Clinical outcome after bioprosthetic aortic root replacement: A Meta-Analysis and Microsimulation model

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Abstract

Background and aim of the study This study aims to provide an overview of clinical outcome after bioprosthetic aortic root replacement and lifetime event-risk estimates of mortality and valve-related events, and the potential effect of type of prosthesis used. Methods A systematic literature search was conducted between January 2000 and August 2019. Inclusion criteria: aortic root replacement in adults. Data were pooled by inverse-variance weighting and entered a microsimulation model to calculate lifetime event-risk and (event-free) life expectancy. Results Of 2,106 publications, 31 were included (N = 5,227 patients, 74% stentless valves). Mean age was 65.4 years (74% male). Pooled early mortality was 5.5% (95% CI: 4.3-7.2%). During follow-up (mean 4.1 years, total 22.706 patient-years), late mortality was 4.8%/patient-year and reoperation 0.9%/patient-year. Linearized-occurrence-rates for thromboembolism, endocarditis, and hemorrhagic events:1.2; 0.9 and 0.5 %/patient-year; no significant difference between stented and stentless prosthesis. Translating into a 60-year-old patient, an estimated life expectancy of 14 years (general population: 22 years) and lifetime risks of thromboembolism, endocarditis and reintervention of 21%, 13%, and 8%, respectively is expected. Conclusions The study shows impaired survival and a notable lifetime risk of valve-related events after bioprosthetic aortic root replacement. The risk of thromboembolism is prominent, especially during earlier follow-up, suggesting higher risk of thromboembolism early after operation. Type of prosthesis, stented or stentless, is not associated with higher valve-related events. Moreover, this study could be used as a benchmark to compare outcome with other aortic root replacement procedures.

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Results

Of 2,106 publications, 31 were included (N = 5,227 patients, 74% stentless valves). Mean age was 65.4 years (74% male). Pooled early mortality was 5.5% (95% CI: 4.3-7.2%). During follow-up (mean 4.1 years, total 22.706 patient-years), late mortality was 4.8%/patient-year and reoperation 0.9%/patient-year. Linearized-occurrence-rates for thromboembolism, endocarditis, and hemorrhagic events:1.2; 0.9 and 0.5 %/patient-year; no significant difference between stented and stentless prosthesis. Translating into a 60-year-old patient, an estimated life expectancy of 14 years (general population: 22 years) and lifetime risks of thromboembolism, endocarditis and reintervention of 21%, 13%, and 8%, respectively is expected.

Conclusions

The study shows impaired survival and a notable lifetime risk of valve-related events after bioprosthetic aortic root replacement. The risk of thromboembolism is prominent, especially during earlier follow-up, suggesting higher risk of thromboembolism early after operation. Type of prosthesis, stented or stentless, is not associated with higher valve-related events. Moreover, this study could be used as a benchmark to compare outcome with other aortic root replacement procedures.

Background and aim of the study

In young patients with aortic root disease, composite mechanical graft replacement - Bentall-procedure- (1) is widely used due to its long-term durability (2). In elderly, biological aortic root replacement is more common, because reoperations are less prominent due to shorter life-expectancy and less structural valve degeneration (SVD) (3, 4). This age 'turning-point' however is arbitrary and biological valves are increasingly implanted in middle-aged patients recently. Interestingly, there are no large studies presenting outcome after bioprosthetic aortic root replacement and our knowledge is mainly based on data reported on aortic valve replacement. Additionally, most published studies have limited follow-up duration, which is a limitation for the interpretation of the results, particularly regarding SVD and reoperation hazard (5). Moreover, it is not known how a stentless biological valve prosthesis compares to stented prosthesis with regard to durability and valve-related outcome (6). Stentless valves may have hemodynamic advantages, especially in smaller aortic annulus, however, survival and long-term durability have not yet been proved (7).

Conspicuously, transcatheter aortic valve implantation (TAVI) procedures are gaining ground and with satisfying results, indicating that surgical aortic valve replacement will probably become limited in the near future (8). Nevertheless, when the aortic root is affected and should be replaced, surgery is still the only solution. To provide comprehensive data on outcome after bioprosthetic aortic root replacement and the possible effect of the type of prosthesis, we conducted a systematic review of observational reports on patient

characteristics and valve-related morbidity, mortality and reintervention with both stented and stentless prostheses and explored potential determinants of outcome.

Materials and methods

Search Strategy

On 30 August 2019, a systematic literature search was conducted in MEDLINE, Embase, The Cochrane Collaboration and Web of Science, and Google Scholar (Supplementary file 1). Studies published from January 2000 onwards were screened by two independent reviewers (BA, RvV) using the following inclusion criteria: reporting morbidity and mortality after bioprosthetic aortic root replacement with stentless (no homografts) or stented prosthesis, cohorts [?] 50 patients (to prevent including early experience reports highlighting the learning curve), and mean age at surgery [?] 18 years. Exclusion criteria were: > 25% acute type A aortic dissection, studies limited to reintervention or mechanical valve prosthesis, studies reporting only early results, > 10% use of subcoronary technique, > 50% children included (aged <18 years), and state of the art, case reports, experimental studies and reviews. In case the same cohort was published more than once, the most complete publication was selected. All included studies were cross-referenced to identify additional publications. In case of disagreement, studies were assessed by another, independent reviewer (MV) and agreement was negotiated until consensus was reached.

Data Extraction

Data extraction was performed in duplicate with Microsoft Excel (Microsoft Office 2010, Microsoft, Redmond, WA, USA) by two of the authors (BA and JE) according to the guidelines for reporting mortality and morbidity after cardiac valve interventions (9). Events were not included in our database when adherence to the reporting guidelines could not be ascertained. For each article with missing information on important variables, the corresponding author was requested to provide the missing data. Institutional review board approval was not applicable for this study, and informed consent was waived. An overview of extracted variables is presented in Supplementary file 2.

Data Analysis

Data analysis was performed with Microsoft Excel (Microsoft Office 2010, Microsoft, Redmond, WA, USA) and IBM SPSS version 21.0 (IBM, Somers, NY, USA) and in the R statistical software (version 3.1.0. R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria) using the metaphor package. Pooled baseline patient characteristics were calculated with the use of sample-size weighting. Early mortality and linearized occurrence rates (LOR) of late valve-related complications were pooled on a logarithmic scale with the use of inverse variance weighting in a random-effects model. Reported study characteristics and pre- and peri-operative patient characteristics are presented as mean +- standard deviation for continuous variables and percentages for discrete variables. For outcome variables, individual and pooled statistics are presented as LOR and 95% confidence interval (CI). In studies where median and ranges instead of mean and variance were reported, the method described by Hozo et al. (10) was used to calculate the mean. In case of absence of total number of patient-years, this was calculated by multiplying the number of patients with the mean follow-up duration in years. In case a certain event did not occur in an individual study, we assumed that 0.5 events occurred for that particular outcome for the purpose of inverse variance weighting. When an event was not reported, this study was excluded from the analysis of that event. For late mortality and reintervention, subgroup analyses were performed stratifying the root replacement by prosthesis type (stented vs. stentless), follow-up duration (individual study mean follow-up less than pooled mean follow-up versus individual study mean follow-up more than pooled mean follow-up), and age at surgery. To assess the association of these variables with late mortality and reintervention rates, linear regression analyses were performed with weighting the studies according to the inverse variance of the occurrence rate. Heterogeneity between the studies was assessed using the I^2 test. Funnels plots were used to investigate publication bias. To investigate the potential influence of publication bias on pooled outcome, sensitivity analyses were conducted by temporarily excluding the smallest quartile (by sample size) of included studies. This systematic review and meta-analysis was conducted according to the PRISMA guidelines (11).

Microsimulation model: the concept

The microsimulation model is a computer application that simulates the life of a patient after aortic valve replacement, considering the morbidity and mortality events that the patient could experience. The calculated mortality of a patient is composed of the background mortality of the general population, operative mortality, mortality due to valve-related events and an additional "excess mortality". This so-called excess mortality in the patient compared to a matched person in the general population reflects mortality associated with the underlying left ventricular function, valve pathology, and the root replacement procedure. All pooled and weighted occurrence rates of (operative) mortality risk, the occurrence rate of valve-related events together with the risk of mortality and reintervention directly due to valve-related events were obtained from the meta-analysis. The occurrence rates of all events were assumed to be linear and non-age dependent.

For patients aged 61-70 and > 70 years, these "excess mortality" hazard ratios were 1.2 and 0.8 for males, and 2.2 and 1.3 for females, respectively. The background mortality of the general population was obtained from the 2004 United States Life Tables, as 2004 was the pooled median year of intervention, assuming a constant incidence rate over time in each study (12).

To obtain age-specific estimates of life expectancy and lifetime risk of valve-related morbidity, the microsimulation model was run for the ages of 60, 65 and 70 years for 10,000 iterations each and separately for males and females. The age-specific outcomes of both genders were then pooled at the male/female ratio obtained from our meta-analysis. For the internal validation of the model, we performed an additional run for 10,000 iterations at the pooled mean age (65.5 years) and male/female ratio (70%) of the meta-analysis. The actuarial survival obtained from the microsimulation model for these data was then plotted against the pooled (overall) mortality observed in the meta-analysis. A more detailed account of the microsimulation and the methodology has been supplied previously (13).

Results*Study and baseline patient characteristics*The initial literature search exposed 2,106 publications. The selection procedure is illustrated in Figure 1. Cross-referencing did not result in additional papers. Thirty-one studies were finally included in this systematic review with a total number of 5,227 patients, mean follow-up of 4.1 years (range 1-10 years), and total follow-up of 22,706 patient-years. Root replacements was performed with a stented prosthesis in 26% of patients and 74% were stentless valve prostheses. In one study the implantation period was missing, which was provided by the authors (14). Supplementary file 3 shows an overview of the included publications and study characteristics. Pooled pre- and peri-operative characteristics are presented in Table 1.

Pooled outcome

Early (30 day) mortality occurred in 339 patients, corresponding to a weighted early mortality of 5.5% (95% CI: 4.3 – 7.1%). The linearized occurrence rates (LOR) of mortality, reintervention on the aortic root, hemorrhage, thromboembolism, endocarditis and major adverse valve-related events are presented along with a measure of statistical heterogeneity in Table 2.

Late mortality occurred in 1,037 patients (4.6%/patient-year); in 41% the cause was unknown or not reported. The main cause of late mortality was cardiac (52%), of these were 51% valve-related and 49% non-valve-related cardiac death.

*Publication Bias*Analysis of the funnel plots revealed evidence of underreporting of late mortality, reintervention on the aortic root, and thromboembolism in studies with smaller patient numbers. For other variables, no evidence of publication bias was found (Supplementary file 3).

Sensitivity analyses revealed that this potential publication bias did not have a substantial effect on pooled outcomes, as these remained generally unchanged after temporary exclusion of smallest quartile of the studies.

Type of prosthesis

Twenty-tree studies reported using solely a biological valve-containing prosthesis (14-36): 13 studies with Freestyle bioprostheses, 3 Shelhigh bioconduit, 2 studies Bio-Valsalva prosthesis, 1 Edwards S prima Plus,

2 with mixed stentless prosthesis. In one study the type of the biological valve was unspecified (37). Two studies included both stentless and stented bioprostheses (38, 39). Five studies used (almost) exclusively self-made aortic root prosthesis using a stented bioprostheses (bio-Bentall) to replace the aortic root. (40-44).

No associations were found between late mortality or reintervention, and the type of prosthesis used. Table 3 shows detailed information on valve-related outcome for "stentless" and "stented" subgroups.*Duration of follow-up*

A subgroup analysis was performed with 12 studies with a mean follow-up of at least 5 years pooled weighted mean of 7.4 years (range 5.0 to 10.1 years) with a pooled mean age of 65.9 years, and compared to the other 19 studies, with a mean follow-up of 2.56 years (1.0 to 4.8 years) and pooled mean age of 65.8 were analyzed. Table 4 shows details on outcome.

*Microsimulation predictions of age-specific life expectancy and outcome*Microsimulation-based estimates of life expectancy and lifetime risk of valve-related morbidity for 60, 65 and 70 years old patients are shown in Figure 2. The microsimulation model calibration with the pooled mortality is shown is Supplementary file 4.

Conclusions

This study provides an overview of contemporary published studies on outcome after aortic root replacement with biological valve prostheses and provides age-specific prediction of valve-related outcome. Patient survival is impaired. Type of prosthesis is not associated with (valve-related) outcome. Notably, thromboembolic events occur frequent, especially during early follow-up. This report may be used to benchmark the potential therapeutic benefit of other surgical approaches.

Early mortality

The observed pooled early mortality was 5.5%. This is in accordance with an older review on aortic root replacement (4.5 to 5.3%) and with the recent report of the Society of Thoracic Surgeons database from the U.S. that estimates early mortality after bioprosthetic aortic root replacement to be 6.2% (45, 46). However, these studies include also acute and emergent operative indication like endocarditis and aortic dissection. Early mortality was mainly due to low cardiac output (22.7%) and multi-organ failure (18.1%). Surgical indication was endocarditis in 9.2% of patients and type A aortic dissection in 7.2%. The high mortality could (partly) be explained by operation in emergent setting and partly by the additional procedures (e.g. arch replacement, CABG). Nevertheless, overall early mortality seems not changed significantly last 2 decades.

Late mortality and reintervention outcome There was a high mortality rate (4.8%/pt-year) for a pooled mean age of 65.9 years, which is higher than the general population mortality. Translated to our microsimulation-based life-expectancy, there is a life-expectancy of 14.3 year for a 60 year old patient receiving a bioprosthetic root replacement, while there is a life-expectancy of 22.5 years for the 60 year old U.S. "healthy" population (12). From previous research there is evidence of significant "excess mortality" in (elective) isolated aortic valve replacement, compared to the age-matched general population (47). Additionally, patients in this study were diagnosed with a dilated aortic root as well, with about 13% suffering from a dissection of the root and/or connective tissue disease, which are conditions that may influence patient survival due to complication other than valve-related events.

This microsimulation model shows a life-time reintervention risk of 9% for patients older than 60 years, which is comparable to previous predictions on biological aortic valve prostheses (3). It is known that younger patients, especially younger than 60 years, are more likely to have a reintervention after biological aortic valve replacement, mainly due to progressive SVD (3, 48). Of the 8 studies that explicitly tested association between age and reintervention, 3 found indeed that older age is associated with lower reintervention hazard.

*Thromboembolic events*We found a high incidence of thromboembolic events, with a life-time risk of more than 20% after bioprosthetic aortic root replacement. Data on TE events are not comprehensive, thus discriminating between TIA and disabling ischemic CVA is not possible. However, a previous systematic

review and microsimulation study on aortic valve replacement with isolated biological stented valve, published by Puvimanasinghe et al. (3), reports similar TE event rates (1.4%/patient-year). Additionally, the incidence of thromboembolic events is known to increase with age (49, 50) and might partly explain this high incidence of thromboembolic events.

Subsequently the question arises whether there is a difference with patients receiving a classical Bentall prosthesis. Although this comparison is hampered by the differences in patient characteristics, mainly due to the younger age in patient receiving mechanical valves; a recently published meta-analysis on the Bentall procedure (mean age 50 years), shows lower thromboembolic event rates (0.77%/patient-year) (51). Another study on mechanical valve replacement in non-elderly showed suboptimal survival and considerable lifetime risk of anticoagulation-related complications (52). However, the anticoagulation therapy after mechanical valve implantation in these patients plays a protective role in prevention of thromboembolic events, as it also occurs irrespective of the aortic valve replacement due to the aging process (50).

Additionally, TE hazard is less likely to occur during long-term follow-up, suggesting a larger hazard in the early postoperative period, which may be related to anticoagulation therapy. There were also some studies that included (a small portion of) patients diagnosed with endocarditis and aortic dissection, which may have led to additional TE rate. However, excluding these studies from the analysis did not changed the results. According to the current US and European guidelines on the management of valvular heart disease, antiplatelet therapy is reasonable and may be considered for the first 3 months after biological valve replacement (2, 53). Additionally, the European guidelines state that the need for a 3 months postoperative period of anticoagulation therapy has been challenged in patients with bioprostheses, with low-dose aspirin being favored as an alternative.

Hence, it is questionable whether the proposed anticoagulation therapy is appropriate in patient receiving a bioprosthetic aortic root replacement. Nevertheless, due to a lack of data on the exact anticoagulation therapy and patient compliance, it is not possible to make broad inference about this possible association. Further studies are needed to determine the most optimal anticoagulation therapy after biological aortic valve replacement.*Endocarditis and type of prostheses*Although the rate of endocarditis after bioprosthetic aortic root replacement varies widely in the literature (54), our findings are comparable to an older study on biological aortic valve replacement [3]. Nine studies included patients with acute endocarditis, of which three with an endocarditis rate of more than 2.8%/patient-year (22, 26, 55), all including stentless valve prostheses. However, these studies included a relatively high proportion of patients with active endocarditis which may explain the higher re-endocarditis rate, although the severity of endocarditis was not provided. Hence, the trend toward more endocarditis in stentless valves could possibly be explained by the latter. Based on these data it is reasonable to assume that stented bioprosthetic grafts are at least not inferior to stentless bioprosthetic grafts to be used in case of endocarditis, although the extent of endocarditis may allow for different inference. Moreover, we found no difference in other valve-related events between stentless and stented prosthesis. We believe that both prostheses are safe to use in the average patient undergoing aortic root replacement.

The position of bioprosthetic aortic root replacement

There is no perfect valve substitute for the individual patient with aortic valve and/or root disease as all prostheses are associated with certain valve-related events of varying nature. Careful weighting of the advantages and disadvantages of biological and mechanical valve substitutes tailored to the patient's unique characteristics and preferences, is the current gold standard. Interestingly, there is a trend toward using a biological valve in younger patients (5, 56). Although evidence is lacking, perhaps this is emerging due to the potential prospect of transcatheter valve-in-valve therapy as a future solution for bioprosthetic SVD.

According to the ESC/EACTS guidelines on valvular heart disease, age limits contain an arbitrary element, and the choice of prostheses type should be individualized in a joint decision between the patient and doctor. Although SVD is known to occur earlier in younger patients (57), mechanical valve prostheses are not the preferred alternative in all young patients. Nevertheless, as individual patient norms, values and goals in life

vary widely, the decision for a particular valve prosthesis should be individualized in a shared decision making process, and together with surgical experience, the most suitable surgical approach should be determined (2, 53). Our systematic review adds to the body of evidence by showing in a middle-aged patient population, undergoing bioprosthetic aortic root replacement, acceptable reintervention rates and valve-related event occurrence, and may be used as a benchmark to compare outcome with other type of prosthesis, e.g. Bentall and valve-sparing procedures.

*Limitations*As in all systematic reviews and meta-analysis of retrospective observational studies, limitations of this type of study should be taken into consideration (58). Furthermore, recall bias inherent to the retrospective design of all but one study and publication bias may have affected the observed outcome. In addition, the included studies represent a heterogeneous population of patients with different patient characteristics, with patients operated in different era spanning over 20 years, and considering improvements in anticoagulation strategies, medical management of valvular heart disease and surgical techniques over the past decades, which may have influenced outcome. Moreover, a lack of uniform data reporting as proposed by the guidelines (9) may have influenced the uniformity of the pooled data.

The pooled late outcome estimates are based on the linearity assumption, while occurrence of outcome events may not be linear in nature. However, due to the lack of randomized trials where homogeneous data are present, this meta-analysis was performed to provide an overview of published outcomes after bioprosthetic aortic root replacement.

Conclusion

This study provides an overview of contemporary outcome after bioprosthetic aortic root replacement and demonstrates impaired survival and notable valve-related events, irrespective of the type of valve prosthesis. Thromboembolic events occur relatively frequent and may be associated with higher thrombogenicity of the biological valve, at least in the early postoperative period. This should be considered when choosing the most optimal treatment, especially in younger patients. Given the observed heterogeneity of the pooled study results, in-depth analysis of potential risk factors remains challenging. It requires a collective international effort employing uniform data definitions and high quality data collection, to push forward the knowledge on outcomes and provide clues toward optimization of treatment selection for patients requiring aortic root replacement (59). Nevertheless, this study provides comprehensive outcome and may be used as a benchmark to compare with other types of procedures (e.g. Bentall or valve-sparing procedures).

Data availability statement The data that support the findings of this study are available at PubMed, at https://pubmed.ncbi.nlm.nih.gov, references are the studies included into this systematic review. These data were derived from the following resources available in the public domain: MEDLINE (PubMed), Embase, The Cochrane Collaboration and Web of Science, and Google Scholar.

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Tables

Table 1. Pooled pre-operative and peri-operative characteristics.

Variable		**Pooled data**	**Range**	**Included studies (N)**
Total patient number		**5227**	50 - 421	31
Surgical period		**1992 - 2014**		30
Mean age		**65.4 years**	47 – 73 years	30
Gender	Male	**67.6%**	30 – 85%	31
Etiology	Valve pathology			18
	Aortic stenosis	**49.8%**	3 – 100%	
	Aortic regurgitation	**37.7%**	0 – 92%	
	Stenosis & regurgitation	**17.9%**		
	Connective tissue disease	**2.9%**	0 – 32%	13
	Bicuspid aortic valve	**28.0%**	0 – 42.6%	14
Prior surgery	Cardiac	**14.2%**	0 – 39%	23
Other indications	Acute type A dissection	**7.2%**	0 – 24%	20
	Acute endocarditis	**9.1%**	1 – 11%	9
Valve type	Stentless	**99.7%**	95 – 100%	23
	Stented	**92.8%**	84 – 100%	5
	Mixed	**50%**	50 – 50%	2
Concomitant procedures	Aortic hemiarch repair	**18.2%**	0 – 44%	19
	Aortic arch repair	**5.9%**	3 – 21%	19
	CABG	**28.9%**	0 – 44%	19
	Mitral valve surgery	**3.3%**	0 – 17%	19

Variable		Pooled data	Range	Included studies (N)
Re-exploration for bleeding		**10.8%**	1 – 28%	14
Early mortality		**5.5%**	0 – 16%	31
Causes of early mortality *	*Low cardiac output*	**22.7%**	1 – 44%	
	Multi-organ failure Hemorrhage	**18.1% 7.5%**	13 – 100% 0 – 13%	
	Sepsis Myocardial infarction	**5.0% 4.0%**	6 – 25% 0 – 100%	
	Unknown / unreported	**9.6%**	10 – 55%	

CABG indicates coronary artery bypass grafting. * major causes of early mortality. Data indicate the pooled mean % of occurrence and the pooled range of occurrence. Included studies are publications reporting on the specific characteristic. The percentages mentioned are means of the reported variables in the studies that provided these variable numbers. The range indicates the lowest and the highest reported % of that specific variable within all studies, and N indicates the number of studies reporting on that specific variable.

Table 2. Linearized occurrence rates of late outcome events.

Pooled late outcome events	LOR (%/yr) + 95% CI*	Heterogeneity (I^2)	Included studies (N)	Events
Late mortality	**4.61** (3.98 – 5.36)	71	31	1037
Root reintervention	**0.72** (0.47 – 1.10)	73	31	167
Hemorrhage	**0.56** (0.33 – 0.94)	68	27	83
Thromboembolism	**1.41** (0.96 – 2.06)	73	26	180
Endocarditis	**0.94** (0.69 – 1.32)	69	27	130
SVD*	**0.32** (0.16 – 0.62)	76	26	74
NSVD*	**0.21** (0.13 – 0.34)	49	21	15

LOR indicates linearized occurrence rates; CI, confidence interval; SVD, structural valve degeneration; MAVRE, major adverse valve-related events. * not all (N)SVD led to reintervention

Table 3. Mortality and valve-related outcome for stentless and stented valve prosthesis.

	Stentless	Stentless	Stentless	Stentless	Stented	Stented	Stented	Stented
	LOR	**95% CI -**	**95% CI +**	**N**	**LOR**	**95% CI -**	**95% CI +**	**N**
Early Mortality	6.5	5.1	8.4	23	5.5	4.0	7.6	5
Late Mortality	4.9	4.2	5.6	23	4.3	3.1	6.0	5
Reintervention	1.0	0.7	1.4	23	0.9	0.3	2.6	5
TE	1.5	1.1	2.2	20	0.5	0.2	1.4	5
Bleeding	0.3	0.2	0.6	19	0.6	0.2	1.9	5
Endocarditis	1.0	0.8	1.4	22	0.4	0.2	0.8	4
SVD	0.4	0.3	0.7	20	0.7	0.2	3.1	5

LOR indicates linearized occurrence rates; CI confidence interval; N number of studies included in analysis

Table 4. Mortality and valve-related outcome for mean follow-up (FU) more than 5 years and less than 5

years.

	FU < 5 yrs	**FU < 5 yrs**	**FU < 5 yrs**	**FU < 5 yrs**	**FU > 5 yrs**	**FU > 5 yrs**	**FU >**
	LOR	**95% CI -**	**95% CI +**	**N**	**LOR**	**95% CI -**	**95% C**
Early Mortality	6.2	4.8	8.0	18	5.7	4.5	7.2
Late Mortality	4.4	3.5	5.6	18	4.8	3.9	5.8
Reintervention	1.2	0.7	1.9	15	0.4	0.2	0.7
TE	1.6	1.0	2.5	15	0.7	0.3	1.5
Bleeding	0.6	0.3	1.3	13	0.5	0.3	0.8
Endocarditis	1.4	1.0	1.9	15	0.5	0.3	0.8
SVD	0.3	0.2	0.5	12	0.3	0.2	0.5

LOR indicates linearized occurrence rates; CI confidence interval; N number of studies included in analysis

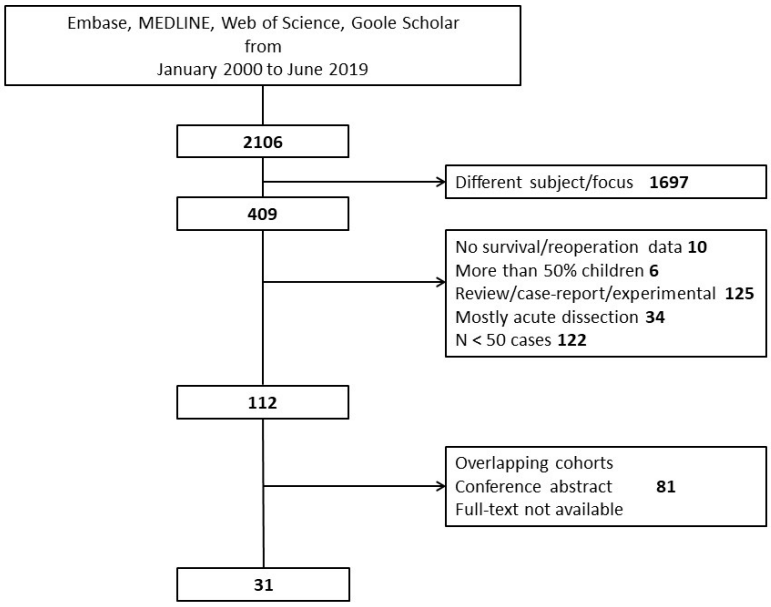

Figure 1. Flowchart of systematic search and included articles

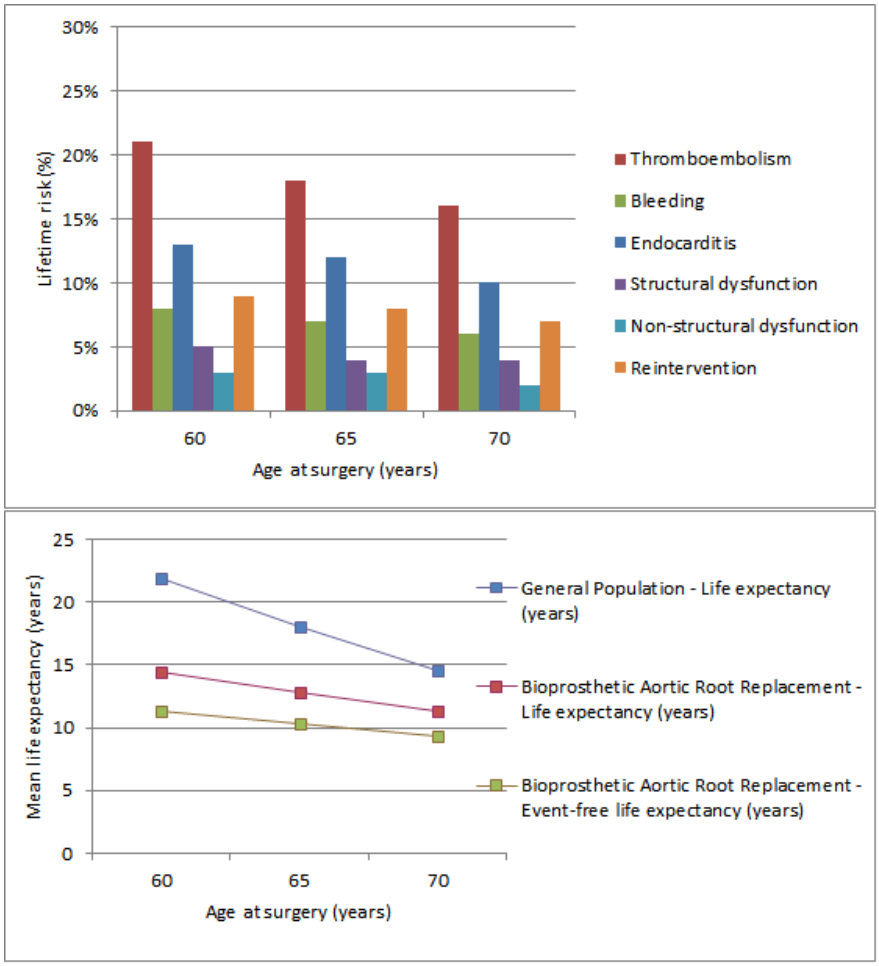

Figure 2. Microsimulation-based life expectancy and lifetime risk of valve-related morbidity for 60, 65 and 70 years old patients.

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