostheses is shorter than for allografts (6.7 vs 8.5 years in studies on bioprostheses versus allografts). These differences make it impossible to draw meaningful conclusions about the differences in performance between bioprostheses and allografts based on the results of this study.

In many institutions, root replacement instead of subcoronary valve replacement is the technique of choice for implanting allografts in the aortic position since the mid-1990s [4, 16, 17]. This trend is also reflected in our review where studies with a larger proportion of root replacement as the surgical technique are generally studies with a more recent implantation period.

Early mortality

Bioprostheses. The early mortality risk after AVR with bioprostheses is lower in recent years, which reflects improvements in the past decades in diagnosis and perioperative management of AVR patients.

Our results indicated that studies on bioprostheses with a high proportion of male patients reported lower early mortality risks and NSD rates. The relative worse outcomes for women may be caused by the different preoperative risk profiles compared with men: women undergoing AVR are older, more symptomatic (i.e. advanced NYHA class), have smaller body surface areas, and more comorbidities, and more often require emergency operations than men [18–20]. Delayed presentation of valve problems and/or later referral of women to cardio-thoracic surgery may explain some of the differences in risk profile [19]. There is some controversy about the impact of these risk profile differences on the outcomes after AVR between men and women. Some studies found an increased early mortality risk in women undergoing AVR with concomitant CABG [19, 21], but there is no evident association between gender and early mortality after isolated AVR [18, 21, 22].

Allografts. More recent studies on AVR with allografts reported a relatively high early mortality risk. A possible explanation is that the indication for using allografts for AVR has changed over time from a broad range of patients to mostly complex patients with

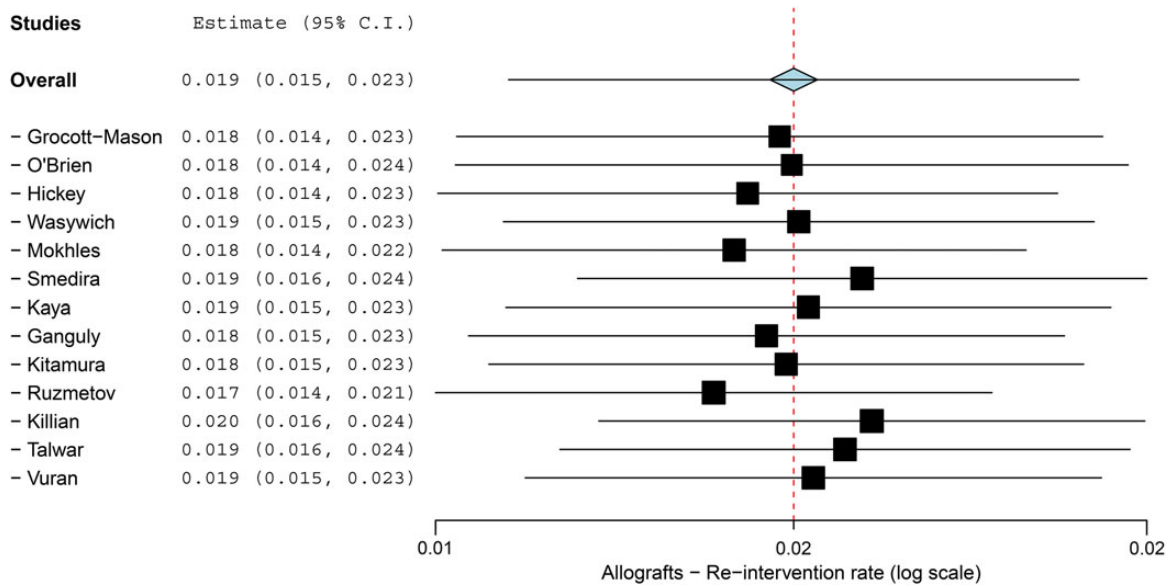

Figure 2: Forest plot of leave-one-out analysis of early mortality risk in studies on allografts. CI: confidence interval.

Table 4: Subgroup analysis stented versus stentless bioprostheses

	Stented bioprostheses	Reported in no. of studies	Stentless bioprostheses	Reported in no. of studies
Study characteristics				
No. of studies	37		13	
No. of patients	44 208		3412	
Mean follow-up, years ± SD	6.6 ± 4.9	37	7.4 ± 3.3	13
Mean age, years ± SD	71.9 ± 9.5	35	70.6 ± 8.4	13
Male (%)	61.9	31	55.0	13
Concomitant CABG (%)	41.5	34	28.9	11
Early mortality				
Early mortality, %	5.15 (4.43–5.98)	32	4.17 (3.08–5.65)	11
Early valve-related events				
SVD, %	0.03 (0.00–0.19)	2		1
NSD, %		2		1
Valve thrombosis, %	0.20 (0.06–0.68)	3		1
Thromboembolism, %	1.41 (0.52–3.81)	5	3.64 (0.40–32.71)	2
Re-exploration for bleeding, %	3.62 (2.53–5.16)	11	6.96 (5.08–9.55)	5
Endocarditis, %	0.10 (0.04–0.24)	3		2
Late mortality				
Late mortality, %/year	6.01 (5.10–7.08)	32	4.56 (3.70–5.61)	12
Late valve-related events				
Cardiac late mortality %/year	2.31 (1.73–3.09)	19	2.21 (1.50–3.26)	8
Valve-related late mortality, %/year	0.93 (0.74–1.16)	24	0.89 (0.43–1.84)	8
SUUD, %/year	0.19 (0.11–0.35)	16	0.05 (0.02–0.18)	5
SVD, %/year	0.48 (0.38–0.62)	26	1.10 (0.65–1.86)	9
NSD, %/year	0.16 (0.10–0.27)	18	0.33 (0.06–1.77)	3
Valve thrombosis, %/year	0.04 (0.02–0.07)	11		2
Thromboembolism, %/year	1.04 (0.83–1.30)	26	0.99 (0.66–1.47)	8
Bleeding, %/year	0.43 (0.32–0.57)	21	0.31 (0.14–0.70)	7
Endocarditis, %/year	0.34 (0.27–0.43)	25	0.43 (0.33–0.58)	8
Reinterventions				
Total, %/year	0.65 (0.51–0.83)	34	1.06 (0.77–1.46)	12
Valve-related, %/year	0.63 (0.51–0.78)	32	0.99 (0.69–1.41)	12
SVD, %/year	0.33 (0.24–0.44)	24	0.82 (0.57–1.19)	11
NSD, %/year	0.08 (0.05–0.13)	19	0.27 (0.14–0.50)	9
Valve thrombosis, %/year	0.03 (0.02–0.04)	19	0.04 (0.01–0.10)	8
Endocarditis, %/year	0.16 (0.13–0.20)	22	0.24 (0.15–0.37)	9

95% CIs of the pooled estimates are provided in parentheses.
Pooled estimates are only reported when ≥3 studies reported the outcome measure.
Total numbers of early and late valve-related events are not reported because few studies reported all valve-related events.
SVD: structural valve deterioration; NSD: non-structural valve dysfunction; SUUD: sudden unexpected unexplained death.

active endocarditis [4, 6]. Indeed, in this review, three relatively recent studies with endocarditis as indication for surgery in more than 40% of the patients reported relatively high early mortality risks [23–25].

Early valve-related events

Bioprostheses. The results of our study reflect low risks for most early events after AVR with bioprostheses, with bleeding and thromboembolism being most common. They reflect that AVR is a safe procedure; however, these low risks can also reflect underreporting since most included studies did not report early event occurrence. Of note, although we reported an early event risk for endocarditis during the first postoperative month, the risk of experiencing endocarditis still increases until 6 months postoperatively after which it reaches a plateau close to zero [26].

Allografts. Occurrences of early valve-related events after AVR with allografts were not or rarely reported.

Late mortality

This review nicely illustrates that late deaths after AVR are only in part cardiac, and valve-related and SUUDs comprise only part of cardiac mortality. The remaining non-valve-related cardiac mortality can be ascribed to the excess mortality risk in patients after AVR, due to underreporting of valve-related events and left ventricular dysfunction associated with heart valve disease [27–29].

Bioprostheses. Our meta-regression confirmed the commonly reported finding that higher patient age at implant is associated with a higher risk of late mortality after AVR with bioprostheses [14, 30, 31].

Allografts. For allografts, there was a lower late mortality in the studies with a high proportion of patients with pre-intervention NYHA class III/IV. This seems counterintuitive, but might be explained by the fact that the indication in most patients receiving allografts is endocarditis, which is often accompanied by a worse pre-intervention NYHA class. Mokhles *et al.* [32] have shown that the late mortality of hospital survivors after AVR for endocarditis is comparable with the general population. This indicates that although these patients have a worse functional class before surgery, after surgery their endocarditis is cured and their mortality hazard returns to that of the general population. This can also explain why the late mortality rate is lower in studies on allografts with a more recent implantation period; in recent years, the indication for using allografts for AVR is often endocarditis [4, 6]. Indeed, three relatively recent studies in this review, where the indication for surgery was endocarditis in more than 40% of the patients, reported relatively low late mortality rates [23–25]. Furthermore, the low mean age of two studies with a high proportion of concomitant procedures [33, 34] might explain why studies with a high proportion of concomitant procedures report lower late mortality rates.

Surprisingly, prospective studies on allografts reported lower late mortality rates than retrospective studies. This observation is probably caused by more common use of prospective design in more recent years. Indeed, three 'old' retrospective studies (studies where the implantation period ended before 2000) [35–37] in this review report relatively high late mortality rates.

Late valve-related events

Bioprostheses. For bioprostheses, the most commonly reported late valve-related event was not SVD but thromboembolism, reflecting the advanced age of the patient population and the common occurrence of atrial fibrillation in this age group. The occurrence of SVD was less than 1% per year and more common in studies with a lower mean patient age, which confirms previous observations [26].

Prospective studies on bioprostheses reported lower SVD rates compared with retrospective studies. This was unexpected because one would expect that prospective studies report higher SVD rates because of more accurate patient follow-up. The most likely explanation for this counterintuitive observation is the more common use of prospective study design in more recent years which results in relatively short follow-up periods, while the occurrence of SVD increases over time [26].

Allografts. For allografts, SVD was the most commonly occurring late valve-related event. In this review, the occurrence of endocarditis after AVR is low. This is remarkable because the indication for AVR with allografts is often endocarditis. These results confirm that allografts have a good resistance to infection.

In the meta-regression, several associations were observed related to late occurrence of different valve-related events after allograft AVR. However, given the observational design of studies included in the review, the small number of studies reporting late valve-related events after allograft AVR and the low event occurrence rates; these associations should be interpreted cautiously and will not be further discussed here.

Reinterventions

Bioprostheses. As would be expected, valve-related reinterventions in bioprostheses studies showed low occurrence rates and were usually for SVD, whereas endocarditis and NSD were less common indications. Studies with a relatively old patient population reported

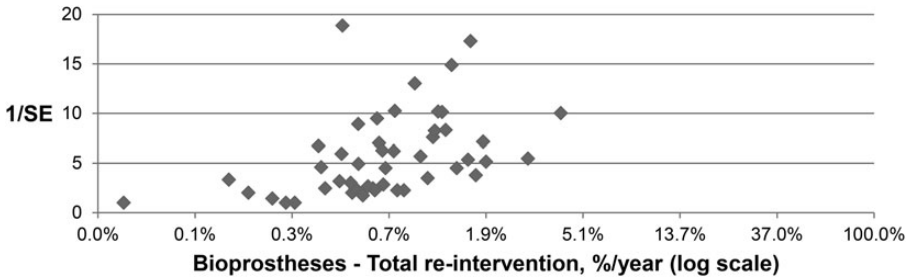

Figure 3: Funnel plot of the total reintervention rate in studies on bioprostheses.

lower reintervention rates. This is in accordance with previous reports that show that older patients are less likely to be reoperated on [17, 38, 39].

Allografts. Valve-related reinterventions in allografts were most often for SVD, and to a lesser extent for NSD or endocarditis. Prospective studies on allografts reported lower reintervention rates compared with retrospective studies. The effect is probably caused by the more common use of prospective study design in more recent years. Indeed, 'old' retrospective studies in this review report slightly higher reintervention rates.

Stented versus stentless bioprostheses

Although it should be noted that in stented bioprostheses studies, the proportion of males is higher, as is the proportion of patients undergoing concomitant CABG, the results of the present study indicate that early mortality risk and late mortality rate appear lower in studies on stentless bioprostheses compared with stented bioprostheses. In contrast, we found that SVD and reintervention rates appear higher in studies on stentless bioprostheses compared with stented bioprostheses. The observed lower late mortality rate in stentless bioprostheses is in accordance with the hypothesis that the haemodynamic superiority of stentless bioprostheses results in survival benefits compared with stented bioprostheses [3], but may also be the result of patient selection. The lower late mortality rate in stentless bioprosthesis studies makes it difficult to directly compare the durability of stentless with that of stented bioprostheses as the risk of death competes with the risk of SVD and reintervention.

Concomitant coronary artery bypass grafting

Many studies included AVR with concomitant CABG and therefore, the results of our study do not reflect the outcomes after isolated AVR. To explore the influence of including studies reporting on outcomes of AVR with concomitant CABG (in a proportion of the patient population), we have performed a subgroup analysis in the studies on bioprostheses comparing the outcomes of studies including and excluding concomitant CABG. This subgroup analysis showed that there are differences in the outcomes of AVR with or without CABG. However, the differences were not statistically significant (i.e. the CIs of the subgroups overlapped). Furthermore, concomitant CABG is a common concomitant procedure with AVR and therefore, the results presented in our study are relevant for clinical practice.

Limitations

First, inherent limitations of meta-analyses and combining data from (retrospective) observational studies should be taken into consideration [40]. Secondly, selection bias (of patients included in the studies) might have influenced the study outcomes due to the nature of observational studies (i.e. no randomized allocation of patients to treatment options). Thirdly, publication bias may have potentially led to underestimation of the pooled estimates when studies with relatively poor outcomes are not published. Fourthly, by reporting LORs, we assumed a constant hazard for the valve-related events and late mortality, while in fact the distributions of these events are time-related [26]. Fifthly, initially we wished to provide separate results for different age groups. However, this was not possible because most studies included patients of all ages. Finally, there was substantial heterogeneity between studies in most outcome measures, which may potentially lead to inaccurate results. However, we pursued a thorough examination of possible sources of heterogeneity using univariable meta-regression analysis and we identified several covariates that may explain the heterogeneity between studies in the outcome measures. We deliberately did not perform multivariable meta-regression analysis because the underlying data were based on observational studies.

CONCLUSION

This comprehensive systematic review and meta-analysis provided an overview of the outcomes after surgical AVR with bioprostheses and allografts during the last 15 years. The results of this systematic review and meta-analysis can support patients and doctors in the prosthetic valve choice and can be used in microsimulation models to predict patient outcomes and estimate the cost-effectiveness of AVR with bioprostheses or allografts compared with current and future heart valve prostheses.

REVIEW

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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