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RESEARCH

Prognosis after surgical replacement with a bioprosthetic aortic valve in patients with severe symptomatic aortic stenosis: systematic review of observational studies

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Abstract

Objective To determine the frequency of survival, stroke, atrial fibrillation, structural valve deterioration, and length of hospital stay after surgical replacement of an aortic valve (SAVR) with a bioprosthetic valve in patients with severe symptomatic aortic stenosis.

Design Systematic review and meta-analysis of observational studies.

Data sources Medline, Embase, PubMed (non-Medline records only), Cochrane Database of Systematic Reviews, and Cochrane CENTRAL from 2002 to June 2016.

Study selection Eligible observational studies followed patients after SAVR with a bioprosthetic valve for at least two years.

Methods Reviewers, independently and in duplicate, evaluated study eligibility, extracted data, and assessed risk of bias for patient important outcomes. We used the GRADE system to quantify absolute effects and quality of evidence. Published survival curves provided data for survival and freedom from structural valve deterioration, and random effect models provided the framework for estimates of pooled incidence rates of stroke, atrial fibrillation, and length of hospital stay.

Results In patients undergoing SAVR with a bioprosthetic valve, median survival was 16 years in those aged 65 or less, 12 years in those aged 65 to 75, seven years in those aged 75 to 85, and six years in those aged more than 85. The incidence rate of stroke was 0.25 per 100 patient years (95% confidence interval 0.06 to 0.54) and atrial fibrillation 2.90 per 100 patient years (1.78 to 4.79). Post-SAVR, freedom from structural valve deterioration was 94.0% at 10 years, 81.7% at 15 years, and 52% at 20 years, and mean length of hospital stay was 12 days (95% confidence interval 9 to 15).

Conclusion Patients with severe symptomatic aortic stenosis undergoing SAVR with a bioprosthetic valve can expect only slightly lower survival than those without aortic stenosis, and a low incidence of stroke and, up to 10 years, of structural valve deterioration. The rate of deterioration increases rapidly after 10 years, and particularly after 15 years.

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Data supplements on bmj.com (see http://www.bmj.com/content/354/bmj.i5065?tab=related#datasupp)

Supplementary appendices: Appendices A to H

Introduction

Aortic valve replacement is the treatment of choice for patients with severe symptomatic aortic stenosis.[1] Surgical aortic valve replacement (SAVR) reduces morbidity and mortality related to aortic stenosis and has been the procedure of choice for younger, low to intermediate risk patients, typically defined by the Society of Thoracic Surgeons predicted risk of mortality (STS-PROM) score of 8% or less.[1] Because such patients require lifelong treatment with oral anticoagulants,[2] use of mechanical valves has decreased and most SAVR procedures now use bioprosthetic valves.

Options facing patients with severe aortic stenosis include delaying any major procedure, undergoing SAVR with a mechanical valve, undergoing SAVR with a bioprosthetic valve, and undergoing transcatheter aortic valve implantation. Crucial to this decision is mortality after SAVR and structural valve deterioration resulting in heart failure, with possible need for a second valve replacement.

A recent systematic review and meta-analysis of observational studies reporting on long term outcomes with bioprosthetic valves suggest a low incidence for early and late mortality (5.03% per patient year and 1.68% per patient year, respectively) and a very low rate of reintervention (0.75% per patient year).[3] Limitations of this review included failure to age stratify for mortality, the unlikely assumption of a constant hazard for the incidence rate for reintervention, failure to address outcomes of stroke and atrial fibrillation incidence, and failure to formally address the quality of evidence underlying the findings.

We therefore initiated our own systematic review of the prognosis of patients undergoing SAVR with a bioprosthetic valve. We conducted the review in parallel with systematic reviews addressing relative effects of transcatheter aortic valve implantation versus bioprosthetic SAVR in low and intermediate risk patients,[4] and a related review of patients' values and preferences.[5] Our review addressed patient important outcomes of survival, stratified by patients' age, and of stroke, atrial fibrillation, length of hospital stay, and structural valve deterioration with SAVR. These outcomes were chosen with the participation of patients who had undergone SAVR.

We conducted these reviews to inform recommendations[6] for the first in a new series in *The BMJ* of trustworthy recommendations published in response to potentially practice changing evidence,[7] so called Rapid Recommendations. For such recommendations, the panel overseeing the new series requires estimates of absolute risk obtained by applying relative risk estimates from randomised trials to best estimates of baseline risk. Such baseline risks ideally come from observational studies that typically enrol more representative patients than do randomised trials, and follow patients for far longer.

Methods

Data sources and searches

We created the search strategy informed by a previously published comprehensive systematic search,[8] with modifications to capture observational studies. We searched Medline, Embase, PubMed (non-Medline records only), Cochrane Database of Systematic Reviews, and Cochrane CENTRAL from conception to 30 June 2016. Supplementary appendix A presents the search strategy. We identified additional references by searching the reference lists of included publications and relevant narrative reviews.

Study selection

Eligible observational studies enrolled adults (≥18 years) with symptomatic aortic stenosis undergoing SAVR using a bioprosthetic valve. We included studies reporting on patients with mechanical valves if results in patients receiving bioprosthetic valves were reported separately or if 80% or greater of the participants received bioprosthetic valves. Patient important outcomes were identified by the Rapid Recommendations panel responsible for creating recommendations, composed of clinicians, researchers, methodologists, and patients.[6] Eligible SAVR studies, unrestricted by language, reported on mortality, stroke, atrial fibrillation, structural valve deterioration, index admission length of stay, or postoperative pain. To ensure that our review was relevant to current technologies, we included only studies published after 2006; for the sake of efficiency, we excluded studies enrolling fewer than 50 patients. When more than one study reported on the same population, we used data from all studies that provided relevant comprehensive information.

Seven reviewers, working in pairs, independently screened titles and abstracts of identified citations, evaluating the full text of potentially eligible articles using a standardised screening form (see supplementary appendix B). The Covidence systematic review platform provided software for screening.[9]

Data abstraction and risk of bias assessment

Ten reviewers, working in pairs and using a standardised form, independently extracted data from eligible studies, including source of data, time frame of recruitment, definition and number of events, and population characteristics, including age, sex, history of coronary artery disease, chronic obstructive pulmonary disease, diabetes, hypertension, atrial fibrillation, and left ventricular ejection fraction, New York Heart Association classification, prior coronary artery bypass grafting, prior myocardial infarction, prior percutaneous coronary intervention, prior stroke or transient ischemic attack, logistic EuroSCORE, STS-PROM score, and concomitant coronary artery bypass grafting. For survival and structural valve deterioration post-SAVR, we applied Digitizeit[10] to published Kaplan-Meier curves to obtain patient level freedom-from-event estimates over time. For stroke, atrial fibrillation, and structural valve deterioration in studies not presenting Kaplan-Meier curves, we collected the total number of events along with median follow-up time and incidence rates per 100 patient years, and captured information on postoperative length of hospital stay. Data from the Social Security Administration of United States of America[11] provided life expectancy for the general population for comparison with estimates of survival post-SAVR obtained in our review.

The quality in prognostic studies (QUIPS)[12] instrument provided criteria for assessing risk of bias in individual studies, including patient selection, study attrition, measurement of prognostic factors, outcome measurement, study confounding, and statistical analysis and reporting (see supplementary appendix C). The instrument rates studies as high, moderate, or low risk of bias. We classified studies with five or six low risk domains as at overall low risk of bias, studies with two or more high risk domains as at overall high risk of bias, and remaining studies as at overall moderate risk of bias.

The grading of recommendations, assessment, development, and evaluation (GRADE) system provided the structure for assessing confidence in prognostic risk estimates[13] as high, moderate, low, or very low based on considerations of risk of

bias, consistency, precision, directness, and publication bias. The last was assessed using visual inspection of funnel plots.

Data synthesis and statistical analysis

Using an established algorithm, we estimated and pooled individual patient data to obtain an overall estimate of survival and freedom from structural valve deterioration.[14] Owing to the lack of Kaplan-Meier curves for stroke and atrial fibrillation, we combined and presented the study results as incidence rates per 100 patient years post-intervention for each outcome using Metaprop's DerSimonian and Laird random effects model, with a binomial distribution to model within study variability or stabilise variances by applying Freeman-Tukey double arcsine transformation.[15]

We addressed statistical heterogeneity through consistency of point estimates and extent of overlap of confidence intervals. Heterogeneity was not assessed with I^2 statistics, as this is typically not useful in prognostic studies with a large sample size and resulting precise estimates.[13] To identify potential sources of heterogeneity, we performed subgroup analyses for age, valve type, and risk of bias, specified a priori. We hypothesised higher adverse event rates in older patients, in studies that included only bioprosthetic valves versus studies that also included mechanical valves. We established age thresholds consistent with the requirements for Rapid Recommendations: study mean or median age of ≤65, 65 to <75, 75 to <85, and ≥85.[6] For survival estimates, we used the log-rank test to compare survival across the different age groups. We defined a half weighted threshold age in which close to 50% of the total sample, within each age subgroup, is above and below this threshold. For these age thresholds, we obtained life expectancy estimates from the Social Security Administration of United States of America.[11] We compared our median survival estimates with life expectancy estimates of the US general population.

A two sided P value of 0.05 or less was considered statistically significant. Review Manager 5 and STATA[16 17] provided software for statistical analyses, as well as forest plots and funnel plots.

Patient involvement

The parallel Rapid Recommendations guideline panel, which included two patients, requested this meta-analysis and included two people with experience of severe aortic stenosis. The patient panel members helped choose the outcomes examined in this systematic review and uniquely highlighted pain and physical function. We were unable to find direct evidence for either of those outcomes. Feedback from the community panel members guided the interpretation and dissemination of our results.

Results

Study selection and characteristics

The 93 eligible studies enrolled patients from 1977 to 2013 and reported on 53 884 predominantly male patients with aortic stenosis (mean age 53 to 92 years) undergoing aortic valve replacement. Figure 1⇓ presents the flow diagram for study selection following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) format. Supplementary appendix C summarizes the characteristics of the eligible studies.

Risk of bias in individual studies

Supplementary appendix D summarizes the quality assessment of individual studies. Of the 93 studies, 51 proved at overall low risk of bias.[18-68] Twenty one of the remaining 42 proved at overall moderate risk of bias[69-89] and 21 at overall high risk of bias.[90-110]

Survival post-SAVR

All 85 studies that reported survival post-SAVR analyzed data using a Kaplan-Meier method. Studies provided pooled survival estimates of 89.7% at two years, 78.4% at five years, 57.0% at 10 years, 39.7% at 15 years, and 24.7% at 20 years. Supplementary appendix H provides the life table that informed estimates for Rapid Recommendations.[6] A subgroup analysis comparing studies with a mean or median age of ≤65, 65 to 75, 75 to 85, and more than 85 showed survival at five years of 83.7%, 81.4%, 67.4%, and 52.2%, respectively (interaction P<0.001, fig 2⇓). Studies provided approximate median survival estimates of 16 years in patients aged 65 or less (half weighted group age 59, US general population life expectancy 22.2), 12 years in those aged 65 to 75 (half weighted group age 68, US general population life expectancy 15.6), seven years in those aged 75 to 85 (median age 79, half weighted US general population life expectancy 8.7), and six years in those aged more than 85 (mean age 92, US general population life expectancy 3.5).[11] Studies provided similar estimates of survival across risk of bias and valve type. The overall confidence in the estimate of mortality is moderate (table1⇓), with the main limitation being serious inconsistency in survival estimates across individual studies.

Stroke post-SAVR

The seven studies reporting stroke post-SAVR[23-90] provided number of events both within and beyond the postoperative period as well as median follow-up time, allowing for calculation of incidence rate per 100 patients years. Studies provided a pooled estimate for incidence of stroke of 0.25 per 100 patient years (95% confidence interval 0.06 to 0.54, table 1⇓). Subgroup analysis comparing studies revealed that chance easily explained differences between studies restricted to patients receiving bioprosthetic valves and those including patients receiving mechanical valves (bioprosthetic only, 0.38 per 100 patients years, 0.22 to 0.58; mixed population, 0.12 per 100 patients years, 0.00 to 0.49; interaction P=0.26), and based on age categories (<75, 0.28 per 100 patients years, 0.08 to 0.57; >75, 0.55 per 100 patient years, 0.15 to 1.15; interaction P=0.26). The overall confidence in the estimate of stroke is moderate because of imprecision (table 1⇓).

Atrial fibrillation post-SAVR

Two studies including a total of 177 patients reported that 21 developed atrial fibrillation post-SAVR.[23 106] The pooled incidence rate of these studies was 2.90 per 100 patient years (1.78 to 4.79) (table 1⇓). The small number of studies precluded subgroup analysis. The overall confidence in the estimate of atrial fibrillation is low owing to serious risk of bias and imprecision (table 1⇓).

Structural valve deterioration

Twelve studies[21-90] with published Kaplan-Meier curves including 7603 patients reported on structural valve deterioration after SAVR. Supplementary appendix F presents the definition for structural valve deterioration across all 12 studies. Although the definitions are worded slightly differently, they all objectively defined valve dysfunction as severe stenosis or regurgitation through echocardiographic assessment. Studies estimated a cumulative incidence of 6.0% by 10 years, 19.3%

by 15 years, and 48.0% by 20 years (fig 3⇓). Risk of bias assessment deemed all but one study to be at low risk of bias. The overall confidence in the estimates of structural valve deterioration post-SAVR is high.

Length of hospital stay

The pooled mean estimate for length of hospital stay in 11 studies[20-31] 3962 [64-103] that enrolled 6405 patients undergoing SAVR was 13 days (95% confidence interval 10 to 16, table 1⇓). Subgroup analysis comparing studies at low risk of bias with those at moderate and high risk of bias showed an interaction P value of 0.05 (low risk of bias, 12 days, 95% confidence interval 9 to 15; high risk of bias, 15 days, 14 to 16). Given the P value on the test for interaction, we considered the low risk of bias studies to be more trustworthy, providing high confidence in the estimate of length of hospital stay (table 1⇓).

Postoperative pain

No eligible studies reported on postoperative pain.

Discussion

In this systematic review and meta-analysis of outcomes after surgical aortic valve replacement (SAVR) we provide prognostic estimates for patient important outcomes needed to determine absolute effects of SAVR for patient important outcomes. The timeliness of the review is underscored by the potentially practice changing evidence emerging from the Partner 2 trial concerning transcatheter aortic valve implantation as an alternative to SAVR in patients at low to intermediate risk of perioperative mortality.[111] Our findings, together with linked systematic reviews on treatment effects and patient preferences and values, inform trustworthy recommendations for clinical practice developed in the new *The BMJ* series Rapid Recommendations.[6]

Principal findings

From the time of surgery, the approximate median survival in patients undergoing SAVR is 16 years in those aged 65 or less years, 12 years in patients aged 65 to 75, seven years in those aged 75 to 85, and six years in those older than 85 (fig 2⇓). The median survival in patients aged 65 or less years is approximately five years less than that of the general population, but it is similar to the general population in patients older than 65. Evidence in patients with an average age of more than 85, taken from a single study, suggested a longer life span than that of the general population of the same age. This likely reflects that only exceptionally healthy patients of this advanced age were considered for SAVR.

Over the decade after SAVR, patients participating in these studies experienced a risk of stroke less than 3%, a risk of atrial fibrillation less than 30%, and a risk of structural valve deterioration less than 10%. The rate of structural valve deterioration, however, increases rapidly after 10 years, with deterioration occurring in almost 50% of patients by 20 years.

Age has a strong association with mortality; estimates differed according to risk of bias only for duration of hospital stay (lower risk of bias studies reported shorter hospital stay). With respect to stroke, age did not influence the frequency. We found only one study reporting on stroke in patients of mean age 65 or less, and no studies of mean age 85 or more. Thus there is need for future research to better understand the extent to which risk of stroke varies across age groups.

In these studies, patients undergoing SAVR stayed in hospital an average of 12 days (95% confidence interval 9 to 15 days). We found one study to be an outlier, with a mean length of stay post-SAVR of five days.[39] Most patients in this study were in New York Heart Association class I and II (89%). The relatively normal functional status of these patients may be responsible for the shorter length of stay post-surgery. One study, from the German registry on SAVR (not included in our systematic review because it was published after we had completed our search), reported an average length of stay of 12 days, in keeping with our results.[112]

Strengths and limitations of this review

Strengths of our systematic review include a comprehensive search of databases for all observational studies and a review of citations of not only eligible studies but prior narrative reviews. Reviewers abstracted data and applied the QUIPS instrument for risk of bias, independently and in duplicate. We conducted subgroup analyses exploring the impact of age, risk of bias, and population (all bioprosthetic or mixed) on outcomes. We also rated the confidence in prognostic estimates for each outcome using guidance from the GRADE working group.[13]

One limitation of this review is that the method we used for pooling survival across studies using published Kaplan-Meier curves assumes a constant rate of censoring through time.[14] The algorithm underlying this method does not consider the standard error in survival estimates and thus the variability in results across studies. This method therefore does not account for the varying sample sizes from which the individual patient data are estimated. Thus we are unable to generate confidence intervals around survival estimates and cumulative incidences. Another limitation of this method is the inability to perform competing risk analysis, which would require individual patient data from source studies. The current analysis captures mortality as a censored event when the outcome of interest is structural valve deterioration. As a result, this modifies the probability of structural valve deterioration, resulting in inaccurate cumulative incidence for this event.

In our survival analysis, we subclassified studies based on prespecified age categories. We classified studies using the reported mean or median age. It is possible for some studies to be classified in one category but have patients that belong to another age category (based on the distribution of age). This likely underestimates differences in survival according to age. Furthermore, only one study had participants with a mean age of 92, and thus the age group 85 or older is informed by very few patients (n=119).

Our calculation of incidence rate depended on mean or median follow-up and assumed a constant incidence over time. When this is not the case (as it clearly is not for atrial fibrillation and structural valve deterioration) the incidence rates may be misleading.

For instance, two studies reported the absolute number of patients with new onset atrial fibrillation during the follow-up period. Collectively, they provided an incidence rate of 2.90 per 100 patient years. Based on this incidence rate, the risk of new onset atrial fibrillation by four years is 12%. In the PARTNER 2A trial, approximately 27 of 100 patients developed atrial fibrillation by two years.[111] Our incidence rate is based on a longer median follow-up (four years, versus two years maximum follow-up in PARTNER 2A). The hazard for atrial fibrillation is highest in the postoperative period and much lower thereafter; this to some extent explains the difference in estimates. Other explanations include differences between the

demographics of patients included in our review and those included in the PARTNER 2A trial. For instance, the average age of patients undergoing SAVR in the PARTNER 2A trial is 81.7 years; the two cohorts that inform our atrial fibrillation incidence rate enrolled patients of mean age 58 and 77 years.

We presented our estimate for length of hospital stay post-SAVR using the mean. The length of stay might be expected to have an upward skewed distribution, necessitating the use of median for reporting the central tendency. Therefore, our reported mean length of stay may be an overestimation as a result of improper statistical reporting of source studies.

We found high quality evidence for length of hospital stay and structural valve deterioration. Imprecision was a common limitation in other outcomes, which also limits subgroup analyses (for instance, we found no association between age and risk of stroke, likely because the analysis was underpowered).

Comparison with other findings

Our current paper and the previous systematic review and meta-analysis by Huygens et al both address prognosis after SAVR with bioprosthetic valves over a similar period.[3] The study by Huygens et al, however, failed to age stratify for mortality; our results, not surprisingly, show large differences in mortality across age groups. The study by Huygens et al focused on reinterventions, ignoring the functional deterioration that accompanies structural valve deterioration in those who do not undergo reintervention. In addressing reintervention, these authors made the unlikely assumption of a constant hazard. We utilized a novel method to obtain estimates for structural valve deterioration at all time points post-SAVR, and demonstrate the low rate of structural valve deterioration in the first decade after operation and the rapid increase thereafter, particularly after 15 years. In addition, our review addressed the additional patient important outcomes of atrial fibrillation, stroke, and length of hospital stay. Finally, we utilized the GRADE approach to evaluate confidence in our estimates for all outcomes, establishing that some evidence (structural valve deterioration, stroke) is high quality (and thus trustworthy), some (mortality, stroke) is moderate quality, and some (atrial fibrillation) only low quality.

Conclusion

For patients who undergo SAVR using a bioprosthetic valve, evidence with moderate to high confidence suggests a survival close to that of general populations of the same age, a low incidence of stroke, and infrequent structural valve deterioration for the first decade, with increasing incidence thereafter.

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Contributors: FF performed the literature search and data analysis. FF, RAS, GHG, and POV interpreted the data analysis. FF wrote the first draft of the manuscript. FF, SB, TD, YC, RK, DS, TA, HM, and TS acquired the data and judged risk of bias in the studies. KO, MS, and EB extracted patient level survival data from Kaplan-Meier curve. Steve Fan and Ana Carolina Alba provided statistical advice. CMO, RAS, POV, GHG, SB, TA, Heather Ross, and RB critically revised the manuscript. POV, RAS, TA, and GHG conceived the study idea. FF had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. FF is the guarantor.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organization that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influence the submitted work.

Ethical approval: Not required.

Data sharing: Abstracted study level and patient level survival data, as well as STATA code will be made publicly available on publication.

Transparency: The lead author (FF) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Linked articles in this *BMJ* Rapid Recommendations cluster

- Siemieniuk RA, Agoritsas T, Manja V, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic stenosis at low and intermediate risk: systematic review and meta-analysis. *BMJ* 2016;354:i5130.
  – Meta-analysis of the relative effects of transcatheter aortic valve insertion (TAVI) versus surgical aortic valve replacement (SAVR)
- • Lytvyn L, Guyatt GH, Manja V, et al. Patient values and preferences on transcatheter or surgical aortic valve replacement therapy for aortic stenosis: a systematic review. *BMJ Open* 2016;6:e014327.
  – Review of patients' views of TAVI versus SAVR
- • Vandvik PO, Otto CM, Siemieniuk RA, et al. Transcatheter or surgical aortic valve replacement for patients with severe, symptomatic, aortic stenosis at low to intermediate surgical risk: a clinical practice guideline. *BMJ* 2016;354:i5085.
  – Summary of the results from the Rapid Recommendation process
- • Magic App (www.magicapp.org)
  – Expanded version of the results with multilayered recommendations, evidence summaries, and decision aids for use on all devices

What is already known on this topic

Surgical aortic valve replacement (SAVR) using a bioprosthetic valve for severe aortic stenosis is often associated with acceptable perioperative and long term mortality, though best prognostic estimates from pooled data are unavailable

Valve deterioration is infrequent in the first years after SAVR, but increases subsequently, although best estimates are unavailable

What this study adds

Patients undergoing SAVR for severe aortic stenosis can anticipate only slightly lower survival than that of the general population of the same age

Long term outcome post-SAVR is associated with a low incidence of stroke and, over 10 years, of structural valve deterioration, though 48% experience valve deterioration by 20 years

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Table

Table 1| GRADE evidence profile on risk estimates summarizing findings from observational studies of surgical aortic valve replacement in patients with severe aortic stenosis

No of studies	Quality assessment						Effect			Quality
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of events	No of individuals	Estimate (95% CI)	
Survival (follow-up median 4.7 years; assessed with Kaplan-Meier)										
85	Observational studies	Not serious	Serious*	Not serious	Not serious	None	14 053	45 347	Survival at 5 years ≤65 83.7%; 65-75, 81.4%; 75-85 67.4%; and >85, 52.2%	Moderate
Stroke (follow-up median 5.1 years; assessed with incidence rate per 100 patient years)										
8	Observational studies	Not serious	Not serious	Not serious	Serious†	None	64	6702	Event rate 0.26 per 100 person years (0.06 to 0.54)	Moderate
Atrial fibrillation (follow-up mean 4.1 years; assessed with incidence rate per 100 patient years)										
2	Observational studies	Serious	Not serious	Not serious	Serious†	None	21	177	Event rate 2.90 per 100 person years (1.78 to 4.79)	Low
Structural valve deterioration (follow-up median 6.4 years; assessed with Kaplan-Meier)										
12	Observational studies	Not serious	Not serious	Not serious	Not serious	None	418	7703	6.0% , 19.3%, and 48% by 10, 15, and 20 years, respectively	High
Length of hospital stay (assessed with mean; scale 0 to 100)										
7	Observational studies	Not serious	Not serious	Not serious	Not serious	None	-	6405	Mean 12 (9 to 15)	High

*Wide variety of individual Kaplan-Meier curves around overall mega Kaplan-meier curve.

†Wide confidence interval around the point estimate of incidence rate.

Figures

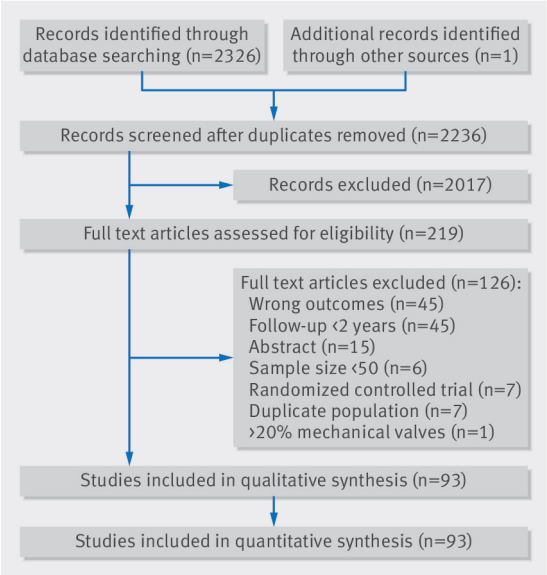

Fig 1 Study flow diagram

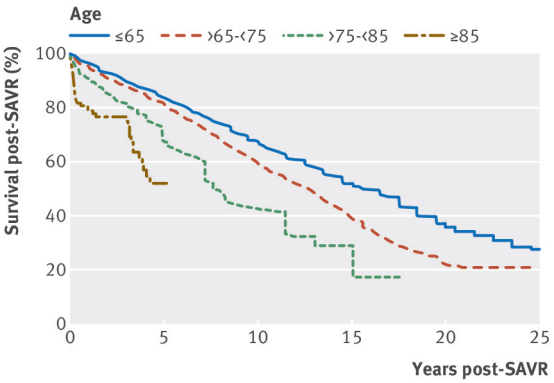

Fig 2 Survival after surgical replacement of an aortic valve with a bioprosthetic valve, stratified by age. Individual patient data estimated using algorithm developed by Guyot et al 2012[14]

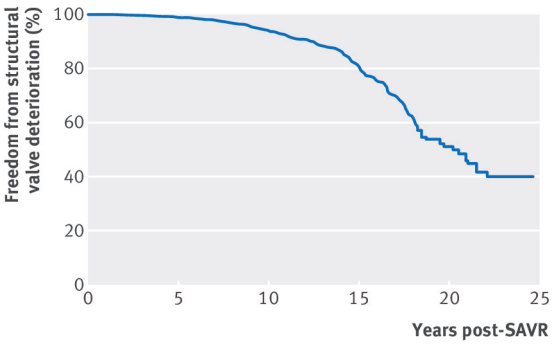

Fig 3 Freedom from structural valve deterioration after surgical aortic valve replacement with a bioprosthetic valve. Individual patient data estimated using algorithm developed by Guyot et al 2012[14]