Bioprosthetic aortic valve replacement in elderly patients: Meta-analysis and microsimulation

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ABSTRACT

Objective: To support decision-making in aortic valve replacement (AVR) in elderly patients, we provide a comprehensive overview of outcome after AVR with bioprostheses.

Methods: A systematic review was conducted of studies reporting clinical outcome after AVR with bioprostheses in elderly patients (mean age ≥ 70 years; minimum age ≥ 65 years) published between January 1, 2000, to September 1, 2016. Reported event rates and time-to-event data were pooled and entered into a microsimulation model to calculate life expectancy and lifetime event risks.

Results: Forty-two studies reporting on 34 patient cohorts were included, encompassing a total of 12,842 patients with 55,437 patient-years of follow-up (pooled mean follow-up 5.0 ± 3.3 years). Pooled mean age was 76.5 ± 5.5 years. Pooled early mortality risk was 5.42% (95% confidence interval [CI], 4.49–6.55), thromboembolism rate was 1.83%/year (95% CI, 1.28–3.61), and bleeding rate was 0.75%/year (95% CI, 0.50–1.11). Structural valve deterioration (SVD) was based on pooled time to SVD data (Gompertz; shape: 0.124, rate: 0.003). For a 75-year-old patient, this translated to an estimated life expectancy of 9.8 years (general population: 10.2 years) and lifetime risks of bleeding of 7%, thromboembolism of 17%, and reintervention of 9%.

Conclusions: The low risks of SVD and reintervention support the use of bioprostheses in elderly patients in need of AVR. The estimated life expectancy after AVR was comparable with the general population. The results of this study inform patients and clinicians about the expected outcomes after bioprosthetic AVR and thereby support treatment decision-making. Furthermore, our results can be used as a benchmark for long-term outcomes after transcatheter aortic valve implantation in patients who were eligible for surgery and other (future) alternative treatments (eg, tissue-engineered heart valves). (*J Thorac Cardiovasc Surg* 2019;157:2189–97)

Microsimulation-based lifetime risks of valve-related events after bioprosthetic AVR.

Central Message

The low risks of SVD and reintervention support the use of bioprostheses in elderly patients in need of AVR. The estimated life expectancy after AVR was comparable with the general population.

Perspective

This study provides a comprehensive overview of reported outcomes after AVR with bioprostheses in elderly patients that can be used as a benchmark for alternative treatments. Extrapolation to life expectancy and lifetime risks of valve-related events enables better understanding of the risks associated with bioprosthetic AVR by patients and thereby allows better use in shared decision-making.

See Commentaries on pages 2198 and 2200.

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Native aortic valve degeneration represents a major public health burden in the aging population of developed countries. In patients older than 75 years, the prevalence of aortic stenosis is 2.8% and of aortic regurgitation 2.0%.¹ Due to the aging population and improvements in health care, it is

Scanning this QR code will take you to the article title page to access supplementary information.

Abbreviations and Acronyms

AVR	= aortic valve replacement
NSVD	= nonstructural valve dysfunction
SVD	= structural valve deterioration
TAVI	= transcatheter aortic valve implantation
TE	= thromboembolism

expected that the number of aortic valve implantations will increase, especially in elderly patients.^{1,2}

When the degenerated aortic valve needs replacement, there are 2 widely used treatment options for elderly patients: surgical aortic valve replacement (AVR) or transcatheter aortic valve implantation (TAVI). For surgical AVR, 2 types of valve substitutes are available: bioprostheses and mechanical prostheses. Current clinical guidelines recommend bioprostheses in patients older than 65³/70⁴ years because their life expectancy is usually shorter than the durability of the valve and therefore they will probably not experience the disadvantages of bioprostheses (ie, increased risk of structural valve deterioration [SVD] and subsequent risk of reintervention).^{3,4} Bioprostheses are preferred over mechanical prostheses because they are not accompanied with an increased risk of thromboembolism (TE) and subsequent need of lifelong anticoagulation, which carries an increased risk of bleeding events.^{3,4}

Ideally, the choice of heart valve substitute should be a shared decision, where the patient is fully informed about the risks and benefits associated with each type of valve substitute and is able to weigh these in relation to his/her values and goals in life.^{3,4} However, a comprehensive overview of published evidence on long-term outcome after AVR in elderly patients to guide this decision-making is lacking. We therefore provide a systematic review and meta-analysis of reported outcomes after AVR with bioprostheses in elderly patients applying the latest methods of meta-analysis and calculating microsimulation-based estimates of age-specific life expectancy and lifetime risks of valve-related events (Video 1).

METHODS

Search Strategy and Study Selection

This systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines⁵ and registered in PROSPERO (CRD42017054849). On September 1, 2016, Embase, MEDLINE, The Cochrane Central, Google Scholar, Web-Of-Science, and PubMed publisher databases were searched by a biomedical information specialist using keywords regarding outcomes of AVR with bioprostheses (Appendix E1). Titles and abstracts were independently screened by 2 reviewers (S.H., M.H.). Inclusion criteria were observational studies or randomized controlled trials reporting on outcomes of isolated AVR (maximum 10% multiple valve replacement was allowed) with bioprostheses of at least 20 patients with mean age ≥ 70 and minimum age ≥ 65 published in or after the year 2000. Studies were excluded if they

exclusively enrolled patients with pre-existing comorbidities or certain prosthesis sizes or only reported results of propensity matched study populations (because of less generalizability of the study population). In case of multiple publications on the same patient population, the publication with most follow-up patient-years and/or overall completeness of data was included. In case of disagreement between the reviewers, an agreement was negotiated.

Data Extraction

Data extraction was performed with independently by 2 researchers (S.H., M.H.) using Microsoft OfficeExcel 2011 (Microsoft Corp, Redmond, Wash) and then jointly verified. Recorded study characteristics, baseline patient and procedural characteristics, and outcome measures are listed in Appendix E2. Occurrence of valve-related events, reintervention, and mortality were documented according to the 2008 American Association for Thoracic Surgery/European Association for Cardio-Thoracic Surgery/Society of Thoracic Surgeons guidelines.⁶ Early outcome events were defined as occurring within the first 30 postoperative days, regardless of the patient's location. Late outcome events were defined as occurring after the first 30 postoperative days. If total follow-up duration in patient-years was not reported, it was calculated by multiplying the mean follow-up with the number of patients of that study.

Statistical Analyses

Statistical software used is listed in Appendix E3. Continuous variables are presented as mean $\pm$ standard deviation. Categorical variables are presented as counts and percentages. Linearized event occurrence rates are presented as percentages per year.

Meta-Analysis

Pooled baseline patient characteristics were calculated with the use of sample size weighting. Early risks of mortality and valve-related events and linearized occurrence rates of late mortality, valve-related events, and reintervention were calculated for each individual study and pooled using 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.⁷ Outcomes were pooled on a logarithmic scale, as the Shapiro–Wilk test revealed a significantly skewed distribution among the included studies in the majority of outcome measures. Inverse variance weighting was conducted according to the number of patients for early mortality and according to the number of follow-up patient-years for late events. In case an event was reported not to occur in an individual study, it was assumed that 0.5 patient experienced that event for the purpose of inverse variance weighting.

Pooled Kaplan–Meier time-to-event meta-analysis was conducted by extracting and combining estimates of individual patient time-to-event data from published Kaplan–Meier curves. Published Kaplan–Meier curves were digitized. An estimate of the individual patient time-to-event data was then extracted from the digitized curve coordinates, assuming a constant rate of censorship between each time point at which the number of patients at risk were specified.⁸ If there were no Kaplan–Meier curves available, but time points of each event were reported or there were no events, the individual patient time-to-event data was manually reconstructed up to a maximum follow-up of the mean follow-up plus two standard deviations, under the same assumption of a constant rate of censorship. Reconstructed individual patient time-to-event data of each study were then combined.

Heterogeneity

The Cochrane-Q statistic and I^2 statistic were used to assess heterogeneity between studies. Potential causes of heterogeneity were explored with univariable random effects meta-regression in the main outcome measures with significant heterogeneity and more than three studies reporting the

VIDEO 1. Introduction and explanation of the importance and relevance of this systematic review, meta-analysis, and microsimulation study on the outcomes after bioprosthetic aortic valve replacement in elderly patients. Video available at: [https://www.jtcvs.org/article/S0022-5223\(18\)32794-6/fulltext](https://www.jtcvs.org/article/S0022-5223(18)32794-6/fulltext).

outcome measure. The following covariates were explored: study design (retrospective/prospective), region of origin, median year of valve implantation period, mean follow-up duration, mean patient age, proportion of male patients, emergency surgery, preoperative New York Heart Association class, hemodynamics, and concomitant coronary artery bypass graft. The influence of potential publication bias on pooled outcomes was investigated by conducting sensitivity analyses where the quartile of studies with the smallest sample size was temporarily excluded.

Microsimulation

A microsimulation model parametrized with the pooled outcomes of our meta-analysis was used to extrapolate the results from the meta-analysis to age-specific life expectancy and lifetime risk of valve-related morbidity (Figure 1).⁹ The risks of mortality and reintervention as a direct result of the events were derived from a study on patients after bioprosthetic AVR (mean age: 70 years).¹⁰

The occurrence rates of valve-related events had to be extrapolated beyond the observation period of the meta-analysis. The occurrence rate of SVD after bioprosthetic AVR was modeled by fitting a Gompertz distribution to our pooled time-to-event data (Figure E1), showing an increasing occurrence rate of SVD over time. There was no time-to-event data

available for other valve-related events (nonstructural valve dysfunction, endocarditis, TE, valve thrombosis, and endocarditis); therefore, we assumed constant hazard rates for these events.

Total mortality consists of death due to valve-related events and death due to non-valve-related causes. Death due to non-valve-related causes consists of background mortality in the general population and excess mortality not directly resulting from valve-related events. The background mortality of the general population was obtained for the pooled median year of intervention among included studies (1998, assuming a constant incidence rate over time in each study), adjusted for sex (54.8% male), and the regions of origin of the included study populations (Europe:52%, North America:45%; Asia:3%).^{11,12}

To estimate the hazard ratios of additional excess mortality not directly resulting from valve-related events relative to background mortality, we compared the survival simulated by the microsimulation model with the observed survival in our meta-analysis of time-to-event data (temporarily excluding early mortality, as early mortality was a separate input in our microsimulation model). In these microsimulations, we repeatedly simulated the survival of 10,000 patients with a mean age and proportion of males of the study population using the same background mortality and mortality due to valve-related events, but with various hazard ratios of excess mortality. The hazard ratio that resulted in the smallest difference between the simulated and observed survival according to the least squares method was chosen as the appropriate hazard ratio for excess mortality. This hazard ratio was assumed to be constant over time.

To obtain age-specific estimates of life expectancy and lifetime risk of valve-related events, the microsimulation model simulated cohorts of 10,000 patients aged 75 or 85 years, of which 54.8% were males (ie, pooled male/female ratio included studies).

To reflect the uncertainty in the input parameters of the microsimulation model (second-order uncertainty) and to describe what this means for uncertainty in the outcomes, we performed probabilistic sensitivity analyses. In the probabilistic sensitivity analyses, the model was run for 500 different sets of randomly drawn input parameters with a sample size of 1000 patients per set. The values of the input parameters of the model were randomly drawn from the following distributions: beta distribution for early mortality risk and probabilities of reintervention and death after events, log-normal distributions for late events, and uniform distributions for the hazard ratio of mortality after reintervention and excess mortality (varied with $\pm 10\%$). For each set of coefficients, the mean outcomes

FIGURE 1. Schematic overview of microsimulation model. The model starts with the aortic valve replacement. Patients can survive the surgery or not. When patients survive the surgery, they can remain “alive,” die from non-valve-related causes, or experience a valve-related event. Patients experiencing an event can die without receiving treatment or receive treatment for the event. After treatment, patients can die or survive the event. When patients survive the event, they can stay alive, experience another event, or die due to non-valve-related causes.

FIGURE 2. Flowchart of study selection. The systematic literature search identified 13,952 studies. After applying inclusion and exclusion criteria, 42 studies were included in this study; 40 studies were included in the meta-analysis, and 2 additional studies were included in the pooled Kaplan–Meier survival curves. *AVR*, Aortic valve replacement; *BAV*, bicuspid aortic valve.

over the 1000 patients was recorded and the mean and the 2.5% and 97.5% percentile (credible interval) over all 500 mean values for each outcome were calculated.

To assess the internal validity of late survival outcomes of the model, the model was run for 10,000 patients with the pooled mean and standard deviation of age (76.5 ± 5.5 years) and proportion of males (54.9%) of studies included in the pooled Kaplan–Meier survival curve. The Kaplan–Meier survival curve obtained from this model was then plotted against the pooled Kaplan–Meier survival curve of early survivors derived from our meta-analysis (temporarily excluding early mortality, as early mortality was a separate input in our microsimulation model).

RESULTS

Study Selection

The systematic literature search identified 13,952 studies (Figure 2). After we applied inclusion and exclusion criteria, the meta-analysis included 40 studies (34 patient cohorts) reporting on bioprostheses encompassing 12,842 patients (Table E1, references are provided in Appendix E4). Multiple studies on 1 patient cohort were included when studies provided complementary information.

TABLE 1. Pooled estimates of patient and procedural characteristics and outcomes bioprosthetic AVR in elderly patients

	Pooled estimate	Included studies, n	I ² , % (χ^2 P value)
Study characteristics			
Studies	40		
Patients	12842	34	
Follow-up, y, mean $\pm$ SD	5.0 $\pm$ 3.3	25	
Age, y, mean $\pm$ SD	76.5 $\pm$ 5.5	30	
Male, n (%)	5998 (54.9%)	31	
Emergency surgery, n (%)	172 (2.8%)	15	
NYHA class III/IV, n (%)	4948 (71.5%)	22	
Hemodynamics, n (%)			
Stenosis	4012 (65.7%)	17	
Regurgitation	1059 (16.9%)	17	
Combined	1002 (16.5%)	16	
Concomitant procedures, n (%)			
CABG	3831 (42.4%)	23	
Aortic surgery	187 (6.3%)	9	
Other valve repair/replacement	344 (5.0%)	11	
Other/unknown	183 (5.3%)	8	
Early mortality			
Early mortality, %	5.42 (4.49-6.55)	33	74 (0.000)
Early events			
Re-exploration for bleeding, %	4.18 (3.37-5.20)	13	32 (0.129)
Stroke, %	2.73 (1.75-4.28)	8	0 (0.700)
MI, %	0.88 (0.52-1.50)	6	0 (0.426)
Renal failure, %	6.60 (4.57-9.51)	10	69 (0.001)
Late events			
SVD, %/year	0.42 (0.17-1.05)	10	92 (0.000)
NSVD, %/year	0.47 (0.18-1.24)	8	78 (0.000)
Endocarditis, %/year	0.57 (0.43-0.76)	15	20 (0.235)
Thromboembolism, %/year	1.83 (1.28-2.61)	12	78 (0.000)
Valve thrombosis, %/year	0.12 (0.04-0.39)	3	25 (0.262)
Bleeding, %/year	0.75 (0.50-1.11)	13	46 (0.035)
Reintervention			
Reintervention (valve-related), %/year	0.56 (0.35-0.89)	13	87 (0.000)
Late mortality			
Total mortality, %/year	5.43 (4.47-6.60)	20	95 (0.000)
Cardiac mortality, %/year	1.76 (1.07-2.90)	10	93 (0.000)
Valve-related mortality, %/year	0.78 (0.41-1.46)	8	76 (0.000)
SUD, %/year	0.41 (0.17-0.98)	7	54 (0.041)

95% confidence intervals of the pooled estimates are provided in parentheses. *SD*, Standard deviation; *NYHA*, New York Heart Association; *CABG*, coronary artery bypass grafting; *MI*, myocardial infarction; *SVD*, structural valve deterioration; *NSVD*, nonstructural valve dysfunction; *SUD*, sudden unexplained death.

Long-term follow-up was reported in 25 studies with a pooled mean follow-up of 5.0 years. Two studies^{13,14} were not included in the meta-analysis because of overlapping study populations, but these studies were included in the pooled Kaplan–Meier survival curve because the overlapping studies did not report Kaplan–Meier curves.

Meta-Analysis

Pooled estimates of patient and procedural characteristics, mortality, valve-related events, and reintervention risks and rates after AVR are presented in Table 1. The risk estimates of death and reoperation after valve-related events are presented in Table E2. Estimates of outcomes in individual

studies are provided in Tables E3–E5. Early events besides re-exploration for bleeding, stroke, myocardial infarction, and renal failure were reported too inconsistently to include in the analyses.

Figure 3 shows the pooled Kaplan–Meier survival curves after bioprosthetic AVR (n = 6096, mean follow-up 4.1 $\pm$ 2.9 years). The 5-year survival was 72.1%. The survival curve of the general population was based on weighted survival tables of the general population adjusted to the regions of origin of the included study populations (Europe: 50%, United States: 45%, Asia: 5%) for the pooled median year of intervention among included studies (2001). The microsimulation model was run with these survival tables

FIGURE 3. Pooled Kaplan–Meier survival curve of patients after bioprosthetic AVR (with 95% confidence interval) and the age- and sex-matched general population (dotted line). After bioprosthetic AVR, there was an early phase of elevated mortality risk. After approximately 2 years, the survival of patients after bioprosthetic AVR was comparable with the age- and sex-matched general population. AVR, Aortic valve replacement.

at the same mean age and proportion of males as the patient population and with valve-related mortality and events set to zero.^{11,15}

Microsimulation

Least squares regression of modeled versus observed survival revealed that the mortality not directly related to valve-related events (ie, background and excess mortality) was 14% lower after bioprosthetic AVR (hazard ratio: 0.86) compared with the general population (Table E6). The age-specific estimates of (event-free) life-expectancy and lifetime risks of valve-related events based on

TABLE 2. Microsimulation results (event-free) life expectancy and lifetime risks on valve-related events after AVR

Age at surgery	Mean (95% CI)	
	75 y	85 y
Bioprostheses		
Life expectancy, y*	9.8 (9.3-10.6)	5.6 (5.3-6.1)
Event-free life expectancy, y	8.2 (7.7-8.7)	5.0 (4.7-5.4)
Lifetime risks, %		
Structural valve deterioration	7.2 (5.0-10.3)	2.8 (1.6-4.2)
Nonstructural valve dysfunction	4.4 (3.1-5.8)	2.6 (1.6-3.7)
Endocarditis	5.7 (4.2-7.0)	3.1 (2.2-4.4)
Thromboembolism	17.4 (16.1-22.4)	10.2 (8.7-13.3)
Valve thrombosis	1.1 (0.5-2.0)	0.5 (0.2-1.2)
Bleeding	7.4 (5.6-8.9)	4.5 (2.9-5.6)
Reintervention	8.8 (6.5-11.3)	4.2 (3.0-5.9)

CI, Credible interval derived from probabilistic sensitivity analysis. *Life expectancy of the age- and sex-matched general population was 10.2 for 75-year-old patients and 5.6 in 85-year-old patients.

microsimulation analyses are shown in Table 2, Figure 4, and Figure E2. The causes of reintervention and death are presented in Table E7.

Figure E3 shows that the microsimulation model calibrated well with the pooled Kaplan–Meier curves of freedom from SVD and survival of early survivors from our meta-analysis. However, the microsimulation somewhat overestimated mortality within the first 5 years following bioprosthetic AVR and underestimated mortality in later years.

Sensitivity Analyses

Sensitivity analyses showed that potential publication bias did not substantially influence our pooled outcomes, as they remained largely unchanged after temporary exclusion of the quartile with the smallest sample size (before vs after exclusion: early mortality [5.42% vs 5.32%], late mortality [5.43%/year vs 5.39%/year], valve-related reintervention [0.56%/year vs 0.56%/year], SVD [0.42% vs 0.41%], TE [1.83%/year vs 1.78%/year], and bleeding [0.75%/year vs 0.69%/year]).

Heterogeneity

There was substantial heterogeneity in the following outcome measures (Table 1): early mortality, atrial fibrillation, renal failure, and late SVD, nonstructural valve dysfunction (NSVD), TE, bleeding, stroke, and mortality. Univariable random effects meta-regression of bioprostheses studies (Table E8) showed that studies with a greater mean age reported greater early mortality risks.

Studies with a more recent implantation period and studies with a shorter mean follow-up duration reported greater rates of late NSVD after bioprosthetic AVR (moderate correlation between implantation period and mean follow-up duration $r = -0.44$). Studies with a greater proportion of male patients reported greater rates of NSVD. Studies with a greater proportion of aortic stenosis, as opposed to aortic insufficiency, reported greater TE/stroke rates. However, these patients were also relatively old (moderate correlation between proportion aortic stenosis and mean age: $r = 0.57$). Studies with a greater mean follow-up duration reported less bleedings. Studies with a greater mean age or larger proportion of aortic stenosis, as opposed to aortic insufficiency, reported greater late mortality rates. Studies with a greater proportion of porcine valves compared with pericardial valves reported greater early mortality risks and lower late mortality rates. None of the covariates could explain the heterogeneity in early renal failure risks, late SVD, and reintervention.

DISCUSSION

This study summarized the reported contemporary outcomes after surgical AVR with bioprostheses in elderly patients in the current era in a comprehensive systematic

FIGURE 4. Microsimulation-based age-specific lifetime risks of valve-related morbidity after bioprosthetic aortic valve replacement for patients 75 or 85 years old at the time of surgery. TE was the most occurring valve related-event in both patient groups. SVD, Structural valve deterioration; NSVD, nonstructural valve dysfunction; TE, thromboembolism; VT, valve thrombosis.

review and meta-analysis combined with extrapolation of results to age-specific life expectancy and lifetime risks using a microsimulation model. The results of this study can inform patients and clinicians about the expected outcomes after bioprosthetic AVR and thereby support treatment decision-making. The translation of the mortality and event rates to life expectancy and lifetime risks allows for better understanding by patients of the associated risks of bioprosthetic AVR. In addition, our results can be used as a benchmark for long-term outcomes after TAVI in patients who were eligible for surgery once they become available. Furthermore, we will use the results of this study to estimate the potential cost-effectiveness of new alternative interventions for conventional surgical AVR (such as in situ tissue-engineered heart valves).

Mortality

In line with previous research, microsimulation revealed that, despite the early mortality risk, life expectancy after bioprosthetic AVR in elderly patients is comparable with the general population.¹⁶ Careful selection of relatively healthy elderly to undergo AVR, whereas frail elderly patients are rejected for surgery, might explain this finding. This also explains why we found a decreased background mortality in patients compared with the age- and sex-matched general population (ie, hazard ratios for excess mortality <1). The existence of this selection bias is also reflected in lower health care costs of nursing homes in elderly patients after surgical valve replacement compared with the general population.¹⁷

Prosthetic Valve Dysfunction, Endocarditis, and Reintervention

The main disadvantage of bioprostheses is that they are subject to valve degeneration over time. Bioprostheses are known to exhibit lower SVD rates with increasing patient age.^{13,18,19} This is reflected in the SVD rate of 0.42%/

year, which is considerably lower than previously reported for young adults (1.59%/year).²⁰ Our microsimulation results show that 8% of 75-year-old patients and 3% of 85-year-old patients who received a bioprosthesis developed SVD. Subsequently, reintervention rates in these patients were low (0.56%/year vs 1.82%/year in young adults).²⁰ Besides the lower incidence of SVD, these low reintervention rates may also reflect less-diligent follow-up or contraindications to perform surgical reinterventions in older compared with younger patients.²¹ However, the mortality risk after reoperation has significantly decreased over the past decade.^{22,23} Furthermore, valve-in-valve TAVI is emerging as a less-invasive option for reintervention of failing bioprostheses.²⁴

Bleeding, TE, and Valve Thrombosis

Although bioprostheses do not require lifelong anticoagulation treatment, we found a greater occurrence of bleedings than in the general population (0.75%/year vs 0.14%/year).²⁵ This may be explained by early bleedings that occur during the first 3 postoperative months during which anticoagulants are often prescribed.^{3,4} This is supported by our finding that studies with a shorter follow-up reported greater bleeding rates, suggesting the bleedings occur relatively early during follow-up. The greater bleeding rate may also be due to other indications for anticoagulation, such as atrial fibrillation, arising during follow-up in these patients.

TE was the most frequently occurring valve-related event. This TE rate is close to the occurrence rate in the age- and sex-matched general population (1.50%/year).²⁵ This suggests that factors other than heart valve disease (such as increasing incidence of atherosclerotic disease with age) may have a larger influence on the risk of TE in elderly patients.²⁶ The occurrence of valve thrombosis was only reported in 3 studies but appears to be very low.

Prosthetic Valve Selection

In prosthetic valve selection, the risk of SVD and subsequent reintervention associated with bioprostheses is generally weighed against TE and bleeding risk associated with mechanical prostheses. The clinical guidelines recommend bioprostheses in elderly patients requiring AVR.^{3,4} The main reason is that elderly patients are not likely to outlive their bioprosthesis and therefore would not experience the disadvantages of bioprostheses. Our results support the recommendations to use bioprostheses in elderly patients in need of AVR. We demonstrated that the occurrence of SVD after bioprosthetic AVR in elderly patients is low and that reintervention is rarely necessary. Even when a reintervention is necessary, this does not have to be associated with increased operative mortality risks due to the improvements in the safety and outcome of surgical reintervention and the emergence of less invasive transcatheter valve-in-valve replacement for this age group.

Within bioprostheses, one can choose porcine or pericardial valves. In contrast to previous studies, our meta-regression analysis did not reflect prolonged freedom from SVD in pericardial compared to porcine valves.²⁷ However, the majority of the included studies was not designed to determine differences between valve types.

SAVR Versus TAVI

TAVI has emerged as an alternative to surgical AVR in recent years, especially in elderly patients who are often inoperable or at high operable risk.^{28,29} In addition, 2 large randomized clinical trials have shown that TAVI is noninferior to SAVR in intermediate surgical risk patients regarding mortality and disabling strokes.^{30,31} Our study can be used as a benchmark for the long-term outcomes after TAVI in intermediate surgical risk patients once they become available. Although TAVI is a less-invasive procedure than SAVR, there are also disadvantages such as the greater occurrence of paravalvular regurgitation, permanent pacemaker requirement, strokes, subclinical valve thrombosis, and vascular and access site-related complications.³² According to the clinical guidelines, the decision between SAVR and TAVI in elderly patients should be made by a heart team (ie, multidisciplinary group of health care professionals) according to the individual patient characteristics, procedural risks, values, and preferences.^{3,4}

Limitations

First, inherent limitations of meta-analyses and combining data from (retrospective) observational studies should be taken into consideration.³³ Second, selection bias of patients included in the studies might have influenced the study outcomes due to the nature of observational studies (ie, no randomized allocation of patients to treatment options). Third, the presence of publication bias was

not investigated with funnel plots, as assessment of publication bias in absolute risk outcomes (as are all of our outcomes) is associated with substantial methodological limitations which may in itself give rise to funnel plot asymmetry.³⁴ Instead, we conducted sensitivity analyses where the quartile of studies with the smallest sample size was temporarily excluded. Fourth, there was substantial heterogeneity between studies in most outcome measures, which may potentially lead to inaccurate results. However, possible sources of heterogeneity were examined using univariable random effects meta-regression analysis and several covariates that may explain the heterogeneity between studies in the outcome measures were identified. Fifth, because most of the included studies originated from Europe and the United States, the results are less generalizable to patients from other regions in the world. Finally, there are limitations to the microsimulation model that should be taken in to account. The relationship between valve-related events rates after AVR and age, sex, follow-up duration and history of valve-related events remains poorly defined and could, thus, not be incorporated into our model. The model requires assumptions about the evolution of event occurrence rates and the hazard ratio for excess mortality beyond the observed follow-up period, which has introduced uncertainty in the extrapolation of these events.

CONCLUSIONS

Our results support the recommendation to use bioprostheses in elderly patients in need of AVR, since it is associated with low risks of SVD and reintervention. The estimated life expectancy after bioprosthetic AVR was comparable with the general population. The results of this study can be used to inform patients facing AVR on the risks and benefits of surgical bioprosthetic AVR, and they can serve as a benchmark for the long-term outcomes after TAVI in patients who were eligible for surgery and future alternative treatments (eg, tissue-engineered heart valves). Patients who are facing AVR should be fully informed about the risks and benefits of all treatment options in a shared decision-making process.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: surgical aortic valve replacement, bioprostheses, elderly, meta-analysis, systematic review, microsimulation

APPENDIX E1. SEARCH TERMS

Embase.com

('aorta valve replacement'/de OR 'aorta valve prosthesis'/de OR ('heart valve prosthesis'/de AND 'aorta valve'/de) OR (aort* AND (valve*) NEAR/6 (replace* OR transplant* OR xenotransplant* OR xenograft* OR heterotransplant* OR heterograft* OR prosthesis* OR bioprosthesis* OR stent*)):ab,ti) AND (xenograft/de OR (xenograft* OR xenotransplant* OR heterograft* OR heterotransplant* OR ((xeno* OR hetero* OR porcine* OR swine OR pig OR bovine* OR nonhuman OR animal OR calf OR cow OR 'Carpentier-Edwards' OR Shiley OR hancock) NEAR/6 (graft* OR transplant* OR prosthesis* OR bioprosthesis* OR valve* OR aort*)):ab,ti) OR ('heart valve bioprosthesis'/de OR 'Carpentier Edwards bioprosthesis'/de OR 'Hancock valve prosthesis'/de OR 'Mosaic bioprosthesis'/de OR (('Carpentier-Edwards' OR Shiley OR hancock OR freestyle* OR mosaic OR '3f enable' OR biocor OR 'toronto spv') NEAR/6 (valve* OR bioprosthesis* OR prosthesis*)):ab,ti) NOT ([animals]/lim NOT [humans]/lim) AND ('clinical study'/de OR 'case control study'/exp OR 'clinical article'/de OR 'clinical trial'/exp OR 'intervention study'/de OR 'longitudinal study'/exp OR 'major clinical study'/de OR 'prospective study'/de OR 'retrospective study'/de OR mortality/de OR 'cardiovascular mortality'/de OR 'surgical mortality'/de OR 'treatment outcome'/exp OR survival/exp OR 'graft survival'/de OR 'quality of life'/de OR 'follow up'/de OR 'evaluation study'/de OR 'comparative effectiveness'/de OR reoperation/de OR (clinical* OR trial* OR prospect* OR retrospect* OR longitudin* OR mortali* OR outcome* OR failure* OR surviv* OR (quality NEAR/3 life) OR result* OR (follow* NEXT/1 up*) OR 'long-term' OR longterm OR death OR evaluat* OR effectiv* OR reoperat*)):ab,ti) AND [english]/lim NOT ([Conference Abstract]/lim OR [Conference Paper]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim OR [Conference Review]/lim)

Medline (OvidSP)

((('heart valve prosthesis' AND 'aortic valve') OR (aort* ADJ6 (valve*) ADJ6 (replace* OR transplant* OR xenotransplant* OR xenograft* OR heterotransplant* OR heterograft* OR prosthesis* OR bioprosthesis* OR stent*)):ab,ti.) AND (heterografts/ OR (xenograft* OR xenotransplant* OR heterograft* OR heterotransplant* OR ((xeno* OR hetero* OR porcine* OR swine OR pig OR bovine* OR nonhuman OR animal OR calf OR cow OR "Carpentier-Edwards" OR Shiley OR hancock) ADJ6 (graft* OR transplant* OR prosthesis* OR bioprosthesis* OR valve* OR aort*)):ab,ti.) OR (((("Carpentier-Edwards" OR Shiley OR hancock OR freestyle* OR mosaic OR "3f enable" OR biocor OR "toronto spv") ADJ3 (valve* OR bioprosthesis* OR prosthesis*)):ab,ti.) NOT (exp animals/ NOT humans/) AND ("Clinical Trial".pt. OR exp "Case-

Control Studies"/ OR "Intervention Studies"/ OR exp "Longitudinal Studies"/ OR exp mortality/ OR mortality.xs. OR exp "treatment outcome"/ OR survival/ OR "graft survival"/ OR "quality of life"/ OR (clinical* OR trial* OR prospect* OR retrospect* OR longitudin* OR mortali* OR outcome* OR failure* OR surviv* OR (quality ADJ3 life) OR result* OR (follow* ADJ up*) OR "long-term" OR longterm OR death OR evaluat* OR effectiv* OR reoperat*)):ab,ti.) AND english.la. NOT (congresses OR Letters OR Notes OR Editorials).pt.

Cochrane

((aort* AND (valve*) NEAR/6 (replace* OR transplant* OR xenotransplant* OR xenograft* OR heterotransplant* OR heterograft* OR prosthesis* OR bioprosthesis* OR stent*)):ab,ti) AND ((xenograft* OR xenotransplant* OR heterograft* OR heterotransplant* OR ((xeno* OR hetero* OR porcine* OR swine OR pig OR bovine* OR nonhuman OR animal OR calf OR cow OR 'Carpentier-Edwards' OR Shiley OR hancock) NEAR/6 (graft* OR transplant* OR prosthesis* OR bioprosthesis* OR valve* OR aort*)):ab,ti) OR (((('Carpentier-Edwards' OR Shiley OR hancock OR freestyle* OR mosaic OR '3f enable' OR biocor OR 'toronto spv') NEAR/3 (valve* OR bioprosthesis* OR prosthesis*)):ab,ti) AND ((clinical* OR trial* OR prospect* OR retrospect* OR longitudin* OR mortali* OR outcome* OR failure* OR surviv* OR (quality NEAR/3 life) OR result* OR (follow* NEXT/1 up*) OR 'long-term' OR longterm OR death OR evaluat* OR effectiv* OR reoperat*)):ab,ti)

PubMed Publisher

((('heart valve prosthesis'[mh] AND "aortic valve"[mh]) OR (aorta valve*[tiab] OR aortic valve*[tiab]) AND (replace*[tiab] OR transplant*[tiab] OR xenotransplant*[tiab] OR xenograft*[tiab] OR heterotransplant*[tiab] OR heterograft*[tiab] OR prosthesis*[tiab] OR bioprosthesis*[tiab] OR stent*[tiab])) AND (heterografts[mh] OR (xenograft*[tiab] OR xenotransplant*[tiab] OR heterograft*[tiab] OR heterotransplant*[tiab] OR ((xeno*[tiab] OR hetero*[tiab] OR porcine*[tiab] OR swine[tiab] OR pig[tiab] OR bovine*[tiab] OR nonhuman[tiab] OR animal[tiab] OR calf[tiab] OR cow[tiab] OR Carpentier-Edwards[tiab] OR Shiley[tiab] OR hancock[tiab]) AND (graft*[tiab] OR transplant*[tiab] OR prosthesis*[tiab] OR bioprosthesis*[tiab] OR valve*[tiab] OR aort*[tiab])))) OR (((Carpentier-Edwards[tiab] OR Shiley[tiab] OR hancock[tiab] OR freestyle*[tiab] OR mosaic[tiab] OR 3f enable*[tiab] OR biocor[tiab] OR toronto spv*[tiab]) AND (valve*[tiab] OR bioprosthesis*[tiab] OR prosthesis*[tiab])) NOT (animals[mh] NOT humans[mh]) AND ("Clinical Trial".pt. OR "Case-Control Studies"[mh] OR "Intervention Studies"[mh] OR "Longitudinal Studies"[mh] OR mortality[mh] OR mortality[sh] OR "treatment outcome"[mh] OR survival[mh] OR

“graft survival”[mh] OR “quality of life”[mh] OR (clinical*[tiab] OR trial*[tiab] OR prospect*[tiab] OR retrospect*[tiab] OR longitudin*[tiab] OR mortalit*[tiab] OR outcome*[tiab] OR failure*[tiab] OR surviv*[tiab] OR quality of life*[tiab] OR result*[tiab] OR follow up*[tiab] OR long-term*[tiab] OR longterm[tiab] OR death OR evaluat* OR effectiv* OR reoperat*[tiab])) AND english[la] AND publisher[sb]

Google Scholar

“aorta|aortic valve replacement|prosthesis|transplantation” xenograft|xenotransplantation|heterograft|heterotransplantation|“Carpentier-Edwards”|hancock clinical|trial|intervention|longitudinal|prospective|retrospective|mortality|outcome|survival|follow-up

Embase.com (Embase en Medline)

(‘Aorta valve replacement’/de OR ‘Aorta Valve Prosthesis’/exp OR ((‘Aorta Valve’/de OR ‘Aorta Valve Disease’/exp OR ((aortic OR aorta) NEAR/3 (valve OR valvul* OR stenosis* OR insufficien* OR regurgitat* OR incompeten*)):ab,ti) AND (‘Transplantation’/de OR ‘Implantation’/exp OR (replac* OR transplant* OR implant* OR artificial):ab,ti)) OR (AVR AND valve):ab,ti) AND (‘Mechanical heart valve’/exp OR (mechanical OR mechano* OR ATS OR ‘Bjork Shiley’ OR ‘Bjoerk Shiley’ OR CarboMedic* OR ‘Saint Jude’ OR ‘St Jude’ OR ‘St. Jude’ OR ‘Starr Edwards’ OR pyrocarbon OR LTIC OR carbon):ab,ti) AND (‘Survival’/exp OR ‘Mortality’/exp OR ‘Prognosis’/de OR ‘Treatment outcome’/exp OR ‘Evaluation and follow up’/de OR ‘Follow up’/de OR ‘Hazard Assessment’/de OR (surviv* OR mortalit* OR death* OR prognos* OR outcome* OR ‘follow up’ OR ‘long term’ OR hazard*):ab,ti) NOT ([animals]/lim NOT [humans]/lim)

Medline (OVID)

((('Aortic Valve' / OR exp "Aortic Valve Stenosis" / OR "Aortic Valve Insufficiency" / OR ((aortic OR aorta) ADJ3 (valve OR valvul* OR stenosis* OR insufficien* OR regurgitat* OR incompeten*)):ab,ti.) AND ("Transplantation" / OR transplantation.xs. OR "Heart Valve Prosthesis Implantation" / OR (replac* OR transplant* OR implant* OR artificial).ab,ti.)) OR (AVR AND valve).ab,ti.) AND ("Carbon" / OR (mechanical OR mechano* OR ATS OR "Bjork Shiley" OR "Bjoerk Shiley" OR Carbomedic* OR "Saint Jude" OR "St Jude" OR "St. Jude" OR "Starr Edwards" OR pyrocarbon OR LTIC OR carbon).ab,ti.) AND ("Survival" / OR exp "Mortality" / OR mortality.xs. OR "Prognosis" / OR exp "Treatment outcome" / OR "Follow-Up Studies" / OR (surviv* OR mortalit* OR death* OR prognos* OR outcome* OR "follow up" OR "long term" OR hazard*).ab,ti.) NOT (animals NOT humans).sh.

Cochrane Central

(((((aortic OR aorta) NEAR/3 (valve OR valvul* OR stenosis* OR insufficien* OR regurgitat* OR incompeten*)):ab,ti) AND ((replac* OR transplant* OR implant* OR artificial):ab,ti)) OR (AVR AND valve):ab,ti) AND ((mechanical OR mechano* OR ATS OR 'Bjork Shiley' OR 'Bjoerk Shiley' OR CarboMedic* OR 'Saint Jude' OR 'St Jude' OR 'St. Jude' OR 'Starr Edwards' OR pyrocarbon OR LTIC OR carbon):ab,ti) AND ((surviv* OR mortalit* OR death* OR prognos* OR outcome* OR 'follow up' OR 'long term' OR hazard*):ab,ti)

Web of Science

TS=(((aortic OR aorta) NEAR/2 (valve OR valvul* OR stenosis* OR insufficien* OR regurgitat* OR incompeten*))) AND (replac* OR transplant* OR implant* OR artificial)) OR (AVR AND valve)) AND ((mechanical OR mechano* OR ATS OR "Bjork Shiley" OR "Bjoerk Shiley" OR CarboMedic* OR "Saint Jude" OR "St Jude" OR "St. Jude" OR "Starr Edwards" OR pyrocarbon OR LTIC OR carbon)) AND ((surviv* OR mortalit* OR death* OR prognos* OR outcome* OR "follow up" OR "long term" OR hazard*)) NOT ((animal* OR rat OR rats OR mouse OR mice OR pigs OR swine OR sheep) NOT (human* OR people OR patient*))

APPENDIX E2. DATA EXTRACTION

Study Characteristics

- Year of publication
- Country or region
- Study design
- Patients (n)
- Implantation period
- Follow-up (mean, standard deviation [SD], total number of patient-years, and completeness)

Patient Characteristics

- Age (mean, SD, and range)
- Weight (mean, SD, and range)
- Males (n)
- Emergency procedures (n)
- Preoperative New York Heart Association class (n)
- Hemodynamics: stenosis, regurgitation, or combined lesion (n)
- Etiology
 - Congenital (n)
 - Degenerative/calcification (n)
 - Rheumatic (n)
 - Endocarditis (n)
 - Prosthetic valve dysfunction (n)
 - Other/unknown (n)

- Previous cardiac intervention (n)
 - Aortic valve replacement
 - Aortic valve repair
 - Coronary artery bypass graft (CABG)
 - Other/unknown

Surgical Details

- Prosthesis
 - Stented
 - Stentless
 - Porcine
 - Pericardial
 - Other
- Concomitant procedures (n)
 - CABG
 - Aortic surgery
 - Other valve repair
 - Other

Early Outcome

- Mortality (n)
- Reintervention (n)
 - Valve-related reintervention (n)
 - Non–valve-related cardiac reintervention (n)
 - Re-exploration for bleeding (n)
- Structural valve deterioration (SVD) (n)
 - Reintervention (n)
- Nonstructural valve dysfunction (NSVD) (n)
 - Reintervention (n)
- Endocarditis (n)
 - Reintervention (n)
- Thromboembolism (TE) (n)
 - Reintervention (n)
- Valve thrombosis (VT) (n)
 - Reintervention (n)
- TE/VT (n)
 - Reintervention (n)
- Bleeding (n)
 - Reintervention (n)
- Cerebrovascular accident (CVA) (stroke + transient ischemic attack [TIA]) (n)
 - Thromboembolic (n)
 - Hemorrhagic (n)
- Stroke (n)
 - Thromboembolic (n)
 - Hemorrhagic (n)

- TIA (n)
 - Thromboembolic (n)
 - Hemorrhagic (n)
- Myocardial infarction (MI) (n)
 - Reintervention (n)
- Pacemaker implantation (n)
 - Reintervention (n)
- Renal failure (n)
 - Reintervention (n)

Late Outcome

- Mortality (n)
 - Cardiac (n)
 - Valve related (n)
- SUD (n)
 - Other (n)
- Reintervention (n)
 - Valve-related reintervention (n)
 - Mortality (n)
 - Non–valve-related cardiac reintervention (n)
 - Mortality (n)
- Valve dysfunction (n)
 - Mortality (n)
 - Reintervention (n)
 - Mortality
- SVD (n)
 - Mortality (n)
 - Reintervention (n)
 - Mortality
- NSVD (n)
 - Mortality (n)
 - Reintervention (n)
 - Mortality
- Endocarditis (n)
 - Mortality (n)
 - Reintervention (n)
 - Mortality
- TE (n)
 - Mortality (n)
 - Reintervention (n)
 - Mortality

- VT (n)
 - Mortality (n)
 - Reintervention (n)
 - Mortality
- TE/VT (n)
 - Mortality (n)
 - Reintervention (n)
 - Mortality
- Bleeding (n)
 - Mortality (n)
 - Reintervention (n)
 - Mortality
- CVA (stroke + TIA) (n)
 - Mortality (n)
 - Thromboembolic (n)
 - Hemorrhagic (n)
- Stroke (n)
 - Mortality (n)
 - Thromboembolic (n)
 - Hemorrhagic (n)
- TIA (n)
 - Mortality (n)
 - Thromboembolic (n)
 - Hemorrhagic (n)
- MI (n)
 - Mortality (n)
 - Reintervention (n)
 - Mortality
- Pacemaker implantation (n)
 - Mortality (n)
 - Reintervention (n)
 - Mortality
- Renal failure (n)
 - Mortality (n)
 - Reintervention (n)
 - Mortality

APPENDIX E3. STATISTICAL SOFTWARE

Meta-analysis and heterogeneity tests were performed in Microsoft Office Excel 2011 (Microsoft Corp, Redmond, Wash). Published Kaplan–Meier curves were digitized using Engauge Digitizer (version 10.3, <http://markummitcheil.github.io/engauge-digitizer>). Shapiro–Wilk tests, univariable random effects meta-regression analyses, extrapolation of estimated individual patient

time-to-event data from the digitized curves, meta-analysis of the derived Kaplan–Meier curves, and microsimulation were performed in R (version 3.3.2, R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria) using the software RStudio Version 1.0.136 (RStudio, Inc).

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FIGURE E1. Gompertz distribution (shape 0.124, rate 0.003) fitted to pooled Kaplan–Meier curve of freedom from structural valve deterioration (SVD) after bioprosthetic aortic valve replacement (AVR).

FIGURE E3. Calibration plots of the microsimulation model. Microsimulation-based actuarial survival is plotted against observed pooled Kaplan–Meier survival curves (age- and sex-matched). AVR, Aortic valve replacement.

FIGURE E2. Cumulative incidence functions of structural valve deterioration and mortality for different age groups. AVR, Aortic valve replacement.

TABLE E1. Overview of included publications on bioprostheses

First author	Implantation period	No. of patients	Study type	Mean follow-up, years (SD)	Mean age, y (range)	Male, n (%)	Concomitant CABG, n (%)	Emergency surgery (%)	Preoperative NYHA class III/IV (%)	Aortic stenosis (%)
Accola ^{E1}	1989-2003	398	Retrospective	6.3 (–)	74.5 (65.0-89.0)	268 (67.3%)	219 (55.0%)	2 (0.5%)	278 (69.8%)	137 (34.4%)
Ali 2007 ^{E3}	2001-2004	161	Prospective	–	75.5 (65.0–)	79 (49.1%)	59 (36.6%)	0 (0.0%)	–	– (–)
Ali 2006 ^{E2}	2001-2004	161	Prospective	1.9 (0.9)	75.5 (65.0–)	79 (49.1%)	–	0 (0.0%)	–	– (–)
Arinaga ^{E4}	1996-2007	244	Retrospective	4.1 (–)	71.6 (65.0–)	113 (46.3%)	31 (12.7%)	–	–	135 (55.3%)
Ashikhmina ^{E5,*}	1993-2007	2658	Retrospective	5.0 (3.5)	78.0 (70.0–)	1659 (62.4%)	1396 (52.5%)	14 (0.5%)	1947 (73.3%)	– (–)
Aymard ^{E6}	–	28	Prospective	–	75.7 (72.0-89.0)	10 (35.7%)	–	–	28 (100.0%)	– (–)
Bose ^{E7,*}	2001-2004	68	Retrospective	1.9 (–)	83.1 (80.0–)	38 (55.9%)	31 (45.6%)	18 (26.5%)	34 (50.0%)	– (–)
Chiappini ^{E8}	1993-2000	166	Retrospective	–	– (70.0-89.0)	–	–	–	–	– (–)
Colli ^{E9}	2011-2013	791	Retrospective	–	75.2 (67.0-80.0)	421 (53.2%)	177 (22.4%)	18 (2.3%)	420 (53.1%)	652 (82.4%)
de Vincentiis ^{E10}	1991-2005	200	Retrospective	3.3 (2.8)	82.0 (80.0-92.0)	89 (44.5%)	78 (39.0%)	5 (2.5%)	173 (86.5%)	– (–)
Doss ^{E11}	1999-2001	40	Prospective	–	78.5 (75.0–)	19 (47.5%)	5 (12.5%)	0 (0.0%)	35 (87.5%)	– (–)
Dunning ^{E12}	2002-2004	60	Prospective	–	73.0 (65.0-0.0)	37 (61.7%)	–	0 (0.0%)	29 (48.3%)	56 (93.3%)
Ennker ^{E13,*}	1996-2002	76	Retrospective	2.7 (1.8)	82.0 (80.0–)	21 (28.0%)	–	–	44 (58.0%)	– (–)
Filsoof ^{E14}	1998-2006	231	Retrospective	–	83.0 (80.0–)	94 (40.7%)	110 (47.6%)	5 (2.2%)	113 (48.9%)	– (–)
Flameng ^{E15}	2007-2009	32	Retrospective	1.3 (–)	78.0 (75.0-87.0)	14 (45.0%)	62 (193.8%)	–	32 (100.0%)	32 (100.0%)
Florath ^{E16}	1996-2001	247	Retrospective	2.5 (1.5)	76.0 (65.0–)	124 (50.0%)	104 (42.0%)	3 (1.2%)	148 (60.0%)	– (–)
Folliguet ^{E17,*}	2007-2011	208	Prospective	0.8 (1.0)	79.0 (65.0–)	67 (32.2%)	44 (21.2%)	0 (0.0%)	208 (100.0%)	– (–)
Gelsomino ^{E18}	1993-2000	36	Retrospective	3.1 (1.0)	78.1 (75.0–)	18 (50.0%)	13 (36.1%)	0 (0.0%)	35 (97.2%)	24 (66.7%)
Glaser ^{E19,*}	2002-2008	355	Retrospective	7.1 (–)	75.7 (–)	192 (54.1%)	–	4 (1.0%)	–	298 (84.0%)
Hellgren ^{E20}	1985-2003	1031	Retrospective	4.9 (–)	– (70.0–)	–	–	–	–	– (–)
Kawachi ^{E21}	1994-2001	28	Retrospective	2.9 (2.0)	76.0 (70.0-88.0)	15 (53.6%)	–	4 (14.3%)	–	16 (57.1%)
Kurlansky ^{E22}	1976-1999	866	Retrospective	4.8 (–)	77.6 (65.0-93.0)	530 (61.2%)	–	–	–	505 (58.3%)
Lehmann ^{E23,*}	2001-2006	1168	Prospective	1.8 (1.3)	76.0 (70.0–)	580 (49.7%)	515 (44.1%)	–	–	767 (65.7%)
Litmathe ^{E24}	1998-2008	152	Retrospective	–	82.6 (70.0–)	97 (64.0%)	–	88 (58.1%)	–	– (–)
Luciani ^{E25*}	1992-2000	668	Retrospective	3.4 (2.7)	72.2 (65.0–)	341 (51.0%)	186 (27.8%)	–	542 (81.1%)	443 (66.3%)
Martinovic ^{E26}	1996-2004	206	Prospective	4.7 (–)	72.8 (65.0-84.0)	89 (43.2%)	76 (36.9%)	–	168 (81.6%)	62 (30.1%)
Mistiaen ^{E27,*}	1986-2000	60	Retrospective	4.0† (–)	– (80.0–)	22 (36.7%)	–	5 (8.3%)	–	– (–)
Murashita ^{E28}	1993-2013	33	Retrospective	–	91.0 (90.0-97.0)	12 (36.4%)	–	2 (6.1%)	0 (0.0%)	33 (100.0%)
Nishida ^{E29,*}	1981-2013	199	Retrospective	4.6 (0.3)	76.6 (0.0-0.0)	111 (55.8%)	42 (21.1%)	–	–	– (–)
Nishioka ^{E30,*}	2001-2013	136	Retrospective	3.8 (3.0)	76.6 (65.0-88.0)	47 (34.6%)	–	–	–	– (–)
Pavie ^{E31}	1988-1995	100	Retrospective	2.7 (–)	80.0 (70.0-90.0)	37 (37.0%)	26 (26.0%)	–	72 (72.0%)	100 (100.0%)
Pavoni ^{E32,*}	1994-2004	185	Retrospective	5.3 (3.4)	72.0 (65.0–)	82 (44.3%)	51 (27.6%)	0 (0.0%)	127 (68.6%)	78 (42.2%)

(Continued)

TABLE E1. Continued

First author	Implantation period	No. of patients	Study type	Mean follow-up, years (SD)	Mean age, y (range)	Male, n (%)	Concomitant CABG, n (%)	Emergency surgery (%)	Preoperative NYHA class III/IV (%)	Aortic stenosis (%)
Permyer ^{E33,*}	2011-2014	60	Prospective	–	81.3 (70.0-92.0)	32 (53.3%)	23 (38.3%)	–	42 (70.0%)	42 (70.0%)
Riess ^{E34}	1994-1999	167	Prospective	7.9† (–)	72.0 (66.0-82.0)	84 (50.3%)	69 (41.3%)	–	118 (70.7%)	29 (17.4%)
Ruggieri ^{E35}	1983-1994	714	Prospective	13.7 (6.6)‡	– (70.0–)	–	–	–	–	– (–)
Said ^{E36}	1993-2007	2979	Retrospective	5.2 (3.2)	77.0 (65.0–)	1878 (63.0%)	1550 (52.0%)	16 (0.5%)	2161 (72.5%)	– (–)
Sidhu ^{E37}	1977-1997	249	Retrospective	4.1 (–)	74.5 (70.0-90.0)§	138 (55.4%)	–	–	–	– (–)
Sjogren ^{E38}	1990-1993	152	Retrospective	6.2 (3.2)	79.5 (75.0-91.0)	60 (39.5%)	74 (48.7%)	6 (3.9%)	118 (77.6%)	126 (82.9%)
Suttie ^{E39}	1975-1999	616	Retrospective	4.1 (–)	78.9 (75.0-94.6)§	363 (58.9%)	316 (51.3%)	–	–	522 (84.7%)
Varadarajan ^{E40,*}	1993-2003	80	Retrospective	2.5 (–)	83.0 (–)	46 (57.0%)	37 (46.3%)	–	–	80 (100.0%)
Vicchio ^{E41,*}	1992-2006	68	Retrospective	3.4 (2.8)	82.9 (80.0-90.0)	31 (45.6%)	15 (22.0%)	–	50 (73.6%)	– (–)
Walczak ^{E42}	2006-2008	36	Retrospective	–	72.2 (65.0-80.0)	21 (58.3%)	10 (27.8%)	2 (5.6%)	28 (77.8%)	27 (75.0%)

“–” = variable not reported. *SD*, Standard deviation; *CABG*, coronary artery bypass grafting; *NYHA*, New York Heart Association. *Included in pooled Kaplan–Meier survival curve. †Median. ‡Based on total population instead of subgroup of elderly patients. §Based on total population instead of subgroup of patients after bioprosthetic aortic valve replacement.

TABLE E2. Probabilities of dying and reintervention after valve-related events used in the microsimulation model

Event	Probability of dying	Probability of reintervention	Source of the probabilities (probability of dying; reintervention)
Structural valve deterioration	0.17	0.43	van Geldorp et al, 2009*; this meta-analysis (reported in 7 of the included studies)
Nonstructural valve dysfunction	0.05	0.39	van Geldorp et al, 2009*; this meta-analysis (reported in 4 of the included studies)
Endocarditis	0.34	0.49	van Geldorp et al, 2009*; this meta-analysis (reported in 7 of the included studies)
Thromboembolism	0.33	0	van Geldorp et al, 2009*; assumption
Valve thrombosis	0	1	van Geldorp et al, 2009*
Bleeding	0.39	0	This meta-analysis (reported in 4 of the included studies); assumption
Reintervention (hazard ratio)†	2.7		This meta-analysis (reported in 4 of the included studies)

*van Geldorp and colleagues.¹⁰ †Hazard ratio applied to early mortality risk.

TABLE E3. Individual study outcome estimates of early mortality and valve-related events after bioprosthetic AVR

First author	Early mortality (%)	Re-exploration for bleeding (%)	Early stroke (%)	Early MI (%)	Early renal failure (%)
Accola ^{E1}	4.02 (2.49-6.50)	3.77 (2.29-6.19)	–	0.50 (0.13-2.00)	8.04 (5.77-11.21)
Ali 2007 ^{E3}	3.11 (1.31-7.36)	5.59 (2.96-10.55)	–	0.62 (0.09-4.38)	–
Ali 2006 ^{E2}	–	–	–	–	–
Arinaga ^{E4}	2.05 (0.86-4.88)	–	–	–	–
Ashikhmina ^{E5}	–	–	–	–	–
Aymard ^{E6}	7.14 (1.88-27.16)	–	–	–	–
Bose ^{E7}	13.00 (7.03-24.04)	4.41 (1.46-13.34)	1.47 (0.21-10.29)	–	10.29 (5.10-20.76)
Chiappini ^{E8}	7.23 (4.19-12.47)	–	–	–	–
Colli ^{E9}	3.03 (2.05-4.50)	–	–	–	–
de Vincentiis ^{E10}	8.50 (5.39-13.39)	2.00 (0.76-5.28)	–	–	4.00 (2.03-7.89)
Doss ^{E11}	5.00 (1.30-19.30)	–	–	–	–
Dunning ^{E12}	1.67 (0.24-11.64)	–	–	–	–
Ennker ^{E13}	6.58 (2.82-15.35)	–	–	–	–
Filsoufi ^{E14}	5.19 (2.99-9.01)	2.16 (0.91-5.15)	3.90 (2.05-7.39)	0.87 (0.22-3.44)	0.87 (0.22-3.44)
Flameng ^{E15}	1.56 (0.10-24.44)	3.13 (0.45-21.51)	–	–	–
Florath ^{E16}	–	–	–	–	–
Folliguet ^{E17}	2.40 (1.01-5.71)	–	–	–	–
Gelsomino ^{E18}	–	2.78 (0.40-19.19)	–	–	–
Glaser ^{E19}	4.80 (3.02-7.63)	–	–	–	–
Hellgren ^{E20}	–	–	–	–	–
Kawachi ^{E21}	1.79 (0.11-27.85)	–	–	–	–
Kurlansky ^{E22}	7.51 (5.94-9.48)	3.70 (2.63-5.19)	–	0.69 (0.31-1.54)	9.35 (7.60-11.51)
Lehmann ^{E23}	8.00 (6.59-9.72)	–	–	–	–
Litmathe ^{E24}	6.20 (3.34-11.51)	5.70 (2.99-10.88)	–	–	6.40 (3.48-11.75)
Luciani ^{E25}	4.19 (2.92-6.02)	–	–	–	–
Martinovic ^{E26}	4.80 (2.61-8.82)	1.94 (0.74-5.12)	–	–	–
Mistiaen ^{E27}	10.00 (4.68-21.36)	–	–	3.33 (0.85-13.02)	–
Murashita ^{E28}	–	–	1.52 (0.10-23.72)	1.52 (0.10-23.72)	18.18 (8.82-37.49)
Nishioka ^{E30}	0.37 (0.02-5.85)	–	2.21 (0.72-6.75)	–	0.74 (0.10-5.18)
Pavie ^{E31}	15.00 (9.41-23.92)	–	–	–	–
Pavoni ^{E32}	5.40 (2.95-9.87)	–	–	–	–
Permanyer ^{E33}	6.67 (2.59-17.18)	3.33 (0.85-13.02)	3.33 (0.85-13.02)	–	6.67 (2.59-17.18)
Riess ^{E34}	1.80 (0.59-5.51)	–	0.60 (0.08-4.23)	–	–
Ruggieri ^{E35}	–	–	–	–	–
Said ^{E36}	4.06 (3.41-4.84)	5.40 (4.65-6.28)	–	–	–
Sidhu ^{E37}	2.01 (0.84-4.78)	–	–	–	–
Sjogren ^{E38}	2.63 (1.00-6.92)	–	–	–	–
Suttie ^{E39}	9.25 (7.23-11.85)	–	–	–	–
Vicchio ^{E41}	10.29 (5.10-20.76)	–	1.47 (0.21-10.29)	–	–
Walczak ^{E42}	8.33 (2.82-24.62)	8.33 (2.82-24.62)	2.78 (0.40-19.19)	–	2.78 (0.40-19.19)

MI, Myocardial infarction.

TABLE E4. Individual study outcome estimates of late mortality after bioprosthetic AVR

First author	Late mortality (%/pt-year)	Cardiac late mortality (%/pt-year)	Valve-related late mortality (%/pt-year)	SUD (%/pt-year)
Accola ^{E1}	7.86 (6.87-8.98)	—	—	—
Ali 2007 ^{E3}	—	—	—	—
Ali 2006 ^{E2}	2.88 (1.51-5.49)	—	—	—
Arinaga ^{E4}	2.89 (2.00-4.20)	—	1.07 (0.04-0.14)	0.21 (0.05-0.86)
Ashikhmina ^{E5}	9.66 (9.17-10.18)	—	—	—
Aymard ^{E6}	—	—	—	—
Bose ^{E7}	—	—	—	—
Chiappini ^{E8}	—	—	—	—
Colli ^{E9}	—	—	—	—
de Vincentiis ^{E10}	—	—	—	—
Doss ^{E11}	—	—	—	—
Dunning ^{E12}	—	—	—	—
Ennker ^{E13}	1.53 (1.01-2.31)	—	—	—
Filsoufi ^{E14}	—	—	—	—
Flameng ^{E15}	7.12 (2.39-21.19)	—	—	—
Florath ^{E16}	—	—	—	—
Folliguet ^{E17}	12.82 (8.52-19.30)	—	—	—
Gelsomino ^{E18}	—	—	—	—
Glaser ^{E19}	7.49 (6.53-8.59)	1.59 (1.17-2.16)	—	—
Hellgren ^{E20}	—	—	—	—
Kawachi ^{E21}	3.69 (1.22-11.22)	0.62 (0.04-9.76)	0.62 (0.07-18.81)	0.62 (0.04-9.76)
Kurlansky ^{E22}	9.79 (8.89-10.78)	—	—	—
Lehmann ^{E23}	5.16 (4.30-6.20)	2.51 (1.92-3.27)	—	—
Litmathe ^{E24}	—	—	—	—
Luciani ^{E25}	2.94 (2.32-3.72)	1.82 (1.35-2.47)	—	—
Martinovic ^{E26}	1.25 (0.71-2.19)	0.42 (0.16-1.11)	0.10 (0.06-2.92)	0.10 (0.01-0.74)
Mistiaen ^{E27}	6.59 (4.11-10.59)	2.47 (1.12-5.45)	—	1.24 (0.40-3.81)
Murashita ^{E28}	—	—	—	—
Nishioka ^{E30}	—	—	—	—
Pavie ^{E31}	4.45 (2.62-7.57)	—	—	0.17 (0.01-2.73)
Pavoni ^{E32}	6.49 (5.12-8.22)	2.03 (1.31-3.13)	0.51 (0.08-0.48)	—
Permanyer ^{E33}	—	—	—	—
Riess ^{E34}	3.68 (2.76-4.90)	0.74 (0.38-1.41)	0.16 (0.01-0.08)	0.98 (0.56-1.72)
Ruggieri ^{E35}	—	—	—	—
Said ^{E36}	—	—	—	—
Sidhu ^{E37}	4.17 (3.11-5.59)	1.55 (0.95-2.52)	1.16 (0.72-2.23)	—
Sjogren ^{E38}	13.21 (11.22-15.56)	7.19 (5.72-9.04)	2.43 (0.60-1.35)	0.05 (0.00-0.84)
Suttie ^{E39}	9.55 (8.47-10.76)	—	—	—
Vicchio ^{E41}	—	—	—	—
Walczak ^{E42}	—	—	—	—

SUD, Sudden unexplained death.

TABLE E5. Individual study outcome estimates of late valve-related events after bioprosthetic AVR

First author	Reintervention: valve-related (%/pt-year)	SVD (%/pt-year)	NSVD (%/pt-year)	Endocarditis (%/pt-year)	TE (%/pt-year)	VT (%/pt-year)	Bleeding (%/pt-year)	Stroke (%/pt-year)
Accola ^{E1}	0.12 (0.04-0.37)	–	–	–	–	–	–	0.04 (0.01-0.28)
Ali 2007 ^{E3}	–	–	–	–	–	–	–	–
Ali 2006 ^{E2}	–	–	–	0.32 (0.05-2.27)	–	–	–	–
Arinaga ^{E4}	0.43 (0.16-1.14)	0.21 (0.05-0.86)	0.43 (0.16-1.14)	0.21 (0.05-0.86)	0.64 (0.29-1.43)	–	0.32 (0.10-0.99)	0.64 (0.29-1.43)
Ashikhmina ^{E5}	–	–	–	–	–	–	–	–
Aymard ^{E6}	–	–	–	–	–	–	–	–
Bose ^{E7}	–	–	–	–	–	–	–	–
Chiappini ^{E8}	–	–	–	–	–	–	–	–
Colli ^{E9}	–	–	–	–	–	–	–	–
de Vincentiis ^{E10}	–	–	–	–	1.20 (0.60-2.39)	–	0.30 (0.08-1.20)	–
Doss ^{E11}	–	–	–	–	–	–	–	–
Dunning ^{E12}	–	–	–	–	–	–	–	–
Ennker ^{E13}	–	–	–	–	–	–	–	–
Filsoufi ^{E14}	–	–	–	–	–	–	–	–
Flameng ^{E15}	–	–	–	2.37 (0.34-16.46)	1.19 (0.08-18.66)	–	2.37 (0.34-16.46)	–
Florath ^{E16}	0.92 (0.48-1.77)	–	–	0.60 (0.27-1.34)	–	–	1.10 (0.61-1.99)	3.20 (2.27-4.52)
Folliguet ^{E17}	1.28 (0.32-5.08)	–	3.85 (1.75-8.43)	1.92 (0.63-5.90)	6.41 (3.52-11.68)	–	2.56 (0.97-6.75)	1.28 (0.32-5.08)
Gelsomino ^{E18}	–	–	–	–	1.80 (0.46-7.11)	–	0.45 (0.03-7.16)	0.90 (0.13-6.34)
Glaser ^{E19}	0.40 (0.21-0.74)	–	–	–	–	–	–	–
Hellgren ^{E20}	–	–	–	0.61 (0.43-0.87)	2.40 (2.01-2.86)	–	0.97 (0.73-1.28)	–
Kawachi ^{E21}	–	0.62 (0.04-9.76)	0.62 (0.04-9.76)	0.62 (0.04-9.76)	–	–	0.62 (0.04-9.76)	–
Kurlansky ^{E22}	0.05 (0.01-0.21)	–	–	–	–	–	–	–
Lehmann ^{E23}	–	–	–	0.24 (0.10-0.57)	–	0.05 (0.01-0.34)	–	0.43 (0.22-0.82)
Litmathe ^{E24}	–	–	–	–	–	–	–	–
Luciani ^{E25}	0.85 (0.54-1.32)	0.71 (0.44-1.16)	–	–	–	–	–	–
Martinovic ^{E26}	0.31 (0.10-0.97)	–	–	–	1.14 (0.64-2.06)	–	0.05 (0.00-0.83)	0.31 (0.10-0.97)
Mistiaen ^{E27}	–	–	–	0.21 (0.01-3.29)	2.47 (1.12-5.45)	–	1.24 (0.40-3.81)	1.65 (0.62-4.36)
Murashita ^{E28}	–	–	–	–	–	–	–	–
Nishioka ^{E30}	–	0.10 (0.01-1.55)	–	0.58 (0.19-1.80)	–	–	–	0.78 (0.29-2.06)
Pavie ^{E31}	0.68 (0.17-2.73)	0.17 (0.01-2.73)	0.34 (0.05-2.42)	0.68 (0.17-2.73)	0.17 (0.01-2.73)	–	0.34 (0.05-2.42)	–
Pavoni ^{E32}	2.94 (2.05-4.21)	3.34 (2.39-4.68)	1.11 (0.62-2.01)	0.71 (0.34-1.48)	–	–	–	–
Permanyer ^{E33}	–	–	–	–	–	–	–	–

(Continued)

TABLE E5. Continued

First author	Reintervention: valve-related (%/pt-year)	SVD (%/pt-year)	NSVD (%/pt-year)	Endocarditis (%/pt-year)	TE (%/pt-year)	VT (%/pt-year)	Bleeding (%/pt-year)	Stroke (%/pt-year)
Riess ^{E34}	0.74 (0.38-1.41)	0.16 (0.04-0.65)	0.16 (0.04-0.65)	0.16 (0.04-0.65)	1.06 (0.62-1.83)	0.25 (0.08-0.76)	0.33 (0.12-0.87)	0.25 (0.08-0.76)
Ruggieri ^{E35}	-	0.25 (0.16-0.37)	-	-	-	-	-	-
Said ^{E36}	0.70 (0.58-0.84)	-	-	-	-	-	-	-
Sidhu ^{E37}	-	0.10 (0.01-0.69)	0.10 (0.01-0.69)	0.58 (0.26-1.29)	1.84 (1.18-2.88)	0.05 (0.00-0.78)	-	-
Sjogren ^{E38}	-	1.16 (0.65-2.09)	0.05 (0.00-0.84)	0.74 (0.35-1.55)	3.59 (2.58-5.00)	-	0.63 (0.29-1.41)	2.75 (1.88-4.01)
Suttie ^{E39}	0.39 (0.21-0.73)	-	-	-	-	-	-	-
Vicchio ^{E41}	-	-	-	-	-	-	-	-
Walezak ^{E42}	-	-	-	-	-	-	-	-

SVD, Structural valve deterioration; NSVD, nonstructural dysfunction; TE, thromboembolism; VT, valve thrombosis.

TABLE E6. Least squares regression of modeled survival vs observed survival for estimation of excess mortality not directly related to valve-related events

Hazard ratio*	Sum of squared residuals†
0.80	3476.2
0.85	2918.4
0.86	2888.9
0.87	2891.8
0.90	3044.0
1.00	4976.8

Value in bold indicates the selected model. *Hazard ratio of background mortality + excess mortality relative to background mortality. †Sum of squared residuals between microsimulation-based survival and survival observed in our meta-analysis of Kaplan–Meier freedom from all-cause mortality.

TABLE E7. Microsimulation results of the reasons of interventions and causes of death after AVR

Age at surgery	75 y	85 y
Reason for reintervention		
Structural valve deterioration	36%	27%
Nonstructural valve dysfunction	20%	24%
Endocarditis	32%	37%
Valve thrombosis	13%	12%
Cause of death		
Early mortality	5%	5%
Structural valve deterioration	1%	0%
Nonstructural valve dysfunction	0%	0%
Endocarditis	2%	1%
Thromboembolism	6%	4%
Valve thrombosis	0%	0%
Bleeding	3%	2%
Reintervention	1%	1%
Background and excess mortality	81%	87%

TABLE E8. Univariable random effects meta-regression results of bioprostheses studies

	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value
	Early mortality		Early renal failure		Late SVD	
Study design (prospective vs retrospective)	−0.25 (−0.72 to 0.22)	.301	0.02 (−1.33 to 1.37)	.974	−1.06 (−2.81 to 0.69)	.235
Median year of valve replacement	−0.02 (−0.05 to 0.01)	.113	−0.03 (−0.08 to 0.03)	.392	0.02 (−0.12 to 0.16)	.751
Mean follow-up duration (/year increase)					−0.04 (−0.30 to 0.21)	.737
Mean age (/year increase)	0.08 (0.03-0.13)	.001	0.05 (−0.03 to 0.13)	.262	−0.02 (−0.34 to 0.29)	.878
Male	−0.30 (−2.31 to 1.70)	.766	1.87 (−1.66 to 5.40)	.299	−1.96 (−16.04 to 12.11)	.785
Emergency surgery	1.22 (−0.24 to 2.69)	.102	0.63 (−2.18 to 3.43)	.662		
NYHA class I/II	0.14 (−1.86 to 2.15)	.888	−2.93 (−8.83 to 2.97)	.330	2.84 (−16.13 to 21.80)	.769
NYHA class III/IV	−0.42 (−2.21 to 1.37)	.647	0.81 (−3.87 to 5.48)	.736	−2.84 (−21.80 to 16.13)	.769
AS	0.94 (−0.19 to 2.07)	.102	0.90 (−0.31 to 2.11)	.144	0.33 (−3.99 to 4.65)	.881
AI	−0.12 (−2.87 to 2.62)	.929	2.98 (−3.72 to 9.69)	.384	−2.74 (−12.34 to 6.86)	.576
AS/AI	−1.01 (−2.24-0.22)	.109	−0.17 (−1.64 to 1.30)	.822	0.21 (−3.88 to 4.30)	.919
Concomitant CABG	−0.13 (−1.49-1.22)	.845	2.36 (−5.49 to 10.21)	.556	1.74 (−7.65 to 11.13)	.716
Type of valve (porcine vs. pericardial)	0.54 (0.11-0.96)	.013	0.30 (−1.07 to 1.68)	.665	0.24 (−1.89 to 2.37)	.824
	Late NSD		Late TE		Late bleeding	
Study design (prospective vs retrospective)	0.99 (−1.25-3.23)	.388	0.11 (−0.70 to 0.92)	.791	−0.07 (−1.09 to 0.96)	.899
Median year of valve replacement	0.17 (0.08-0.26)	.000	0.01 (−0.05 to 0.07)	.719	0.05 (−0.03 to 0.13)	.188
Mean follow-up duration (/year increase)	−0.39 (−0.77 to −0.01)	.044	−0.10 (−0.30 to 0.10)	.312	−0.21 (−0.39 to 0.03)	.025
Mean age (/year increase)	0.05 (−0.25-0.35)	.742	0.10 (−0.02 to 0.21)	.105	0.09 (−0.07 to 0.25)	.262
Male	−11.82 (−21.04 to 2.60)	.012	−5.40 (−11.15 to 0.35)	.066	−5.48 (−13.41 to 2.44)	.175
Emergency surgery	−7.47 (−63.37 to 48.43)	.793	−7.45 (−30.27 to 15.37)	.522	−5.23 (−21.56 to 11.11)	.530
NYHA class I/II	−7.11 (−17.87 to 3.64)	.195	−4.01 (−9.83 to 1.82)	.178	−2.23 (−7.06 to 2.61)	.367
NYHA class III/IV	7.11 (−3.64 to 17.87)	.195	4.01 (−1.82 to 9.83)	.178	2.23 (−2.61 to 7.06)	.367
AS	−0.47 (−4.17 to 3.22)	.802	0.72 (−1.40 to 2.84)	.507	1.37 (−0.27 to 3.02)	.101
AI	−2.08 (−10.20 to 6.05)	.617	−5.96 (−9.98 to 1.95)	.004	−4.27 (−9.74 to 1.21)	.127
AS/AI	0.05 (−3.84 to 3.94)	.980	−0.02 (−3.00 to 2.95)	.987	−0.77 (−2.63 to 1.10)	.420
Concomitant CABG	−7.29 (−16.85 to 2.28)	.135	−0.01 (−1.92 to 1.91)	.994	0.78 (−0.68 to 2.23)	.295
Type of valve (porcine vs pericardial)	−0.44 (−2.75 to 1.87)	.711	−0.86 (−1.88 to 0.15)	.096	−0.74 (−1.88 to 0.41)	.206
	Late stroke		Reintervention		Late mortality	
Study design (prospective vs retrospective)	−1.00 (−2.09 to 0.09)	.071	−0.64 (−2.08 to 0.80)	.386	−0.36 (−0.79 to 0.07)	.100
Median year of valve replacement	−0.03 (−0.16 to 0.09)	.623	0.10 (−0.01 to 0.22)	.088	−0.01 (−0.05 to 0.02)	.432
Mean follow-up duration (/year increase)	−0.21 (−0.60 to 0.18)	.283	−0.35 (−0.87 to 0.18)	.194	0.06 (−0.04 to 0.17)	.243
Mean age (/year increase)	0.24 (−0.01 to 0.49)	.056	−0.03 (−0.22 to 0.16)	.746	0.08 (0.02-0.13)	.007
Male	−7.97 (−16.39 to 0.45)	.064	−1.77 (−8.33 to 4.78)	.596	1.83 (−0.01 to 3.67)	.051
Emergency surgery	11.31 (−17.87 to 40.49)	.447	0.33 (−19.51 to 20.17)	.974	−2.28 (−8.63 to 4.07)	.482
NYHA class I/II	−0.43 (−8.32 to 7.45)	.914	0.69 (−2.89 to 4.27)	.706	−2.46 (−5.42 to 0.49)	.102

(Continued)

TABLE E8. Continued

	Late stroke		Reintervention		Late mortality	
NYHA class III/IV	0.43 (−7.45 to 8.32)	.914	−0.68 (−4.26 to 2.89)	.708	2.46 (−0.50 to 5.42)	.103
AS	3.88 (1.19-6.57)	.005	1.49 (−2.51 to 5.49)	.466	1.05 (0.02-2.08)	.045
AI	−2.92 (−9.39 to 3.55)	.376	−1.28 (−10.37 to 7.82)	.783	−3.01 (−5.19 to 0.83)	.007
AS/AI	−2.65 (−6.53 to 1.23)	.181	−2.01 (−6.80 to 2.77)	.409	−0.61 (−1.77 to 0.54)	.297
Concomitant CABG	−1.56 (−8.05 to 4.94)	.639	0.14 (−1.55 to 1.82)	.875	0.52 (−0.24 to 1.28)	.180
Type of valve (porcine vs. pericardial)	−0.25 (−1.80 to 1.29)	.747	0.02 (−1.33 to 1.37)	.977	−0.60 (−1.07 to −0.13)	.012

CI, Confidence interval; SVD, structural valve deterioration; NYHA, New York Heart Association; AS, aortic stenosis; AI, aortic insufficiency; CABG, coronary artery bypass grafting; NSD, nonstructural dysfunction; TE, thromboembolism.