# Surgical Aortic Valve Replacement
# In the Era of Transcatheter Aortic Valve Replacement

Mevlüt Çelik

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# Surgical Aortic Valve Replacement

# In the Era of Transcatheter Aortic Valve Replacement

Chirurgische aortaklepvervanging
In het tijdperk van transcatheter aortaklepvervanging

**Thesis**

to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the
rector magnificus

Prof.dr. A.L. Bredenoord

and in accordance with the decision of the Doctorate Board.
The public defence shall be held on
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by

Mevlüt Çelik
Born in Schiedam, the Netherlands.

**Erasmus University Rotterdam**

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*For my mom.*

"It is pointless trying to know where the way leads.
Think only about your first step, the rest will come."

*Shams-i Tabrïzï*

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# 1 Surgical aortic valve replacement in the era of transcatheter aortic valve replacement

Aortic valve disease is the most common valvular disorder in the Western world, with an ever-increasing incidence of aortic stenosis (AS). Surgical aortic valve replacement (SAVR) was performed in the 1960s has been the gold standard for severe aortic stenosis for the last decades.[1] The introduction of transcatheter-based therapies for treating aortic valve disease was a major step forward.[2,3] The latest revolution in treating aortic valve replacement was the introduction of transcatheter aortic valve replacement (TAVR) in the early 2000s.[4] Attractive for its less-invasiveness, TAVR quickly became an established treatment modality for patients with severe AS having high or intermediate surgical risk.[5,6] Results from recently published clinical trials have even challenged the role of SAVR in low-risk AS patients and resulted in increased adoption of TAVR in the United States **Figure 1**.[7,8]

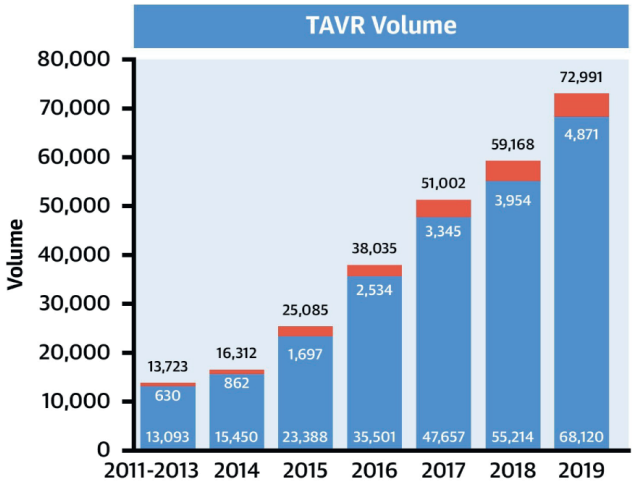



**Figure 1 - Trends in transcatheter aortic valve replacement in the United States of America through 2011-2019** (Reprinted with permission from Carroll DJ et al.)

On the other hand, developments, technical and procedural refinement, and continuous peri-procedural care improvement resulted in substantial improvement of SAVR outcomes over the last decades.[9] New therapies question the status quo and require stringent evaluation. If not evaluated, patients could have been subject to suboptimal treatment. The long-term results of TAVR are highly wanted. These results forecast a new era in treating aortic valvular pathology, where optimal treatment allocation will become increasingly important.

## Aim

This thesis aims to appraise the current evidence regarding surgical aortic valve replacement in patients with aortic valvular disease, especially in light of the expanded indications for transcatheter aortic valve replacement.

## Outline

In **Chapter 2** we describe the current trends of SAVR in the current population with aortic valvular disease over a 30-year period, hereby highlighting the patient-related changes over time. We further depict the long-term relative survival as a method of comparison with the general population. **Chapter 3** elaborates the technical standard for SAVR through an interrupted suture techniques in the aortic valvular position. In **Chapter 4**, we give an outline on the current state of mechanical and bioprosthetic valves. **Chapter 5** is focused on the current state of the mechanical valves, especially for patients receiving an On-X type of valve. **Chapter 6** is concentrated on the newer less-invasive therapy modality, TAVR, in low-risk patients. In **Chapter 7**, we go in-depth on the current bicuspid aortic valve population and the future potential of TAVR in this population. This has been elaborated to patients receiving concomitant aortic surgery with bicuspid valves in **Chapter 8**, which were excluded in **Chapter 7**. In **Chapter 9**, we further describe problems related to the implication of possible coronary artery disease in the future TAVR population within our current SAVR population. Male-female differences in surgery for aortic valve disease are discussed in **Chapter 10**. We further describe the current asymptomatic severe AS population. We give an overview of all the current evidence regarding early intervention in asymptomatic patients with severe AS in **Chapter 11**. We further elaborate on the natural history in the aforementioned patients, i.e., when these patients turn symptomatic and how intervention during follow-up and the timing of intervention impacts the survival of this population in **Chapter 12**. A general overview is presented in **Chapter 13**. A summary is presented in **Chapter 14**.

## REFERENCES


1. Effler DB, Favaloro R, Groves LK. Heart Valve Replacement. Clinical Experience. Ann Thorac Surg. 1965;1:4-24.
2. Cribier A, Savin T, Saoudi N, Rocha P, Berland J, Letac B. Percutaneous transluminal valvuloplasty of acquired aortic stenosis in elderly patients: an alternative to valve replacement? Lancet. 1986;1(8472):63-7.
3. Davies H OB. Catheter-mounten valve for temporary relief of aortic insufficiency. 1965;285(7379):250.
4. Cribier A, Eltchaninoff H, Bash A, Borenstein N, Tron C, Bauer F, et al. Percutaneous Transcatheter Implantation of an Aortic Valve Prosthesis for Calcific Aortic Stenosis. Circulation. 2002;106(24):3006.
5. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739-91.
6. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Fleisher LA, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017;135(25):e1159-e95.
7. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. N Engl J Med. 2019.
8. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. N Engl J Med. 2019.
9. Lee R, Li S, Rankin JS, O'Brien SM, Gammie JS, Peterson ED, et al. Fifteen-Year Outcome Trends for Valve Surgery in North America. The Annals of Thoracic Surgery. 2011;91(3):677-84.

# 2 Outcomes of surgical aortic valve replacement over three decades

Çelik M, Durko AP, Bekkers JA, Oei FBS, Mahtab EAF, Bogers AJJC.

**Journal of Thoracic and Cardiovascular Surgery. 2021.**

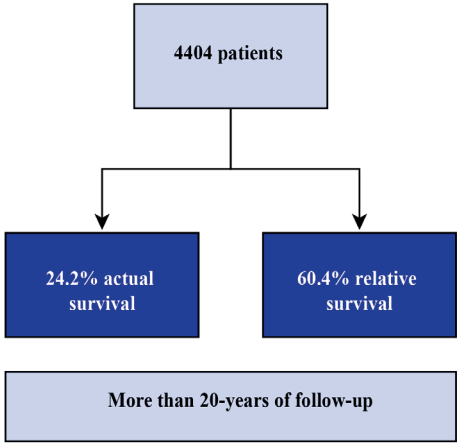
## CENTRAL MESSAGE

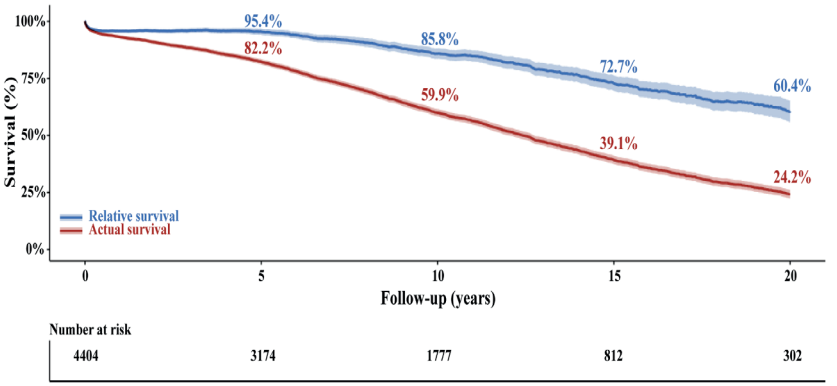
In a large SAVR cohort, relative survival is close to 90% at 10-years. This excellent long-term result reinforces the role of SAVR, especially in younger low-risk patients with long life expectancy.

## PERSPECTIVE STATEMENT

These excellent long-term results, especially in the younger low-risk patient population with long life expectancy and lower operative risk, reinforce the role of SAVR in the treatment of aortic valve disease and serve as a benchmark for future dedicated long-term TAVR studies.

## Long-term survival in a large cohort undergoing surgical aortic valve replacement in our center during the last 30 years




We identify that the relative survival is 60% at 20-years of follow-up. These excellent long-term results reinforce the role of surgical aortic valve replacement, especially in younger low-risk patients with long life expectancy.

## ABSTRACT

**Objective:** To analyze temporal changes in baseline and procedural characteristics and long-term survival of patients undergoing surgical aortic valve replacement (SAVR) over a 30-year period.

**Methods:** A retrospective analysis of patients undergoing SAVR between 1987 and 2016 in the Erasmus MC (Rotterdam, the Netherlands) were conducted. Patient baseline and procedural characteristics were analyzed in periods according to the date of SAVR (period A: 1987-1996; B: 1997-2006; C: 2007-2016). Survival status was determined using the Dutch National Death Registry. Relative survival was obtained by comparing the survival after SAVR to the survival of the age-, sex- and year-matched general population.

**Results**: Between 1987 and 2016, 4404 patients underwent SAVR. From period A to C, the mean age rose from 63.9±11.2 to 66.2±12.3 years ($p<0.001$), and the prevalence of diabetes mellitus, hypertension, hypercholesterolemia, previous myocardial infarction, and previous stroke at baseline increased (p-values for trend for all <0.001). The prevalence of concomitant procedures increased from 42.4% in period A to 48.3% in period C ($p=0.004$). Bioprosthesis use increased significantly (18.8% in period A versus 67.1% in period C, $p<0.001$). Mean survival after SAVR was 13.8 years. Relative survival at 20-year in the overall cohort was 60.4% (95%CI: 55.9-65.2%), and 73.8% (95% CI: 67.1-81.1%) in patients undergoing isolated primary SAVR.

**Conclusions:** The patient complexity is continuously increasing over the last 30 years, yet long-term survival after SAVR remains high compared to the age-, sex- and year-matched general population.

## INTRODUCTION

Invasive treatment of aortic valve disease is continuously evolving since the first surgical aortic valve replacement (SAVR) was performed in the 1960s.[1] Technical and procedural refinements, continuous prosthesis development, and peri-procedural care improvement resulted in a substantial improvement of SAVR outcomes over the last decades.[2] Concurrently, patient characteristics have changed considerably, and the comorbidity burden is increasing.[2,3]

The latest revolution in treating aortic valve replacement was the introduction of transcatheter aortic valve replacement (TAVR) in the early 2000s.[4] Attractive for its less-invasiveness, TAVR quickly became an established treatment modality for patients with aortic stenosis (AS) having high or intermediate surgical risk.[5,6] More recently, clinical trial results have even challenged the role of SAVR in low-risk AS patients.[7,8] These results forecast a new era in treating aortic valvular pathology, where optimal treatment allocation will become increasingly important.

Detailed analysis of patient and procedural characteristics, especially long-term survival after SAVR, is inevitable for informed treatment decisions. This study aimed was to assess the trends in patient and procedural characteristics and the long-term survival in SAVR in a high-volume tertiary center over the last three decades.

## METHODS

### Study design and data collection

Adult patients undergoing SAVR between 1987 and 2016 at the Erasmus Medical Center (Erasmus MC), Rotterdam, The Netherlands, were analyzed. Patients receiving bioprosthetic or mechanical aortic valve prosthesis with or without concomitant cardiac procedures were included. Patients younger than 18 years of age and patients receiving valved conduits were excluded. Baseline and procedural characteristics were collected retrospectively from electronic medical records. Survival status was obtained through the Dutch National Death Registry.

This study was conducted according to the privacy policy of the Erasmus MC and regulations for the appropriate use of data in patient-oriented research, which are based on international regulations, including the Declaration of Helsinki (Institutional MEC number: MEC-2019-0721) and patient informed consent was waived. All the authors vouch for the validity of the data and adherence to the protocol.

### Endpoints and definitions

The primary endpoint was the differences in baseline and procedural characteristics in the overall and primary isolated SAVR cohort, in three, 10-year time periods according to the date of SAVR (period A: 1987-1996; B: 1997-2006; C: 2007-2016). The survival in the overall and primary isolated SAVR cohort was analyzed and compared to the survival of the matched general population (relative survival). SAVR within 24 hours of establishing the indication was classified as urgent. SAVR after 24 hours was classified as (semi-) elective. Left ventricular function was classified as normal if the left ventricular ejection fraction (LVEF) was >50%, as reduced if the LVEF was 30-50% and as severely reduced if the LVEF was less than 30%, as measured or estimated by a trained echocardiographer. Low-, intermediate-, and high-risk patients are defined as logistic EuroSCORE of ≤10, 10-20, and ≥20, respectively.

### Statistical analysis

Categorical variables are presented as numbers, percentages, or proportions and compared with either the $\chi^2$ test or the Fisher Exact test, where appropriate. Continuous variables are presented as means ± standard deviation (SD) or median with the interquartile range (IQR) and compared with either the two-sample t-test or Wilcoxon rank-sum test where appropriate. Patients were classified into 10-year time periods based on surgery date (period A: 1987-1996; period B: 1997-2006; period C: 2007-2016). Trend analysis was performed with the $\chi^2$ test for trend. Two-sided p-values <0.05 were considered to be statistically significant.

The relative survival can be used as an estimate of cause-specific mortality. It is defined as the ratio between the observed survival and the expected survival in the general population.[9] The Human Mortality Database was used to obtain the age-, sex- and year-matched expected survival data of the general population of the Netherlands.[10] The Human Mortality Database is continuously updated and includes mortality data from the Netherlands up until 2016. Relative survival is estimated through the Ederer II method.[11,12] Data management and statistical analyses were performed using SPSS 25.0 (SPSS Inc, Chicago, Illinois) and R software, version 3.5 (R Foundation, Vienna, Austria).

## RESULTS

### Baseline characteristics

Between 1987 and 2016, a total of 4404 patients underwent SAVR with a biological (n=2301) or mechanical (n=2103) valve prosthesis. No patients were lost to follow-up for survival, with a mean follow-up of 13.8 years. Mean age was 65.5 ± 12.1 and 38.2% (n=1683) were female. A total of 46.3% (n=2041) required concomitant procedures and

5.6% (n=247) had redo SAVR. The indication for operation was aortic stenosis (AS) or combined AS and aortic regurgitation (AR) in most cases (83.9%). The most common comorbidities included hypertension (35.1%, n=1545), atrial fibrillation (17.6%, n=775) and diabetes mellitus (14.9%, n=656). The median logistic EuroSCORE (LES) (available since 2003; n=2605) was 5.0%, with 18.8% (n=480) of the patients having a LES of ≥10% and 6.0% (n=153) a LES of ≥20%. Further baseline characteristics are shown in Table 1 for the overall cohort and in Table S1 and S2 for the isolated SAVR and for the SAVR with concomitant CABG cohort.

**Table 1. Baseline characteristics over three decades in the overall cohort**

| | All patients (n=4404) | Period A 1987-1996 (n=911) | Period B 1997-2006 (n=1627) | Period C 2007-2016 (n=1866) | $\chi^2$ p-value |
|---|---|---|---|---|---|
| **Age at operation (mean ± SD)** | 65.5 ± 12.1 | 63.9 ± 11.2 | 65.5 ± 12.3 | 66.2 ± 12.3 | <0.001 |
| **<40** | 180 (4.1) | 33 (3.6) | 67 (4.1) | 80 (4.3) | 0.427 |
| **40-49** | 302 (6.8) | 74 (8.1) | 121 (7.4) | 107 (5.6) | 0.006 |
| **50-59** | 649 (14.7) | 157 (17.2) | 239 (14.7) | 253 (13.6) | 0.013 |
| **60-69** | 1330 (30.2) | 326 (35.8) | 448 (27.5) | 556 (29.8) | 0.012 |
| **70-79** | 1641 (37.3) | 297 (32.6) | 641 (39.4) | 703 (37.7) | 0.041 |
| **≥80** | 303 (6.9) | 24 (2.6) | 111 (6.8) | 168 (9.0) | <0.001 |
| **Female** | 1683 (38.2) | 338 (37.1) | 679 (41.7) | 666 (35.7) | 0.134 |
| **Indication (n=4370)** | | | | | |
| - **AS** | 2894 (66.2) | 499 (55.4) | 1086 (66.9) | 1309 (70.9) | <0.001 |
| - **AR** | 771 (17.6) | 163 (18.1) | 277 (17.1) | 331 (17.9) | 0.966 |
| - **Combined AS+AR** | 705 (16.1) | 239 (26.5) | 260 (16.0) | 206 (11.2) | <0.001 |
| **Bicuspid Aortic Valve** | 697 (15.8) | 234 (25.7) | 255 (15.7) | 208 (11.2) | <0.001 |
| **Endocarditis** | 292 (6.6) | 67 (7.4) | 95 (5.8) | 130 (7.0) | 0.983 |
| **Logistic EuroSCORE (n=2073) (median (IQR))** | 5.0 (2.9-8.4) | N/A | 5.0 (2.7-8.1) | 5.1 (2.9-8.4) | 0.188 |
| - **≥10** | 480 (18.8) | | 127 (18.4) | 353 (18.9) | 0.772 |
| - **≥20** | 153 (6.0) | | 36 (5.2) | 117 (6.3) | 0.320 |
| **Previous cardiac operation** | 553 (12.6) | 146 (16.0) | 200 (12.3) | 207 (11.1) | <0.001 |
| - **SAVR** | 247 (5.6) | 74 (8.1) | 72 (4.4) | 101 (5.4) | 0.023 |
| **Creatinine ≥2mg/dl** | 132 (3.0) | 25 (2.7) | 36 (2.2) | 71 (3.8) | 0.020 |
| **Previous hemodialysis** | 32 (0.7) | 5 (0.5) | 10 (0.6) | 17 (0.9) | 0.240 |
| **Atrial fibrillation** | 775 (17.6) | 160 (17.6) | 258 (15.9) | 357 (19.1) | 0.134 |
| **Diabetes mellitus** | 656 (14.9) | 69 (7.6) | 205 (12.6) | 382 (20.5) | <0.001 |
| **Cardiac decompensation** | 728 (16.5) | 210 (23.1) | 259 (15.9) | 259 (13.9) | <0.001 |
| **Hypertension** | 1545 (35.1) | 186 (20.4) | 456 (28.0) | 903 (48.4) | <0.001 |
| **Hypercholesterolemia** | 720 (16.3) | 47 (5.2) | 207 (12.7) | 466 (25.0) | <0.001 |
| **Previous myocardial infarction** | 507 (11.5) | 92 (10.1) | 178 (10.9) | 237 (12.7) | 0.030 |
| **Previous PCI** | 306 (6.9) | 27 (3.0) | 82 (5.0) | 197 (10.6) | <0.001 |
| **COPD** | 455 (10.3) | 72 (7.9) | 157 (9.6) | 226 (12.1) | <0.001 |
| **History of cancer** | 314 (7.1) | 27 (3.0) | 111 (6.8) | 176 (9.4) | <0.001 |
| **History of stroke** | 398 (9.0) | 45 (4.9) | 132 (8.1) | 221 (11.8) | <0.001 |

**Table 1. Baseline characteristics over three decades in the overall cohort** (*continued*)

| | All patients (n=4404) | Period A 1987-1996 (n=911) | Period B 1997-2006 (n=1627) | Period C 2007-2016 (n=1866) | $\chi^2$ p-value |
|---|---|---|---|---|---|
| **Arterial disease** | 195 (4.4) | 21 (2.3) | 59 (3.6) | 115 (6.2) | <0.001 |
| - **Peripheral** | 170 (3.9) | 20 (2.2) | 51 (3.1) | 99 (5.3) | <0.001 |
| - **Carotid** | 32 (0.7) | 1 (0.1) | 12 (0.7) | 19 (1.0) | 0.010 |
| **LVEF (n=4026)** | | | | | |
| - **Good** | 3147 (78.2) | 577 (77.4) | 1185 (79.3) | 1385 (77.5) | 0.771 |
| - **Reduced** | 729 (18.1) | 120 (16.1) | 264 (17.7) | 345 (19.3) | 0.046 |
| - **Severely reduced** | 150 (3.3) | 48 (6.4) | 46 (3.1) | 56 (3.1) | 0.001 |

Values are presented as n (%) or as mean ± SD or median (interquartile range) if otherwise stated.
AR = aortic regurgitation; AS = aortic stenosis; COPD= chronic obstructive pulmonary disease; LVEF = left ventricular ejection function; IQR = interquartile range; N/A = not available; PCI = percutaneous coronary intervention; SAVR = surgical aortic valve replacement

## Changes in patient profile over three decades

During the 30-year observation period, the annual number of patients undergoing SAVR per period increased, from an annual average of 91 in period A, to 187 in period C (Figure 1). The mean age rose from 63.9 ± 11.2 years in period

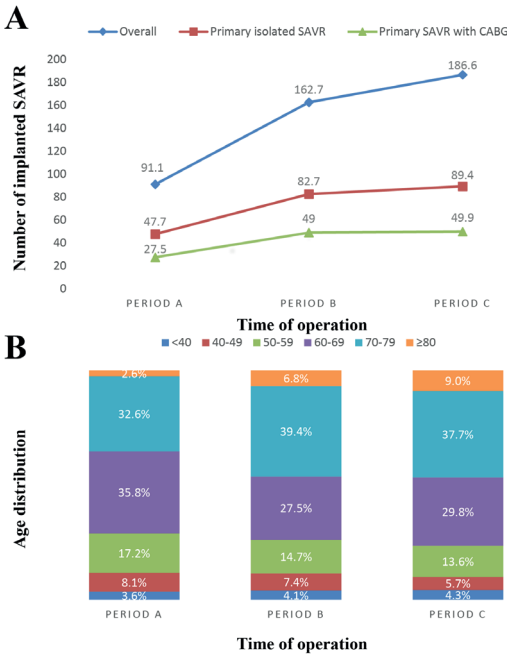



**Figure 1. Age at the operation and the annual number of patients undergoing SAVR over 30 years.**
Over 30-years, the percentage of elderly patients and the annual number of patients undergoing SAVR increased considerably; A) Annual average of patients undergoing SAVR, according to the type of surgery. Y-axis represents the absolute number of patients, B) Age distribution of patients at the time of SAVR. Results are reported according to the time of SAVR (Period A: 1987-1996; B: 1997-2006; C: 2007-2016).

C (p<0.001). The proportion of patients aged 70 years or more increased from 35.2% in period A to 46.7% in period C (p<0.001). Between period A and C, the prevalence of diabetes mellitus in the study population increased from 7.6% to 20.5% (p<0.001), hypercholesterolemia from 5.2% to 25.0% (p<0.001), and COPD from 7.9% to 12.1% (p<0.001). The percentage of patients with previous cardiac operations (p<0.001) and redo SAVR decreased (p=0.023). Further changes in baseline characteristics are shown in Table 1 for the overall cohort and in Tables S1-2 for the primary isolated SAVR and the primary SAVR with concomitant CABG cohort.

**Trends in procedural characteristics and prosthesis use**

During the study period, 46.3% (n=2041) of the SAVR patients underwent concomitant procedures (Table 3), with a significant increase from 42.4% in period A to 48.3% in period C (p=0.004). Most commonly, concomitant CABG was performed (n=1433, 32.5%). Among patients undergoing concomitant CABG, 41.2% (n=590) had single vessel disease and 58.8% (n=843) had multiple vessel disease. The proportion of patients requiring concomitant CABG for single vessel disease remained constant during the 30-year observation period (p=0.412). Patients with concomitant CABG were older compared to patients not requiring revascularization (70.1 ± 8.3 versus 65.0 ± 12.0; p<0.001). From period A to period C, the incidence of concomitant tricuspid and aortic procedures increased. The proportion of patients receiving bioprosthetic valves increased significantly, from 18.8% in period A, to 67.1% in period C (p<0.001, Figure 2). Detailed trends regarding changes in procedural characteristics and concomitant procedures are provided in Table 2.

**Trends in 30-day mortality and long-term survival**

The 30-day mortality in the overall cohort decreased from 2.7% in period A to 1.8% in period C (p=0.003). The 30-day mortality across three decades decreased, non-significantly, from 1.9% to 0.9% (p=0.190) for primary isolated SAVR, and from 4.1% to 3.0% (p=0.384) for primary SAVR with CABG (Table S3). The 10-year survival was 59.8% in the overall cohort, 65.5% in the isolated SAVR cohort and 51.1% in the SAVR with concomitant CABG group (Table 3).

From period A to C, 10-year survival did not change in the overall cohort and patients receiving isolated SAVR from 62.8% to 60.3% (p=0.051) and 66.9% to 67.2%, respectively (Table 3). Further trends in 10-year survival in various subgroups are also displayed in Table 3 and Figures S1-3.

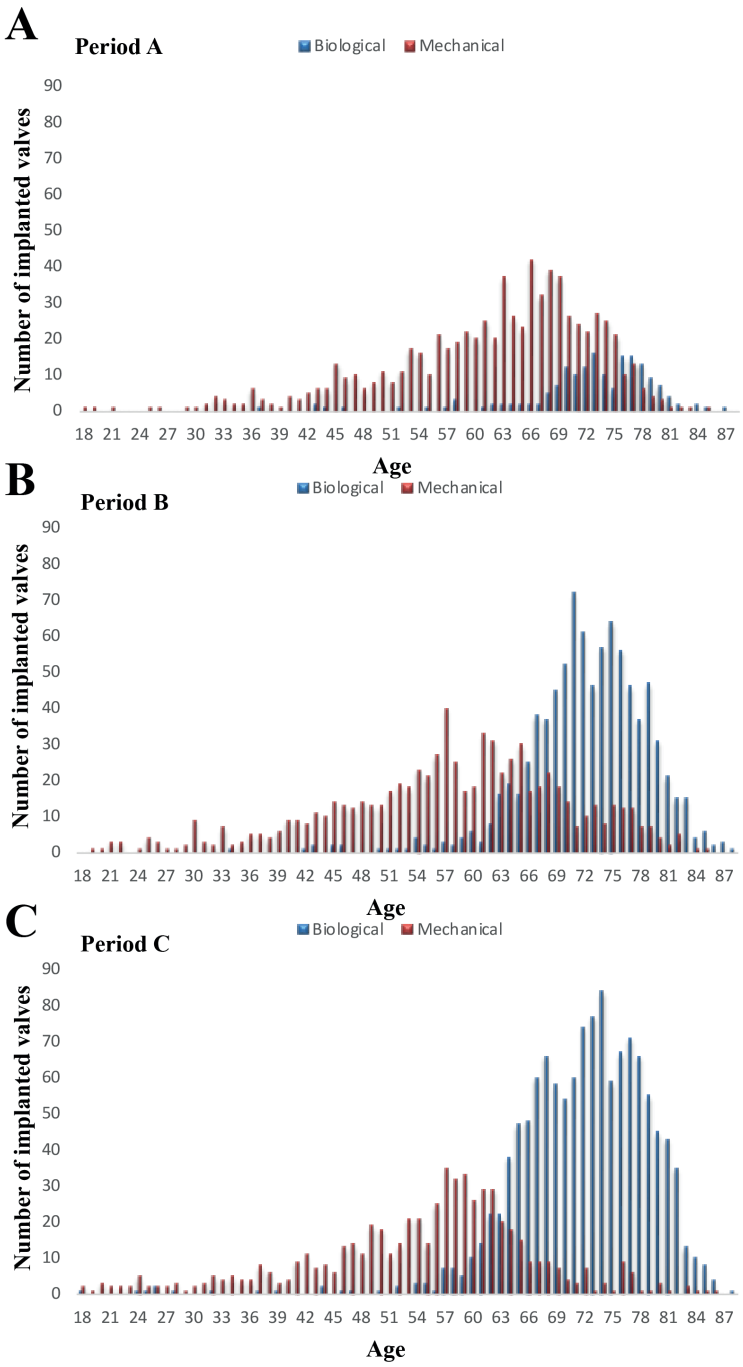



**Figure 2. Mechanical and bioprosthetic valve use across three decades.**
Absolute number of bioprosthetic and mechanical valves implanted according to patient age and the time of SAVR (Period A: 1987-1996; B: 1997-2006; C: 2007-2016). The X-axis represents the age at SAVR.

**Table 2. Procedural characteristics over three decades in the overall cohort**

| | All patients (n=4404) | Period A 1987-1996 (n=911) | Period B 1997-2006 (n=1627) | Period C 2007-2016 (n=1866) | $\chi^2$ p-value |
|---|---|---|---|---|---|
| **Urgency (n=3763)** | | | | | 0.640 |
| - **(Semi-)elective (>24h)** | 98.0 | 97.6 | 98.0 | 98.0 | |
| - **Urgent (<24h)** | 2.0 | 2.4 | 2.0 | 2.0 | |
| **Concomitant cardiac procedure** | 46.3 | 42.4 | 46.3 | 48.3 | 0.004 |
| - **CABG** | 32.5 | 32.8 | 34.0 | 31.1 | 0.226 |
| • **1VD** | 41.2 | 45.2 | 39.1 | 41.1 | 0.412 |
| • **2VD** | 29.2 | 30.4 | 30.0 | 27.7 | 0.362 |
| • **3VD** | 29.7 | 24.4 | 30.9 | 31.2 | 0.060 |
| - **MV procedure** | 10.5 | 10.0 | 10.4 | 10.9 | 0.465 |
| - **TV procedure** | 2.6 | 1.0 | 2.1 | 3.8 | <0.001 |
| - **MV and TV procedure** | 1.8 | 0.9 | 1.5 | 2.6 | 0.001 |
| - **Ascending aorta / arch replacement** | 3.0 | 0.3 | 2.6 | 4.5 | <0.001 |
| **Prosthesis type** | | | | | <0.001 |
| - **Mechanical** | 47.8 | 81.2 | 46.1 | 32.9 | |
| - **Biological** | 52.2 | 18.8 | 53.9 | 67.1 | |
| **Prosthesis size** | 23.6 ± 2.4 | 23.9 ± 2.2 | 23.7 ± 2.5 | 23.3 ± 2.3 | <0.001 |
| - **19** | 3.9 | 1.6 | 3.0 | 5.8 | <0.001 |
| - **21** | 22.6 | 19.3 | 21.8 | 24.9 | 0.001 |
| - **23** | 32.7 | 34.3 | 31.6 | 32.9 | 0.630 |
| - **25** | 24.9 | 28.1 | 24.2 | 23.9 | 0.029 |
| - **27** | 12.1 | 12.6 | 13.2 | 10.9 | 0.106 |
| - **29** | 3.5 | 3.6 | 5.8 | 1.4 | <0.001 |

Values are presented as percentages.
CABG = coronary artery bypass grafting; MV = mitral valve; TV = tricuspid valve; VD= vessel disease

## Relative survival

In the overall cohort, relative survival at 1-, 5-, 10-, and 20-years was 95.7% (CI: 95.0%-96.5%), 95.4% (CI: 94.1%-96.8%), 85.8% (CI: 83.5%-88.1%) and 60.4% (CI: 55.9%-65.2%), respectively (Figure 3). In the cohort undergoing primary isolated SAVR, the relative survival was 98.1% (CI: 97.3%-99.0%), 99.9% (CI: 98.3%-101.6%), 92.4% (CI: 89.4%-95.6%) and 73.8% (CI: 67.1%-81.1%) at 1-, 5-, 10-, and 20-years, respectively (Figure 4). In patients undergoing primary SAVR with CABG the relative survival was 94.8% (CI: 93.2%-96.4%), 94.3% (95% CI: 91.6%-97.3%), 83.4% (95% CI: 78.5%-88.4%) and 41.6% (95% CI: 33.4%-52.0%), at 1-, 5-, 10-, and 20-years respectively (Figure 5). Long-term actual and relative survival in the overall cohort is shown in Figure 6.

**Table 3. 10-year survival after primary SAVR over three decades**

| 10-year survival | All patients | Period A 1987-1996 | Period B 1997-2006 | Period C 2007-2016 | p-value |
|---|---|---|---|---|---|
| **Overall cohort** | 59.9 | 61.8 | 58.7 | 60.5 | 0.243 |
| **Isolated SAVR** | 65.5 | 66.9 | 63.7 | 67.2 | 0.312 |
| **SAVR + CABG** | 51.1 | 54.9 | 49.3 | 50.3 | 0.352 |
| **SAVR + MV procedure** | 64.4 | 65.1 | 59.3 | 70.2 | 0.253 |
| **Isolated SAVR** | | | | | |
| **≥70 year** | 48.8 | 49.7 | 47.5 | 50.2 | 0.772 |
| **60-69 years** | 70.6 | 70.6 | 67.7 | 76.3 | 0.323 |
| **50-59 years** | 81.3 | 76.4 | 80.9 | 85.6 | 0.294 |
| **Mechanical** | 74.6 | 69.3 | 75.2 | 83.6 | 0.001 |
| **Biological** | 55.7 | 56.6 | 53.6 | 58.7 | 0.450 |
| **Female** | 66.7 | 66.7 | 65.7 | 66.8 | 0.676 |
| **Male** | 64.6 | 67.0 | 62.0 | 67.8 | 0.287 |
| **High risk patients (LES ≥20)** | 40.0 | N/A | 45.5 | 30.6 | 0.727 |
| **Intermediate risk patients (LES 10-20)** | 47.3 | N/A | 42.2 | 54.2 | 0.418 |
| **Low risk patients (LES <10)** | 70.4 | N/A | 71.5 | 69.5 | 0.671 |
| **SAVR with CABG** | | | | | |
| **≥70 years** | 41.0 | 40.2 | 39.2 | 44.5 | 0.447 |
| **60-69 years** | 61.3 | 63.7 | 59.9 | 59.8 | 0.909 |
| **50-59 years** | 75.5 | 80.6 | 77.8 | 62.6 | 0.293 |
| **Mechanical** | 57.9 | 55.4 | 62.3 | 54.4 | 0.381 |
| **Biological** | 46.8 | 53.3 | 43.2 | 49.5 | 0.124 |
| **Female** | 48.0 | 51.4 | 45.6 | 49.3 | 0.700 |
| **Male** | 52.6 | 56.6 | 51.0 | 50.7 | 0.484 |
| **High risk patients (LES ≥20)** | 23.6 | N/A | 20.0 | 24.6 | 0.814 |
| **Intermediate risk patients (LES 10-20)** | 46.1 | N/A | 37.6 | 52.4 | 0.322 |
| **Low risk patients (LES <10)** | 55.2 | N/A | 58.2 | 52.2 | 0.412 |

Values are presented as percentages.
CABG = coronary artery bypass graft; LES = logistic EuroSCORE; MV = mitral valve; N/A= not available; SAVR = surgical aortic valve replacement

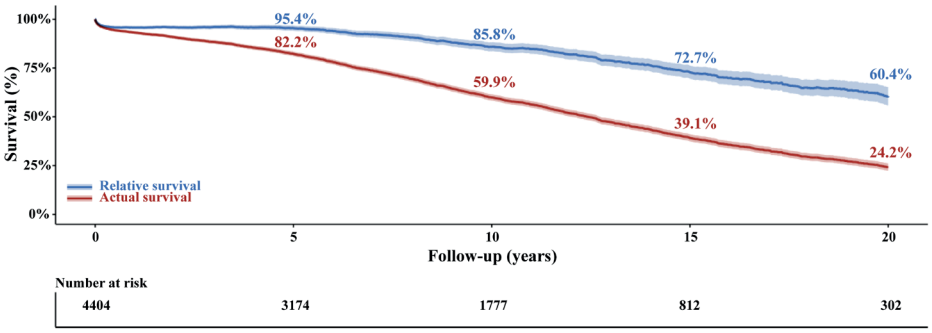



**Figure 3. Long term survival after SAVR.**
Actual survival of patients in the overall SAVR cohort (red line) and relative survival compared to the age-, gender- and year-matched Dutch population (blue line).

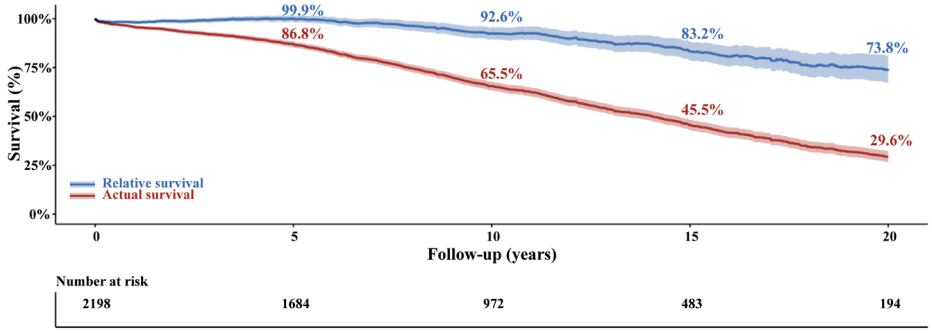



**Figure 4. Long term survival after primary isolated SAVR.**
Actual survival (red line) and relative survival compared to the age-, gender- and year-matched population (blue line).

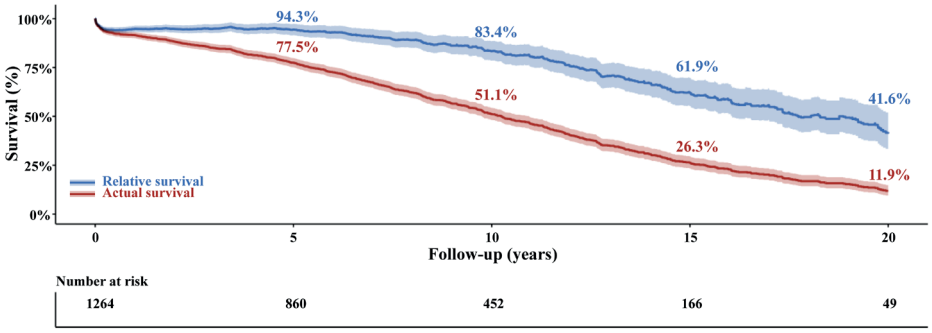



**Figure 5. Long-term actual and relative survival after primary SAVR with concomitant CABG.**
Actual survival (red line) and relative survival compared to the age-, gender- and year-matched population (blue line).

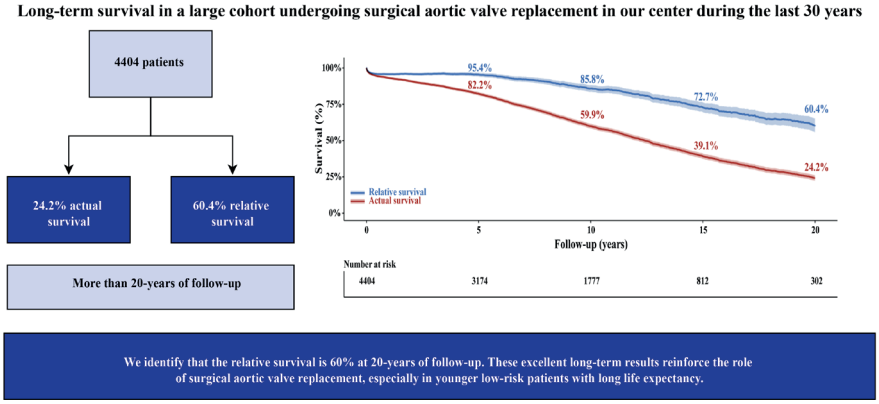



**Figure 6. Long-term actual and relative survival in the overall cohort.**
Long-term survival after SAVR. Actual survival of patients in the overall SAVR cohort (red line) and relative survival compared to the age-, gender- and year-matched Dutch population (blue line).

## DISCUSSION

In this study, while the age, frequency of comorbid conditions and complexity of patients undergoing SAVR increased over a 30-year period, the trends in 10-year survival remained stable or improved. Relative survival after SAVR was 85.8% (CI: 83.5%-88.1%) at 10 years. In patients undergoing primary isolated SAVR, the relative survival was 92.4% (CI: 89.4%-95.6%) and 73.8% (CI: 67.1%-81.1%) at 10- and 20-years, respectively. These excellent long-term results reinforce the role of SAVR in the treatment of aortic valve disease, especially in the younger low-risk patient population with long life expectancy and lower operative risk.

In our cohort, we saw a continuous increase in the number of patients undergoing SAVR. This increase is parallel to the growing number of SAVRs performed annually in Europe and in the United States over the last decades[13], and is most likely a result of a combination of factors. The ageing of the population led to an increase in the prevalence of AS in the Western countries[14,15], and improvements in imaging might have led to an increase of patients being referred for SAVR.[16] Simultaneously, expanding indications for SAVR and practice-related changes had a positive effect on the number of SAVRs performed.[5,17] Of note, this trend might be halted by the growing use of TAVR in elderly patients, which can eventually lead to a decrease in the annual number of SAVRs, a recent trend already observed in some countries.[18,19]

The increasing frequency of comorbidities in our patient population is in accordance with the previously described changes in the profile of patients undergoing cardiac surgery.[20] The prevalence of diabetes mellitus, hypercholesterolemia and hypertension have at least doubled during the 30-year observation period. Diabetes is associated with

worse outcomes in patients undergoing cardiac surgery.[21] Further, 31.1% of the patients in this study underwent concomitant CABG. Hypercholesterolemia and hypertension are well known to be associated with coronary artery disease. Coronary artery disease is present in up to 40% of the patients with AS undergoing SAVR, and in up to 50% in SAVR patients aged 70 years or more.[22,23] Patients with concomitant CABG reflect a population with more advanced heart disease, diminished life expectancy due to higher short- and long-term mortality compared to those undergoing isolated SAVR.[24] Similarly, patients requiring complex or multivalvular surgery represent a group with higher risk.[24-26] These patients should be carefully selected and directed to high-volume centers.[25]

Prosthesis choice is an important element of treatment decisions in aortic valve disease. Both mechanical and bioprosthetic valves are associated with inherent risks.[27] Mechanical valves require lifelong anticoagulation associated with bleeding events and bioprosthetic valves are prone to degeneration, necessitating a second intervention in the long term.[28] In our study, a fourfold increase in bioprosthetic valve use was observed over the last three decades, mimicking a worldwide trend.[28] The shift from mechanical to bioprosthetic valves was most prominent in patients aged between 60 and 70 years.[29] Additionally, the age profile of SAVR patients changed considerably, with an increasing number of elderly patients undergoing SAVR. These patients form the bulk of the contemporary SAVR population and received almost exclusively a bioprosthetic valve. Although the first randomized controlled trial comparing bioprosthetic and mechanical valves showed better survival in patients receiving mechanical valves[30], recent literature supports the benefit of bioprosthetic valves compared to mechanical valves in patients aged 60 and older.[28,31] While younger patients might also benefit from bioprosthetic valves, caution is warranted.[32] Valve-in-valve TAVR in prospect might be an option when considering bioprosthetic valves in younger patients.[33,34]

Despite the increasing patient age and complexity, the 30-day mortality decreased or remained stable over the 30-year observation period in the different cohorts. This may reflect advances in surgical technique and perioperative care over the last decades.[35] While long-term actual survival after SAVR is influenced by the competing risk of mortality due to other factors, relative survival provides a good estimate of the disease- and intervention-related risks, as it compares the survival of the investigated population to the survival of the matched general population.[36] Glaser et al. reported a relative survival of 97% and 88% at 5- and 10-years after SAVR, respectively[37], while Kvidal et al. described a 74.9% relative survival at 15-years in a large SAVR cohort.[23] In our study, the relative survival after isolated SAVR was similar to that of the age-, sex- and year-matched Dutch population at 5-years, was above 90% at 10 years, indicating an excellent long-term result. However, the decrease afterwards in relative survival is not negligible and emphasizes the impact of disease- and intervention-related hazards in the extended long-term.[38]

The growing use of TAVR challenges the traditional role of SAVR in the treatment of aortic valve stenosis. In the light of recent trial results, the elderly SAVR population might have overlapping indications for both TAVR and SAVR in the future.[39,40] The current 5-year data regarding intermediate-risk patients with severe symptomatic aortic stenosis, there was no difference between the incidence of the composite endpoint of mortality and disabling stroke in patients receiving TAVR and SAVR, 47.9% and 43.4%, respectively.[41] The added value even translated to the low-risk population. Patients classified as low-risk had non-inferior outcomes regarding the composite endpoint of mortality and disabling stroke at 2-years of follow-up, 5.3% and 6.7% in TAVR and SAVR, respectively.[40] Further research regarding the long-term durability of TAVR, and the use of TAVR in specific patient groups such as patients with high anatomical risk, including bicuspid morphology, dilated aortic root, heavy annular calcification, and expected future coronary access, remain warranted. Regular formal heart team discussions are recommended by the clinical guidelines.[5,6] These meetings allow for informed decisions in a multidisciplinary setting, where the preferred intervention can be discussed based on the individual patient profile, local resources and expertise, and the evidence available on procedure-related risks and long-term results.[42]

### Limitations

The results presented herein are based on data from a single center in the Netherlands. As with all retrospective studies, inherent shortcomings related to data capture are present. In addition, our study evaluated only survival as a long-term clinical outcome, as other important clinical outcomes (such as quality of life, structural valve dysfunction or valve-related thromboembolic and bleeding events) were not captured in our database. The amount of patients with newer-generation valves such as sutureless valves is very low, which might yield different outcomes. Other potential limitations include selective outcome reporting.

## CONCLUSIONS

The present study demonstrates the patient-related changes over time in patients receiving SAVR and the excellent SAVR related outcomes over the last three decades. Isolated SAVR has proven itself with excellent long-term relative survival (73.8% at 20 years in our study). The existing SAVR cohort overlaps with the expected future TAVR cohort, and therefore, our findings may serve as a benchmark for future TAVR population studies.

## REFERENCES


1. Effler DB, Favaloro R, Groves LK. Heart Valve Replacement. Clinical Experience. Ann Thorac Surg. 1965;1:4-24.
2. Lee R, Li S, Rankin JS, O'Brien SM, Gammie JS, Peterson ED, et al. Fifteen-Year Outcome Trends for Valve Surgery in North America. The Annals of Thoracic Surgery. 2011;91(3):677-84.
3. Thourani VH, Suri RM, Gunter RL, Sheng S, O'Brien SM, Ailawadi G, et al. Contemporary Real-World Outcomes of Surgical Aortic Valve Replacement in 141,905 Low-Risk, Intermediate-Risk, and High-Risk Patients. Ann Thorac Surg. 2015;99(1):55-61.
4. Cribier A, Eltchaninoff H, Bash A, Borenstein N, Tron C, Bauer F, et al. Percutaneous Transcatheter Implantation of an Aortic Valve Prosthesis for Calcific Aortic Stenosis. Circulation. 2002;106(24):3006.
5. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739-91.
6. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Fleisher LA, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017;135(25):e1159-e95.
7. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. N Engl J Med. 2019.
8. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. N Engl J Med. 2019.
9. Perme M, Pavlic K. Nonparametric Relative Survival Analysis with the R Package relsurv. J Stat Softw.2018;87(8):27.
10. Database HM. 2019 [Available from: https://www.mortality.org/.
11. Pohar M, Stare J. Relative survival analysis in R. Comput Methods Programs Biomed. 2006;81(3):272-8.
12. Pohar M, Stare J. Making relative survival analysis relatively easy. Comput Biol Med. 2007;37(12):1741-9.
13. Bonow RO, Greenland P. Population-wide trends in aortic stenosis incidence and outcomes. Circulation. 2015;131(11):969-71.
14. Maganti K, Rigolin VH, Sarano ME, Bonow RO. Valvular heart disease: diagnosis and management. Mayo Clin Proc. 2010;85(5):483-500.
15. Barreto-Filho JA, Wang Y, Dodson JA, Desai MM, Sugeng L, Geirsson A, et al. Trends in aortic valve replacement for elderly patients in the United States, 1999-2011. JAMA. 2013;310(19):2078-85.
16. Zoghbi WA. Cardiovascular imaging: a glimpse into the future. Methodist Debakey Cardiovasc J. 2014;10(3):139-45.
17. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Barwolf C, Levang OW, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. Eur Heart J. 2003;24(13):1231-43.
18. Gaede L, Blumenstein J, Kim WK, Liebetrau C, Dorr O, Nef H, et al. Trends in aortic valve replacement in Germany in 2015: transcatheter versus isolated surgical aortic valve repair. Clin Res Cardiol. 2017;106(6):411-9.
19. Kundi H, Strom JB, Valsdottir LR, Elmariah S, Popma JJ, Shen C, et al. Trends in Isolated Surgical Aortic Valve Replacement According to Hospital-Based Transcatheter Aortic Valve Replacement Volumes. JACC Cardiovasc Interv. 2018;11(21):2148-56.

20. Davierwala PM, Maganti M, Yau TM. Decreasing significance of left ventricular dysfunction and reoperative surgery in predicting coronary artery bypass grafting-associated mortality: a twelve-year study. J Thorac Cardiovasc Surg. 2003;126(5):1335-44.
21. Clough RA, Leavitt BJ, Morton JR, Plume SK, Hernandez F, Nugent W, et al. The effect of comorbid illness on mortality outcomes in cardiac surgery. Arch Surg. 2002;137(4):428-32; discussion 32-3.
22. Rapp AH, Hillis LD, Lange RA, Cigarroa JE. Prevalence of coronary artery disease in patients with aortic stenosis with and without angina pectoris. Am J Cardiol. 2001;87(10):1216-7; A7.
23. Kvidal P, Bergstrom R, Horte LG, Stahle E. Observed and relative survival after aortic valve replacement. J Am Coll Cardiol. 2000;35(3):747-56.
24. Beckmann A, Meyer R, Lewandowski J, Frie M, Markewitz A, Harringer W. German Heart Surgery Report 2017: The Annual Updated Registry of the German Society for Thoracic and Cardiovascular Surgery. Thorac Cardiovasc Surg. 2018;66(8):608-21.
25. Kilic A, Shah AS, Conte JV, Baumgartner WA, Yuh DD. Operative outcomes in mitral valve surgery: combined effect of surgeon and hospital volume in a population-based analysis. J Thorac Cardiovasc Surg. 2013;146(3):638-46.
26. Vassileva CM, Li S, Thourani VH, Suri RM, Williams ML, Lee R, et al. Outcome characteristics of multiple-valve surgery: comparison with single-valve procedures. Innovations (Phila). 2014;9(1):27-32.
27. Head SJ, Celik M, Kappetein AP. Mechanical versus bioprosthetic aortic valve replacement. Eur Heart J. 2017;38(28):2183-91.
28. Goldstone AB, Chiu P, Baiocchi M, Lingala B, Patrick WL, Fischbein MP, et al. Mechanical or Biologic Prostheses for Aortic-Valve and Mitral-Valve Replacement. N Engl J Med. 2017;377(19):1847-57.
29. Huygens SA, Etnel JRG, Hanif M, Bekkers JA, Bogers A, Rutten-van Molken M, et al. Bioprosthetic aortic valve replacement in elderly patients: Meta-analysis and microsimulation. J Thorac Cardiovasc Surg. 2019;157(6):2189-97 e14.
30. Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C, Rahimtoola SH. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. J Am Coll Cardiol. 2000;36(4):1152-8.
31. Glaser N, Jackson V, Holzmann MJ, Franco-Cereceda A, Sartipy U. Aortic valve replacement with mechanical vs. biological prostheses in patients aged 50-69 years. Eur Heart J. 2016;37(34):2658-67.
32. Hirji SA, Kolkailah AA, Ramirez-Del Val F, Lee J, McGurk S, Pelletier M, et al. Mechanical Versus Bioprosthetic Aortic Valve Replacement in Patients Aged 50 Years and Younger. Ann Thorac Surg. 2018;106(4):1113-20.
33. Reul RM, Ramchandani MK, Reardon MJ. Transcatheter Aortic Valve-in-Valve Procedure in Patients with Bioprosthetic Structural Valve Deterioration. Methodist Debakey Cardiovasc J. 2017;13(3):132-41.
34. Dvir D, Webb J, Brecker S, Bleiziffer S, Hildick-Smith D, Colombo A, et al. Transcatheter aortic valve replacement for degenerative bioprosthetic surgical valves: results from the global valve-in-valve registry. Circulation. 2012;126(19):2335-44.
35. Pennington DG. The impact of new technology on cardiothoracic surgical practice. Ann Thorac Surg. 2006;81(1):10-8.
36. Sarfati D, Blakely T, Pearce N. Measuring cancer survival in populations: relative survival vs cancer-specific survival. Int J Epidemiol. 2010;39(2):598-610.
37. Glaser N, Persson M, Jackson V, Holzmann MJ, Franco-Cereceda A, Sartipy U. Loss in Life Expectancy After Surgical Aortic Valve Replacement: SWEDEHEART Study. J Am Coll Cardiol. 2019;74(1):26-33.

38. Glaser N, Persson M, Jackson V, Holzmann M, Franco-Cereceda A, Sartipy U. Loss in life expectancy after surgical aortic valve replacement: SWEDEHEART observational study. Journal of the American College of Cardiology. 2019.
39. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. N Engl J Med. 2019;380(18):1695-705.
40. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. N Engl J Med. 2019;380(18):1706-15.
41. Makkar RR, Thourani VH, Mack MJ, Kodali SK, Kapadia S, Webb JG, et al. Five-Year Outcomes of Transcatheter or Surgical Aortic-Valve Replacement. N Engl J Med. 2020;382(9):799-809.
42. de Jaegere PPT, de Weger A, den Heijer P, Verkroost M, Baan J, de Kroon T, et al. Treatment decision for transcatheter aortic valve implantation: the role of the heart team : Position statement paper of the Dutch Working Group of Transcatheter Heart Interventions. Neth Heart J. 2020;28(5):229-39.

## SUPPLEMENTARY MATERIAL

**Table S1. Baseline and procedural characteristics over three decades in patients undergoing primary isolated SAVR**

| | All patients (n=2198) | Period A 1987-1996 (n=477) | Period B 1997-2006 (n=827) | Period C 2007-2016 (n=894) | $\chi^2$ p-value |
|---|---|---|---|---|---|
| **Age at operation (mean ± SD)** | 65.0 ± 12.0 | 63.7 ± 10.7 | 65.1 ± 12.4 | 65.5 ± 12.3 | 0.029 |
| **<40** | 3.6 | 2.9 | 3.9 | 3.8 | 0.474 |
| **40-49** | 7.6 | 8.4 | 8.1 | 6.6 | 0.188 |
| **50-59** | 15.8 | 16.8 | 15.5 | 15.7 | 0.646 |
| **60-69** | 31.4 | 39.0 | 28.4 | 30.1 | 0.004 |
| **70-79** | 35.0 | 31.0 | 36.9 | 35.3 | 0.197 |
| **≥80** | 6.6 | 1.9 | 7.3 | 8.5 | <0.001 |
| **Female** | 41.1 | 38.8 | 45.6 | 38.1 | 0.387 |
| **Indication (n=2198)** | | | | | |
| - **AS** | 68.2 | 56.8 | 67.2 | 75.3 | <0.001 |
| - **AR** | 13.5 | 13.2 | 14.6 | 12.6 | 0.606 |
| - **Combined** | 18.1 | 29.8 | 18.1 | 11.7 | <0.001 |
| **Bicuspid Aortic Valve** | 20.9 | 35.2 | 20.4 | 13.8 | <0.001 |
| **Endocarditis** | 5.4 | 4.8 | 4.5 | 6.5 | 0.120 |
| **Log_EuroSCORE (n=1239) (median (IQR))** | 4.2 (2.4-7.0) | N/A | 4.2 (2.2-7.2) | 4.2 (2.4-6.9) | 0.965 |
| **- log EuroScore ≥10 n (%)** | 12.7 | | 16.2 | 11.3 | 0.019 |
| **- log EuroScore ≥20 n (%)** | 3.0 | | 3.2 | 2.9 | 0.795 |
| **Previous cardiac operation** | 6.3 | 6.5 | 7.0 | 5.6 | 0.400 |
| **Creatinine ≥2mg/dl** | 2.3 | 2.1 | 1.9 | 2.7 | 0.400 |
| **Previous Hemodialysis** | 0.7 | 0.4 | 0.6 | 0.9 | 0.287 |
| **Atrial fibrillation** | 12.9 | 13.8 | 13.3 | 12.1 | 0.325 |
| **Diabetes mellitus** | 12.3 | 7.8 | 8.9 | 17.9 | <0.001 |
| **Cardiac decompensation** | 14.2 | 23.1 | 12.7 | 10.9 | <0.001 |
| **Hypertension** | 34.4 | 22.4 | 28.4 | 46.4 | <0.001 |
| **Hypercholesterolemia** | 15.2 | 5.0 | 12.3 | 23.3 | <0.001 |
| **Previous myocardial infarction** | 5.6 | 5.5 | 4.4 | 6.7 | 0.187 |
| **Previous PCI** | 5.7 | 1.9 | 4.2 | 9.2 | <0.001 |
| **COPD** | 11.2 | 9.0 | 11.1 | 12.5 | 0.051 |
| **History of cancer** | 6.7 | 2.1 | 7.3 | 8.7 | <0.001 |
| **Stroke** | 8.4 | 4.0 | 8.0 | 11.1 | <0.001 |
| **Arterial disease** | 3.0 | 1.0 | 2.5 | 4.5 | <0.001 |
| - **Peripheral** | 2.6 | 1.0 | 2.3 | 3.8 | 0.002 |
| - **Carotid** | 0.5 | 0 | 0.4 | 0.8 | 0.035 |
| **LVEF (n=2006)** | | | | | |
| - **Good** | 81.8 | 78.4 | 82.8 | 82.4 | 0.161 |
| - **Reduced** | 14.9 | 15.1 | 14.7 | 14.8 | 0.933 |
| - **Severely reduced** | 3.3 | 6.5 | 2.5 | 2.8 | 0.005 |

**Table S1. Baseline and procedural characteristics over three decades in patients undergoing primary isolated SAVR** (*continued*)

| | All patients (n=2198) | Period A 1987-1996 (n=477) | Period B 1997-2006 (n=827) | Period C 2007-2016 (n=894) | $\chi^2$ p-value |
|---|---|---|---|---|---|
| **Urgency (n=1942)** | | | | | 0.910 |
| - **(Semi-) Elective (24h>)** | 98.7 | 98.6 | 1.3 | 1.3 | |
| - **Urgent (<24h)** | 1.3 | 1.4 | 98.7 | 98.7 | |
| **Prosthesis type** | | | | | <0.001 |
| - **Mechanical** | 48.8 | 82.0 | 46.9 | 32.9 | |
| - **Bioprosthetic** | 51.2 | 18.0 | 53.1 | 67.1 | |
| **Prosthesis size** | 23.6 ± 2.4 | 24.0 ± 2.3 | 24.0 ± 2.5 | 23.1 ± 2.3 | <0.001 |
| - **19** | 3.9 | 1.5 | 2.3 | 6.7 | <0.001 |
| - **21** | 22.5 | 17.9 | 20.7 | 26.7 | <0.001 |
| - **23** | 32.0 | 32.8 | 30.7 | 32.7 | 0.884 |
| - **25** | 24.9 | 30.5 | 24.8 | 22.1 | 0.001 |
| - **27** | 11.9 | 12.2 | 13.9 | 10.0 | 0.106 |
| - **29** | 4.4 | 5.0 | 7.0 | 1.6 | <0.001 |

Values are presented as n (%) or as mean ± SD or median (interquartile range) if otherwise stated.
AR = aortic regurgitation; AS = aortic stenosis; CABG = coronary artery bypass graft; COPD= chronic obstructive pulmonary disease; LVEF = left ventricular ejection function; IQR = interquartile range; MV = mitral valve; N/A = not available; SAVR = surgical aortic valve replacement; TV = tricuspid valve; VD= vessel disease

**Table S2. Baseline and procedural characteristics over three decades in in patients undergoing isolated SAVR + CABG**

| | All patients (n=1264) | Period A 1987-1996 (n=275) | Period B 1997-2006 (n=490) | Period C 2007-2016 (n=499) | $\chi^2$ p-value |
|---|---|---|---|---|---|
| **Age at operation (mean ± SD)** | 70.1 ± 8.3 | 68.5 ± 8.0 | 70.0 ± 8.5 | 71.0 ± 8.2 | <0.001 |
| **40-49** | 2.5 | 1.8 | 3.3 | 2.2 | 0.938 |
| **50-59** | 9.2 | 13.1 | 9.4 | 6.8 | 0.004 |
| **60-69** | 29.9 | 35.3 | 26.1 | 30.7 | 0.376 |
| **70-79** | 48.1 | 44.4 | 52.7 | 45.7 | 0.897 |
| **≥80** | 10.3 | 5.5 | 8.6 | 14.6 | <0.001 |
| **Female** | 30.1 | 33.5 | 32.0 | 26.3 | 0.023 |
| **Indication (n=1264)** | | | | | |
| - **AS** | 80.2 | (70.2 | 80.8 | 85.2 | <0.001 |
| - **AR** | 8.8 | (9.1 | 9.2 | 8.2 | 0.632 |
| - **Combined** | 10.9 | (20.4 | 10.0 | 6.6 | <0.001 |
| **Bicuspid Aortic Valve** | 10.5 | 19.3 | 9.0 | 7.2 | <0.001 |
| **Endocarditis** | 1.5 | 2.2 | 1.6 | 1.0 | 0.186 |
| **Log_EuroSCORE (n=697) (median (IQR))** | 5.3 (3.3-8.7) | N/A | 5.5 (3.7-8.4) | 5.3 (3.2-8.9) | 0.977 |
| **- log EuroScore ≥10 n (%)** | 19.1 | | 17.7 | 19.6 | 0.552 |
| **- log EuroScore ≥20 n (%)** | 5.6 | | 5.1 | 5.8 | 0.694 |
| **Previous cardiac operation** | 5.5 | 8.7 | 6.3 | 2.8 | <0.001 |
| **Creatinine ≥2mg/dl** | 2.8 | 2.5 | 2.7 | 3.0 | 0.686 |
| **Previous Hemodialysis** | 0.9 | 1.1 | 0.6 | 1.0 | 0.984 |
| **Atrial fibrillation** | 12.5 | 13.1 | 12.0 | 12.6 | 0.911 |
| **Diabetes mellitus** | 21.2 | 8.0 | 20.0 | 29.7 | <0.001 |
| **Cardiac decompensation** | 15.6 | 18.5 | 16.3 | 13.2 | 0.043 |
| **Hypertension** | 41.2 | 22.5 | 31.4 | 61.1 | <0.001 |
| **Hypercholesterolemia** | 21.8 | 6.9 | 17.8 | 34.1 | <0.001 |
| **Previous myocardial infarction** | 24.4 | 20.0 | 24.7 | 26.7 | 0.046 |
| **Previous PCI** | 10.2 | 5.8 | 7.3 | 15.4 | <0.001 |
| **COPD** | 9.9 | 7.3 | 8.6 | 12.6 | 0.010 |
| **History of cancer** | 7.5 | 3.3 | 6.1 | 11.2 | <0.001 |
| **Stroke** | 9.3 | 4.7 | 8.2 | 12.8 | <0.001 |
| **Arterial disease** | 8.4 | 5.8 | 6.5 | 11.6 | 0.002 |
| - **Peripheral** | 7.2 | 5.5 | 5.7 | 9.6 | 0.016 |
| - **Carotid** | 1.5 | 0.4 | 1.4 | 2.2 | 0.044 |
| **LVEF (n=1185)** | | | | | |
| - **Good** | 75.7 | 75.8 | 76.8 | 74.5 | 0.589 |
| - **Reduced** | 20.5 | 17.8 | 19.7 | 22.6 | 0.114 |
| - **Severely reduced** | 3.8 | 6.4 | 3.5 | 2.9 | 0.033 |
| **Urgency (n=1104)** | | | | | 0.536 |
| - **(Semi-) Elective (24h>)** | 98.6 | 99.4 | 98.5 | 98.5 | |
| - **Urgent (<24h)** | 1.4 | 0.6 | 1.5 | 1.5 | |

**Table S2. Baseline and procedural characteristics over three decades in in patients undergoing isolated SAVR + CABG** (*continued*)

| | All patients (n=1264) | Period A 1987-1996 (n=275) | Period B 1997-2006 (n=490) | Period C 2007-2016 (n=499) | $\chi^2$ p-value |
|---|---|---|---|---|---|
| **Prosthesis type** | | | | | <0.001 |
| - **Mechanical** | 36.1 | 74.9 | 32.2 | 18.4 | |
| - **Biological** | 63.9 | 25.1 | 67.8 | 81.6 | |
| **Prosthesis size** | 23.5 ± 2.2 | 23.6 ± 2.1 | 23.7 ± 2.3 | 23.2 ± 2.1 | 0.003 |
| - **19** | 3.8 | 2.2 | 2.4 | 6.0 | 0.003 |
| - **21** | 21.6 | 20.0 | 21.8 | 22.2 | 0.495 |
| - **23** | 35.5 | 38.9 | 34.5 | 34.7 | 0.296 |
| - **25** | 26.3 | 24.7 | 24.9 | 28.7 | 0.181 |
| - **27** | 10.9 | 12.7 | 13.5 | 7.4 | 0.008 |
| - **29** | 1.5 | 1.5 | 2.2 | 0.8 | 0.307 |

Abbreviations as in Table S1.

**Table S3. 30-day mortality after primary SAVR over three decades**

| 30- day mortality | All patients | Period A 1987-1996 | Period B 1997-2006 | Period C 2007-2016 | p-value |
|---|---|---|---|---|---|
| **Overall cohort** | 2.7 (4157) | 2.7 (837) | 3.7 (1555) | 1.8 (1765) | 0.003 |
| **Isolated SAVR** | 1.5 (2198) | 1.9 (477) | 1.8 (827) | 0.9 (894) | 0.190 |
| **SAVR + CABG** | 3.9 (1264) | 4.1 (275) | 4.7 (490) | 3.0 (499) | 0.384 |
| **SAVR + MV procedure** | 4.8 (235) | 3.8 (57) | 7.7 (92) | 2.3 (86) | 0.220 |
| **Isolated SAVR** | | | | | |
| **≥70 years** | 2.5 (914) | 3.8 (157) | 3.0 (365) | 1.5 (392) | 0.224 |
| **60-69 years** | 0.1 (690) | 0.5 (186) | 0 (235) | 0 (269) | 0.258 |
| **50-59 years** | 1.7 (348) | 2.5 (80) | 1.6 (128) | 1.4 (140) | 0.811 |
| **Mechanical** | 1.7 (1073) | 2.1 (391) | 2.1 (388) | 0.7 (294) | 0.293 |
| **Biological** | 1.3 (1125) | 1.2 (86) | 1.6 (439) | 1.0 (600) | 0.700 |
| **Female** | 1.3 (903) | 2.2 (185) | 1.9 (377) | 0.3 (341) | 0.104 |
| **Male** | 1.5 (1295) | 1.7 (292) | 1.8 (450) | 1.3 (553) | 0.776 |
| **High risk patients (LES ≥20)** | 8.3 (37) | N/A | 9.1 (11) | 7.9 (26) | 0.936 |
| **Intermediate risk patients (LES 10-20)** | 2.5 (120) | N/A | 2.2 (45) | 2.7 (75) | 0.873 |
| **Low risk patients (LES <10)** | 0.7 (1082) | N/A | 1.1 (289) | 0.5 (793) | 0.302 |
| **SAVR with CABG** | | | | | |
| **≥70 years** | 4.8 (738) | 5.2 (137) | 5.3 (300) | 4.0 (301) | 0.719 |
| **60-69 years** | 2.7 (378) | 3.2 (97) | 3.9 (128) | 1.3 (153) | 0.380 |
| **50-59 years** | 0.9 (116) | 0 (36) | 2.2 (46) | 0 (34) | 0.467 |
| **Mechanical** | 4.6 (456) | 4.9 (206) | 4.5 (158) | 4.3 (92) | 0.975 |
| **Biological** | 3.5 (808) | 1.4 (69) | 4.8 (332) | 2.7 (407) | 0.184 |
| **Female** | 4.8 (380) | 4.4 (92) | 5.1 (157) | 4.6 (131) | 0.957 |
| **Male** | 3.5 (884) | 3.9 (183) | 4.5 (333) | 2.5 (368) | 0.325 |
| **High risk patients (LES ≥20)** | 12.8 (39) | N/A | 10.0 (10) | 13.8 (29) | 0.742 |
| **Intermediate risk patients (LES 10-20)** | 5.4 (94) | N/A | 4.0 (25) | 5.9 (69) | 0.725 |
| **Low risk patients (LES <10)** | 2.1 (564) | N/A | 3.1 (163) | 1.8 (401) | 0.323 |

Values are given in percentages with (number of patients).
CABG = coronary artery bypass graft; LES = logistic EuroSCORE; MV = mitral valve; N/A = not available; SAVR = surgical aortic valve replacement

**Table S4. 1-year survival after primary SAVR over three decades**

| 1-year survival | All patients | Period A 1987-1996 | Period B 1997-2006 | Period C 2007-2016 | p-value |
|---|---|---|---|---|---|
| **Overall cohort** | 93.5 | 94.4 | 92.0 | 94.4 | 0.012 |
| **Isolated SAVR** | 95.7 | 95.7 | 94.7 | 96.6 | 0.154 |
| **SAVR + CABG** | 91.5 | 91.7 | 90.8 | 92.1 | 0.727 |
| **SAVR + MV procedure** | 89.9 | 94.3 | 83.2 | 94.1 | 0.026 |
| **Isolated SAVR** | | | | | |
| **≥70 years** | 93.5 | 92.3 | 92.0 | 95.4 | 0.133 |
| **60-69 years** | 98.2 | 98.9 | 97.4 | 98.5 | 0.484 |
| **50-59 years** | 95.9 | 94.8 | 96.1 | 96.4 | 0.831 |
| **Mechanical** | 95.9 | 95.3 | 95.6 | 97.3 | 0.376 |
| **Biological** | 95.5 | 97.6 | 94.0 | 96.3 | 0.131 |
| **Female** | 95.9 | 94.5 | 94.6 | 98.2 | 0.027 |
| **Male** | 95.6 | 96.5 | 94.8 | 95.7 | 0.574 |
| **High risk patients (LES ≥20)** | 89.0 | N/A | 90.9 | 88.1 | 0.797 |
| **Intermediate risk patients (LES 10-20)** | 94.2 | N/A | 93.3 | 94.7 | 0.780 |
| **Low risk patients (LES <10)** | 97.3 | N/A | 97.9 | 97.1 | 0.491 |
| **SAVR with CABG** | | | | | |
| **≥70 years** | 89.4 | 89.3 | 88.3 | 90.6 | 0.639 |
| **60-69 years** | 94.1 | 93.6 | 93.7 | 94.7 | 0.913 |
| **50-59 years** | 96.6 | 97.2 | 97.8 | 94.1 | 0.647 |
| **Mechanical** | 91.3 | 90.5 | 93.0 | 90.2 | 0.659 |
| **Biological** | 91.6 | 95.6 | 89.7 | 92.6 | 0.185 |
| **Female** | 91.7 | 92.1 | 93.6 | 89.2 | 0.432 |
| **Male** | 91.5 | 91.6 | 89.5 | 93.2 | 0.215 |
| **High risk patients (LES ≥20)** | 76.9 | N/A | 90.0 | 72.4 | 0.282 |
| **Intermediate risk patients (LES 10-20)** | 89.2 | N/A | 91.8 | 88.3 | 0.628 |
| **Low risk patients (LES <10)** | 94.1 | N/A | 93.8 | 94.2 | 0.841 |

Abbreviations as in Table S3.

**Table S5. 5-year survival after primary SAVR over three decades**

| 5-year survival | All patients | Period A 1987-1996 | Period B 1997-2006 | Period C 2007-2016 | p-value |
|---|---|---|---|---|---|
| **Overall cohort** | 82.4 | 84.5 | 80.9 | 82.9 | 0.059 |
| **Isolated SAVR** | 86.8 | 86.9 | 85.8 | 87.8 | 0.454 |
| **SAVR + CABG** | 77.5 | 79.7 | 75.3 | 78.4 | 0.301 |
| **SAVR + MV procedure** | 79.3 | 82.8 | 73.0 | 84.6 | 0.143 |
| **Isolated SAVR** | | | | | |
| **≥70 years** | 81.2 | 79.9 | 80.3 | 82.6 | 0.624 |
| **60-69 years** | 89.6 | 91.4 | 87.8 | 89.8 | 0.471 |
| **50-59 years** | 91.4 | 86.9 | 91.3 | 94.0 | 0.210 |
| **Mechanical** | 89.7 | 87.2 | 89.2 | 93.9 | 0.019 |
| **Biological** | 84.0 | 85.6 | 82.9 | 84.7 | 0.618 |
| **Female** | 88.8 | 86.0 | 87.3 | 92.1 | 0.049 |
| **Male** | 85.5 | 87.4 | 84.6 | 85.1 | 0.546 |
| **High risk patients (LES ≥20)** | 75.6 | N/A | 81.8 | 71.5 | 0.559 |
| **Intermediate risk patients (LES 10-20)** | 78.7 | N/A | 80.0 | 78.0 | 0.766 |
| **Low risk patients (LES <10)** | 89.1 | N/A | 89.0 | 89.2 | 0.928 |
| **SAVR with CABG** | | | | | |
| **≥70 years** | 71.9 | 72.4 | 69.2 | 74.4 | 0.343 |
| **60-69 years** | 84.1 | 84.1 | 84.1 | 84.1 | >0.999 |
| **50-59 years** | 90.3 | 94.4 | 88.9 | 87.4 | 0.596 |
| **Mechanical** | 81.2 | 80.2 | 83.2 | 79.7 | 0.716 |
| **Biological** | 75.3 | 78.3 | 71.5 | 78.1 | 0.097 |
| **Female** | 80.0 | 81.3 | 80.7 | 78.2 | 0.813 |
| **Male** | 76.4 | 79.0 | 72.7 | 78.5 | 0.120 |
| **High risk patients (LES ≥20)** | 50.4 | N/A | 40.0 | 54.7 | 0.694 |
| **Intermediate risk patients (LES 10-20)** | 73.1 | N/A | 66.8 | 75.3 | 0.431 |
| **Low risk patients (LES <10)** | 81.0 | N/A | 81.3 | 80.8 | 0.947 |

Abbreviations as in Table S3.

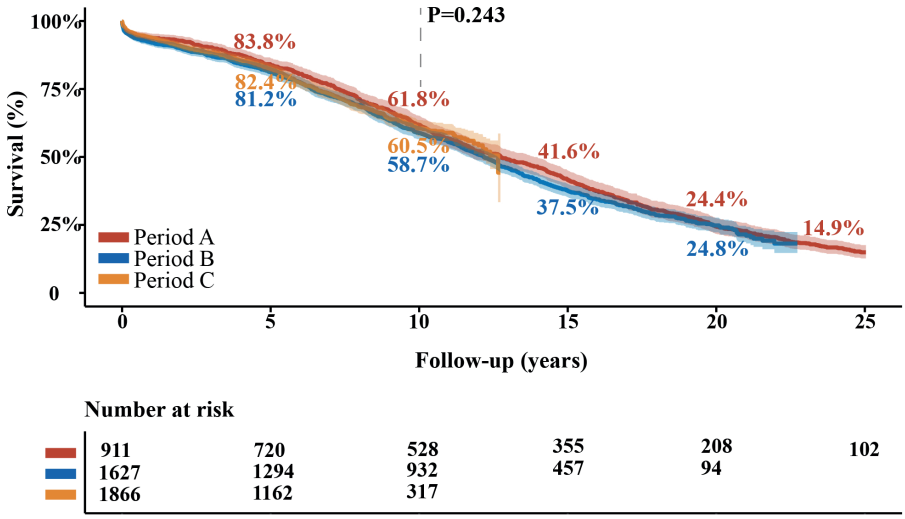



**Figure S1. Long-term survival after SAVR in the overall cohort according to period operated.**
Actual survival of patients in the overall SAVR cohort. Patients operated between 1987-1996 (period A) are shown with the red line; patients operated between 1997 and 2006 (period B) are shown with the blue line; and patients operated between 2007 and 2017 (period C) are shown with the orange line. Comparison within periods is done for 10-years of follow-up and shown as p-value.

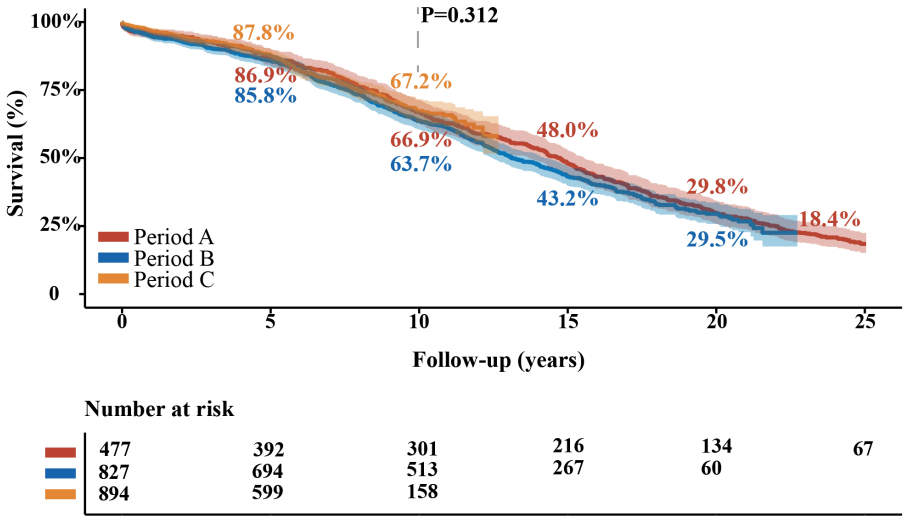



**Figure S2. Long-term survival after primary isolated SAVR according to period operated.**
Actual survival of patients with primary isolated SAVR. Patients operated between 1987-1996 (period A) are shown with the red line; patients operated between 1997 and 2006 (period B) are shown with the blue line; and patients operated between 2007 and 2017 (period C) are shown with the orange line. Comparison within periods is done for 10-years of follow-up and shown as p-value.

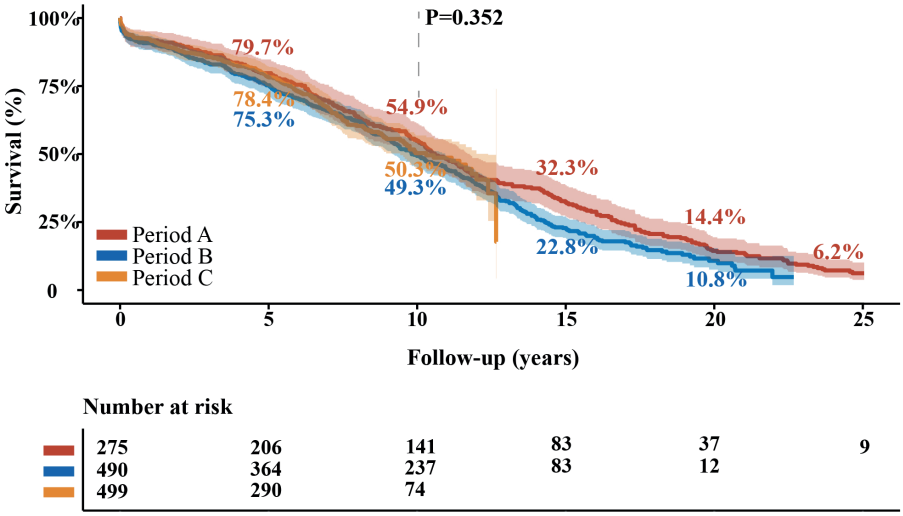



**Figure S3. Long-term actual after primary SAVR with concomitant CABG according to period operated**.

Actual survival of patients with primary SAVR and concomitant CABG. Patients operated between 1987-1996 (period A) are shown with the red line; patients operated between 1997 and 2006 (period B) are shown with the blue line; and patients operated between 2007 and 2017 (period C) are shown with the orange line. Comparison within periods is done for 10-years of follow-up and shown as p-value.

# 3 Technique of surgical aortic valve implantation using single interrupted annular sutures

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## ABSTRACT

The introduction of the first surgical prosthetic heart valves in the early 1960's made effective treatment of aortic valve disease possible. The goal of surgical aortic valve replacement (SAVR) is to replace the diseased aortic valve with a properly functioning, large enough prosthesis, while avoiding intraoperative complications such as conduction disturbances, coronary artery occlusion or paravalvular leaks. Although most commonly, non-everting pledgeted mattress sutures are used to implant the prosthesis during SAVR, the use of interrupted single sutures without pledgets can be a useful alternative especially in patients with a small tissue annulus, since it theoretically maximizes the orifice available for flow. This tutorial discusses the surgical technique of SAVR using interrupted single annular sutures.

## INTRODUCTION

The introduction of the first surgical prosthetic heart valves (SHVs) to the daily practice in the early 1960's made effective treatment of aortic valve disease possible.[1] Although transcatheter aortic valve replacement (TAVR) has recently challenged the ultimate role of surgical aortic valve replacement (SAVR)[2,3], SAVR remains the treatment of choice for many patients with severe aortic valve stenosis or regurgitation**.**

During SAVR, the diseased aortic valve is completely excised and replaced by a SHV, which is fixed to the patient tissue annulus with sutures. The goal of SAVR is to replace the diseased valve with a properly functioning, large enough prosthesis, while avoiding intraoperative complications such as conduction disturbances, coronary artery occlusion or paravalvular leaks. Besides other factors, suturing technique can have an important effect on outcomes.[4] During SAVR, both everting and non-everting mattress sutures with or without pledgets, figure-of-eight, continuous or interrupted single sutures can be used.

Although most commonly non-everting mattress sutures with pledgets are used, SAVR with interrupted single sutures can be performed safely and it can be a useful alternative especially for patients with a small tissue annulus, as it theoretically maximizes the orifice available for flow in the left ventricular outflow tract.[4,5] Additionally, avoiding the use of pledgets can make eventual later reoperations easier. This tutorial discusses the surgical technique of aortic valve replacement using interrupted single sutures.

## SURGICAL TECHNIQUE

### 1. Exposure and excision of the aortic valve and annular debridement

After cardioplegia is administered and complete diastolic arrest is achieved, left vent suction is resumed and a transverse aortotomy is performed approximately 1 cm above the sinotubular junction. In case of a transverse aortotomy, ½ - ⅔ of the total circumference of the aorta is incised to expose the aortic valve. Stay sutures are placed at the top of the commissures to facilitate exposure.

After adequate exposure is achieved, the valve is excised. Valve excision starts at the right coronary (RC) – noncoronary (NC) commissure, to remove the RC cusp first. Valve excision is typically performed with scissors, applying counter-traction on the corresponding leaflet with heavy forceps. Alternatively, scalpel can be used. It is important to avoid excessive manipulation of the cusps as it can cause particles to fracture and embolize to the left ventricle or the coronary ostia. During valve excision or annular debridement, wall suction can be used to remove small mobile particles and to protect the coronary ostia.

After the bulk of the cusps are excised, annular debridement is performed to remove residual calcium deposits from the aortic annulus. These can be removed by twisting with heavy forceps, or with a rongeur or a scalpel. The surgeon's finger can be used to confirm complete annular debridement. If calcium deeply penetrates in the annulus, annular reconstruction might be necessitated. When valve excision is completed, the left vent is stopped, and the LV cavity is irrigated with physiological saline to remove any debris or calcium particles from the operative field.

## 2. Implanting the prosthesis, interrupted single suture technique

After annular debridement, the annulus is sized to select the SHV that fits the patient. Besides sizing with the valve-related tubular sizer, replica sizing is recommended to verify the final position and fit of the SHV. If the predicted effective orifice area (EOA) of the largest fitting SHV is not satisfactory to fulfill the patient's circulatory requirements, annular enlargement should be considered.[6,7]

Typically, 2/0 non-absorbable braided sutures (e.g. Ethibond, Ethicon Inc., Bridgewater, NJ, US) are used to implant the prosthesis. With the interrupted single suture technique, sutures are often placed in the sewing ring of the SHV directly after passing them through the aortic annulus. This method can speed up the implantation, avoids the need of a suture organizer and facilities exposure of the aortic root when suturing.

Suturing starts at the LC cusp (LCC) sector, starting at the LC-RC commissure and working towards the LC-NC commissure (counter-clockwise). In the LCC sector, sutures are passed through the *sewing ring first* (from the aortic to the ventricular side, forehand) and the annulus second (from the ventricular to the aortic side, starting in backhand at the commissure and finishing in forehand from the LCC nadir). When suturing, attention should be paid for the correct distance (approximately 2-3 mm) and sequence of the sutures, and that sutures are not crossed. The assistant should apply a gentle tension on both ends of the sutures to facilitate exposure.

Suture placement is continued at the RC cusp (RCC) sector, starting at the LC-RC commissure, working towards the RC-NC commissure (clockwise). In the RCC sector, sutures are passed through the *annulus first* (from the aortic to the ventricular side, forehand) and the sewing ring second (from the ventricular to the aortic side, forehand).

Finally, suturing is completed in the NC cusp (NCC) sector. Suturing starts at the RC-NC commissure, working towards the LC-NC commissure. At the NCC sector, sutures are passed through the *sewing ring first* (from the aortic to the ventricular side, forehand) and the annulus second (from the ventricular to the aortic side, forehand).

After finishing each sector, a mosquito clamp is placed on the sutures, and the needles are removed. When all sectors are finished, the SHV is parachuted down into the aortic annulus. Before tying the annular sutures, the proper suture order and the position of the SHV should be verified. The SHV holder is removed taking care to completely remove

all holding sutures. Annular sutures are tied with 5 square knots and cut, taking care not to touch or damage the prosthetic leaflets. Commissural stay sutures are removed and the final position of the SHV, absence of annular defects and patency of the coronary ostia is verified. If correct positioning of the SHV is confirmed, rewarming is started.

## REFERENCES


1. Herr RH, Starr A, Pierie WR, Wood JA, Bigelow JC. Aortic valve replacement. A review of six years' experience with the ball-valve prosthesis. Ann Thorac Surg. 1968;6(3):199-218.
2. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. N Engl J Med. 2019;380(18):1706-15.
3. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. N Engl J Med. 2019;380(18):1695-705.
4. Cameron D. Little things matter. The Journal of Thoracic and Cardiovascular Surgery. 2015;149(3):918-9.
5. Tasca G, Vismara R, Fiore GB, Romagnoni C, Redaelli A, Antona C, et al. Does the type of suture technique affect the fluid-dynamic performance of bioprostheses implanted in small aortic roots? Results from an in vitro study. J Thorac Cardiovasc Surg. 2015;149(3):912-8.
6. Grubb KJ. Aortic Root Enlargement During Aortic Valve Replacement: Nicks and Manouguian Techniques. Operative Techniques in Thoracic and Cardiovascular Surgery. 2015;20(3):206-18.
7. Roeser ME. The Konno-Rastan Procedure for Anterior Aortic Annular Enlargement. Operative Techniques in Thoracic and Cardiovascular Surgery. 2015;20(3):219-33.

# 4 Mechanical versus Bioprosthetic Aortic Valve Replacement

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## ABSTRACT

Mechanical valves used for aortic valve replacement (AVR) continue to be associated with bleeding risks because of anticoagulation therapy, while bioprosthetic valves are at risk of structural valve deterioration requiring reoperation. This risk/benefit ratio of mechanical and bioprosthetic valves has led American and European guidelines on valvular heart disease to be consistent in recommending the use of mechanical prostheses in patients younger than 60 years of age. Despite these recommendations, the use of bioprosthetic valves has significantly increased over the last decades in all age groups. A systematic review of manuscripts applying propensity-matching or multivariable analysis to compare the usage of mechanical versus bioprosthetic valves found either similar outcomes between the two types of valves or favourable outcomes with mechanical prostheses, particularly in younger patients. The risk/benefit ratio and choice of valves will be impacted by tevelopments in valve designs, anticoagulation therapy, reducing the required International Normalized Ratio, and transcatheter and minimally invasive procedures. However, there is currently no evidence to support lowering the age threshold for implanting a bioprosthesis. Physicians in the Heart Team and patients should be cautious in pursuing more bioprosthetic valve use until its benefit is clearly proven in middle-aged patients.

## INTRODUCTION

Aortic valve replacement (AVR) has been performed since the 1950s.[1] Since then, the surgical procedure has been optimized to reduce the risk of procedure-related complications. In addition, technical advances in the design of valves have significantly improved long-term prognosis. After the initial use of mechanical ball-caged valves, numerous monoleaflet and bileaflet valves have been introduced and evaluated.[2] Moreover, bioprosthetic valves came on the market in the 1960s as an alternative to mechanical valves.



Besides the overwhelming number of AVRs that are performed each year[3], surgical techniques in which there is no need to implant a prosthetic valve have also been developed. In younger patients, the Ross operation is an alternative to mechanical valve replacement.[4, 5] In selected patients with aortic valve regurgitation, isolated aortic valve repair or in combination with replacement of a dilated aortic root maintains the native aortic valve.[6-8] However, these highly specialized operations with specific indications are often only performed in exclusive centers. In Germany through 2015 there were 21,120 aortic valve procedures, which included only 92 Ross procedures, 124 isolated aortic valve repairs, and 603 David or Yacoub valve-sparing aortic root procedures.[9]

The main question for patients that require AVR remains whether a mechanical or bioprosthetic valve should be implanted.[10] This review provides an overview of (i) the risks and benefits of mechanical and bioprosthetic valves, (ii) data on the use of mechanical and bioprosthetic valves, (iii) results of studies comparing mechanical versus bioprosthetic valves, (iv) new developments in mechanical and bioprosthetic valves, and (v) alternatives to conventional surgical mechanical or bioprosthetic valve use.

## RISKS AND BENEFITS

Because of thrombogenicity of materials used in mechanical valves, high shear stress around the hinge points, and backflow jets that damage blood and activate clotting-pathways, patients require lifelong anticoagulation therapy to avoid blood clot formation. Bioprosthetic valves are generally made of either bovine pericardium or porcine aortic valves, but may also be produced from equine or porcine pericardium. The advantage of these bioprosthetic valves is that they do not require anticoagulation. On the other hand, the use of tissue does introduce the possibility for 'wear and tear' and degeneration of the valve, which is virtually non-existent in mechanical valves. As a result of these features, certain risks are related to the use of mechanical and bioprosthetic valves.

The primary risks of mechanical valves are related to anticoagulation therapy, and this is often reported by physicians as well as patients to be the reason to refrain from

choosing a mechanical prosthesis. Patients not taking anticoagulation have a high risk of developing valve thrombosis (Figure 1A), and even with the use of anticoagulation this risk is apparent when the International Normalized Ratio (INR) is outside the range of the targeted 2.0-3.0 for valves in the aortic position. On the other hand, higher than normal INR ranges introduce the risk of spontaneous bleeding (e.g. gastrointestinal bleeding) or trauma-related bleedings (e.g. subdural hematoma), which cause considerable mortality and morbidity.[11] Even in dedicated patients aiming at INR ratios in perfect range, severe fluctuations are observed that increase the risk of bleeding or thromboembolic events and even survival.[12, 13] The major benefit of mechanical valves, however, is that structural valve deterioration (SVD) is rare. There are cases reported of leaflet escape [14], but since Björk-Shiley valves in the 1980s were associated with strut fractures and were taken of the market, these are extremely rare. There are causes for reoperation beyond SVD, e.g. non-structural valve deterioration like pannus growth, endocarditis, and valve thrombosis, but the rate of repeat aortic valve procedures is low.[15]

The primary risk related to bioprosthetic valves is that of reoperation due to limited durability of bioprosthetic valves as a result of SVD (Figure 1B). The average lifespan of a bioprosthetic valve is estimated at 15 years in elderly patients, but this risk increases significantly in younger patients in whom SVD is accelerated due to a more pronounced immunologic response of the body to the valve and enhanced calcification of the valve.[16-18] In addition, older patients generally have shorter anticipated survival during which they are at risk for requiring replacement of a deteriorated bioprosthetic valve. Most patients that require reoperation have this need as the result of SVD, as risks of non-structural valve deterioration are considered to be equally low to that of mechanical valves. Particularly important is the risk of prosthetic valve endocarditis (Figure 1C); a devastating diagnosis that often requires the need for reoperation. Rates of major bleeding, stroke and valve thrombosis are considered to be low with bioprosthetic valves, although recent reports have questioned previous rates of thrombosis by showing that multislice computed tomography (MSCT) during follow-up identified 7% of patients after AVR to have reduced leaflet motion as the result of thrombosis.[19]

## CLINICAL GUIDELINES

The risk/benefit ratio of mechanical and bioprosthetic valves has led American and European guidelines on valvular heart disease to be consistent in recommending the use of mechanical aortic valve prostheses in patients younger than 60 years of age (Figure 2).[20, 21] Recommendations for using a bioprosthetic valve are above the age of 65 in European guidelines and above the age of 70 in American guidelines. The span of 5-10 years in between represents an area of uncertainty in which both mechanical

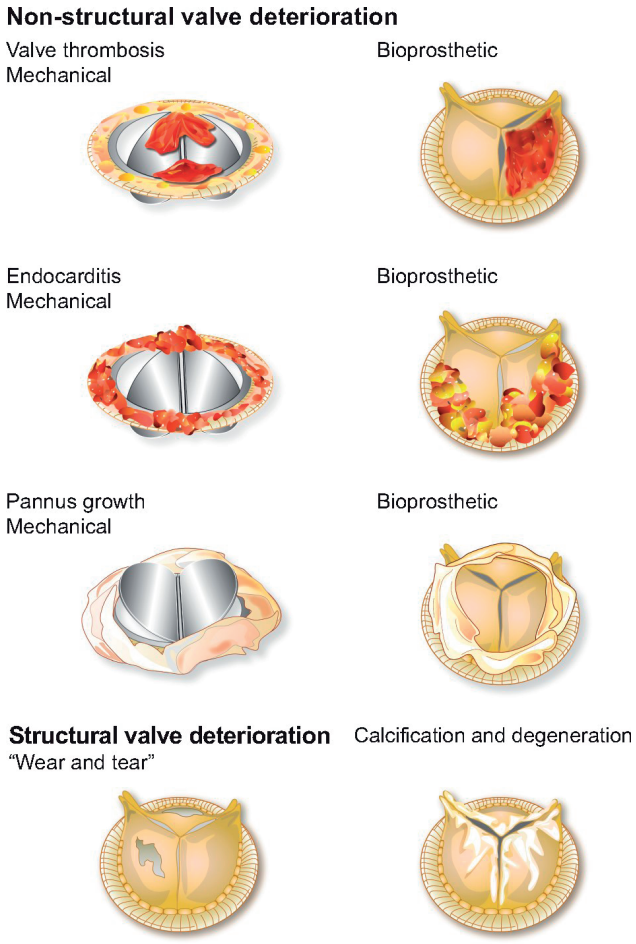


**Figure 1. Examples of structural and non-structural valve deterioration.**

or bioprosthetic valves can be used, depending on the surgeons' and patients' preference as well as certain patient characteristics. A class of recommendation and level of evidence IIa B and IIa C support these recommendations in, respectively, American and European guidelines.

The ESC/EACTS guidelines list the following reasons for choosing a specific valve: (i) life expectancy; (ii) the estimated risk of a potential reoperation in the future; (iii) bleeding risk, which may be higher because of specific comorbidities, compliance concerns, or geographic, lifestyle and occupational conditions; (iv) comorbidities, such as atrial fibrillation (AF), peripheral vascular disease, a hypercoagulable state, or other conditions that require use of oral anticoagulation; (v) the risk of structural valve deterioration that may be accelerated in patients with hyperparathyroidism or renal failure; (vi) the wish of a patient to become pregnant; and (vii) patient preferences.[20] American guidelines add

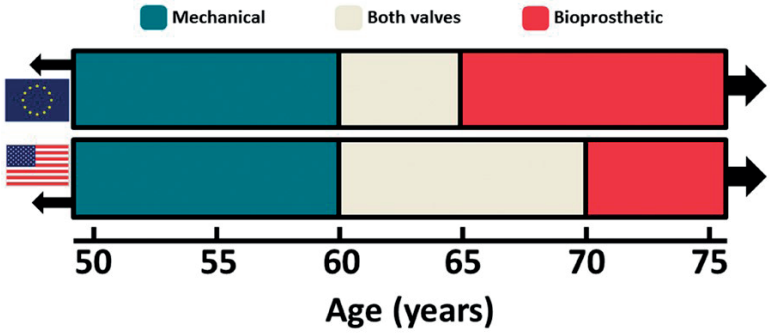


**Figure 2. Guideline recommendations for the use of mechanical and bioprosthetic prostheses for aortic valve replacement.** Recommendations from the North American AHA/ACC and European ESC/EACTS guidelines.[69,70]

the expected hemodynamics for a specific valve type and size as an important factor when considering the type of prosthesis.[21]

## USE OF MECHANICAL AND BIOLOGICAL VALVES

Despite guideline recommendations, the use of bioprosthetic valves has significantly increased over the last decades. Dunning and coauthors reported from the Great Britain and Ireland National Database that the use of bioprosthetic valves increased from 65.4% to 77.8% between 2004-2009.[22] Remarkably, patients in age categories of <55 and 55-60 year of age showed a similar increase to patients in older age categories (Figure 3). An analysis of the Netherlands Cardiac Surgery National Database showed an increase in bioprosthetic valve use between 1995-2010, particularly in age categories of patients 55-65, 65-70 and 70-100 but not in patients aged 18-55.[23] The use of bioprostheses between 1999-2011 in the United States increased largest in patients aged 55-64.[24]

The change in use of bioprosthetic and mechanical valves is somewhat counterintuitive for two reasons. First, it is well recognized that bioprosthetic valve deterioration is accelerated in younger patients.[16] Now that the general population is living in better health up to an older age, elderly patients can potentially experience faster valve deterioration. Second, a continuously improving life expectancy exposes patients to a higher risk of (multiple) reoperation(s) by increasing the necessary implantation time of prosthetic valves.

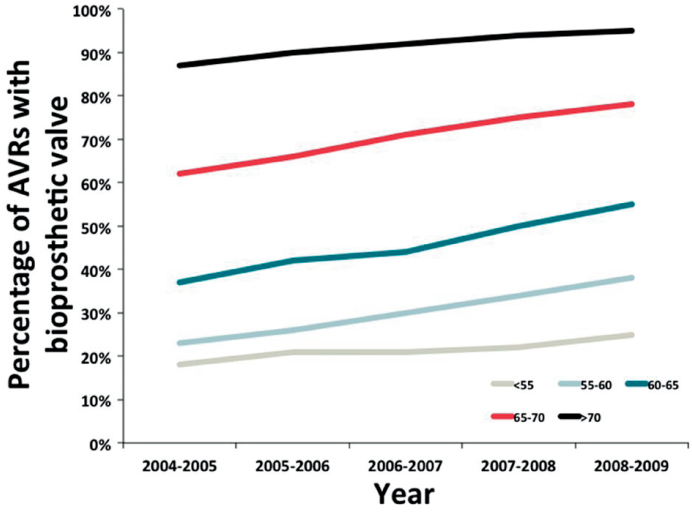


**Figure 3. Percentage of aortic valve replacements with biological prostheses in Great Britain and Ireland.** Data from Dunning and coauthors.[71]



## MECHANICAL VERSUS BIOLOGICAL VALVES

### Initial Randomized Trial Data

Two large randomized trials in the 1970s and '80s compared valve replacement using mechanical versus bioprosthetic valves.[25, 26] The Veterans Affairs (VA) trial in the United States randomly assigned 394 male patients undergoing AVR that were followed to a 15-year endpoint, and found that survival was significantly improved in patients whom received a mechanical prosthesis as opposed to those with a bioprosthesis (34% versus 21%, $P$=0.02).[25] As expected, reoperation rates were significantly higher with a bioprosthesis (10% versus 29%, respectively; $P$=0.004) but bleeding complications were significantly higher with a mechanical valve (51% versus 30%, respectively, $P$=0.0001). Stroke, endocarditis, and valve thrombosis occurred at similar rates.

The Edinburgh trial randomly assigned 211 patients that were followed for 20 years.[26] Survival was 31.3% for patients with a bioprosthesis versus 28.4% for patients with a mechanical valve ($P$=0.57). Secondary endpoints showed similar results as those of the VA trial: reoperation rates were significantly higher with a bioprosthesis (56.2% versus 7.4%, respectively; $P$<0.0001); major bleeding events occurred significantly more often with a mechanical valve (32.0% versus 37.8%, respectively; $P$=0.021); and rates of thromboembolisms and endocarditis were comparable between the groups.

### Recent Randomized Trial Data

After the initial large randomized trials, only a single trial has been performed to compare long-term outcomes.[27] Stassano and coauthors randomly assigned 310 patients aged 55-70 to either receive a mechanical or bioprosthetic valve. In a patient population that averaged ~64 years-of-age, survival was comparable between the groups after a mean follow-up of nearly 9 years. A multivariate model identified that the type of valve was not an independent predictor of late mortality: hazard ratio associated with a mechanical valve = 0.73, 95% confidence interval 0.45-1.20 (*P*=0.2). Bioprostheses showed to have a higher linearized rate of valve failure (*P*=0.0001) and higher rates of reoperation (*P*=0.0003), while there was a trend towards higher rates of bleeding with mechanical valves (*P*=0.08).

### Data From Observational Studies

There are no randomized trials that include results from contemporary valves, however numerous observational studies have been performed comparing mechanical and bioprosthetic valves. A PubMed search (Appendix) was performed in September 2016 to systematically identify studies that included multivariate analysis to adjust for baseline differences or applied propensity-matching to allow for a more substantiated comparison between mechanical and bioprosthetic prostheses. A check of reference lists was also completed to identify articles missed with the PubMed search. A total of 11 studies reported results from propensity-matched cohorts, and an additional 8 studies reported results from multivariable analysis (Table 1).

Two recent large, propensity-matched studies have reported conflicting results. Chiang and coauthors in a statewide analysis out of New York found that among 1001 matched pairs, aged 50-69 years, survival at 15-year follow-up was 60.6% versus 62.1% in the bioprosthetic versus mechanical valve groups, respectively (*P*=0.74).[28] Glaser and coauthors performed a similar analysis with data from the Swedish national registry. They were able to propensity-match 2198 patients aged 50-69 years and reported that 15-year survival was significantly improved in patients with a mechanical prosthesis (59% versus 50% with a bioprosthesis; *P*=0.006).[29] An important subgroup analysis according to age produced that the benefit of a mechanical over a bioprosthetic valve was only evident in patients aged 50-59 (*P*=0.03) but not in those aged 60-69 (*P*=0.54). Chiang and coauthors in an additional requested analysis were unable to confirm these findings by reporting comparable adjusted survival in age groups 50-59 and 60-69 between prosthesis types.[11, 30]

Data from the Society of Thoracic Surgeons database in the United States recently confirmed the importance of age in the prediction of long-term survival with different prostheses. Brennan and coauthors analyzed nearly 40,000 patients aged ≥65 years out of 605 hospitals.[31] Long-term survival was significantly improved with mechanical ver-

**Table 1. Long-term survival from observational studies applying propensity matching or performing multivariable analysis comparing mechanical with bioprosthetic aortic valve replacement**

| Author, year | Design | Patient inclusion | Number of patients | Patient age inclusion | Mean age (Mech. vs Bio.) | Mean follow-up (Mech. vs Biol.) | Outcome | Survival rates (Mech. vs Biol.) HR associated with biological versus mechanical valve |
|---|---|---|---|---|---|---|---|---|
| **STUDIES WITH PROPENSITY MATCHING** | | | | | | | | |
| **Sakamoto et al, 2016** [109] | Retrospective | 1995-2014 | N=56 | 60-70 years | 64 vs 65 (p=0.11) | 7.0 vs 7.8 years (p=0.60) | 15-year survival | 88% versus 85% (p=0.73) |
| **Okamoto et al, 2016** [110] | Retrospective | 2001-2004 | N=104 | ≥75 years | 79 vs 79 (p=0.82) | 4.8 vs 4.0 years (p=0.22) | 8-year survival | 73% versus 73% (p=0.47) |
| **Wang et al, 2015** [111] | Retrospective | 2002-2009 | N=224 | <60 years | 49 vs 50 (p=0.65) | Overall 8.6 years (no comparison) | 10-year survival | 88% versus 89% (p=0.86) |
| **Glaser et al, 2015** [29] | Retrospective | 1997-2013 | N=2198 | 50-69 years | 62 vs 62 (p=0.44) | 6.7 vs 6.6 years (no p-value) | 15-year survival | 59% versus 50% (p=0.006) HR=1.34, 95% CI 1.09-1.66 |
| **Roumieh et al, 2015** [112] | Retrospective | 1996-2008 | N=120 | 55-65 years | 62 vs 61 (p=0.4) | 10.7 vs 8.8 years (no p-value) | 15-year survival | 53% versus 54% (p=0.95) |
| **Chiang et al, 2014** [28] | Retrospective | 1997-2004 | N=2002 | 50-69 years | 62 vs 62 (p=0.94) | 10.9 vs 10.6 years† (no p-value) | 15-year survival | 62% versus 61% (p=0.74) HR=0.97, 95% CI 0.83-1.14 |
| **McClure et al, 2014** [113] | Retrospective | 1992-2011 | N=722 | Adults <65 years | 53 vs 54 (p=0.30) | 6 versus 7 years† (no p-value) | 15-year survival | 75% versus 65% (p=0.75) |
| **Badhwar et al, 2012** [114] | Retrospective | 2003-2007 | N=98 | ≤65 years | Not provided | Not provided | 8-year survival | 100% versus ±83% (p=0.04)* |
| **Weber et al, 2012** [115] | Retrospective | 2000-2009 | N=206 | <60 years | 50 vs 55$ (p=0.03) | Overall 2.8 years (no comparison) | Survival during follow-up | 98% versus 90% (p=0.04) HR=0.24, 95% CI 0.05-0.92 |
| **Ashikhmina et al, 2011** [116] | Retrospective | 1993-2007 | N=458 | ≥70 years | Not provided | Not provided | 15-year survival | 19% versus 7% (p=0.81) |
| **Brown et al, 2008** [117] | Retrospective | 1991-2000 | N=440 | 50-70 years | 66 vs 67 (p<0.01) | 8.6 vs 6.3 years (no p-value) | 10-year survival | 68% versus 50% (p<0.01) HR=0.48, 95% 0.35-0.67 |

**Table 1. Long-term survival from observational studies applying propensity matching or performing multivariable analysis comparing mechanical with bio-prosthetic aortic valve replacement** (*continued*)

| Author, year | Design | Patient inclusion | Number of patients | Patient age inclusion | Mean age (Mech. vs Bio.) | Mean follow-up (Mech. vs Biol.) | Outcome | Survival rates (Mech. vs Biol.) HR associated with biological versus mechanical valve |
|---|---|---|---|---|---|---|---|---|
| **STUDIES WITH MULTIVARIABLE ANALYSIS** | | | | | | | | |
| **Polomsky et al, 2014** [118] | Retrospective | 2002-2011 | N=909 | Adults | 50 vs 69‡ (p<0.001) | Not provided | Propensity-score adjusted 10-year survival | HR=1.32, 95% CI 0.83-2.04 |
| **Brennan et al, 2013** [31] | Retrospective | 1991-1999 | N=39199 | >65 years | 73 vs 73 (p=0.94) | 13.0 vs 12.4‡ (p<0.0001) | Propensity-score adjusted 12-year survival | HR=1.04, 95% CI 1.01-1.07 |
| **Gaca et al, 2013** [119] | Retrospective | 1986-2009 | N=2148 | >16 years | 61 vs 73† (no p-value) | Overall 7 years‡ (no comparison) | Multivariable adjusted 10-year survival | Valve type was not a significant predictor (p=0.44) |
| **Ruel et al, 2007** [120] | Retrospective | 1969-2004 | N=314 | Adults <60 years | 48 vs 48 | Overall 13.4 years‡ (no comparison) | Multivariable analysis of survival beyond 20 years | HR=0.95, 95% CI 0.7-1.3 |
| **Carrier et al, 2001** [121] | Prospective | 1982-1999 | N=526 | 55-65 years | 61 vs 61‡ (p=0.1) | 4 vs 7 years‡ (p=0.01) | Multivariable analysis of 10-year survival | Type of prosthesis was not associated with long-term mortality. |
| **Khan et al, 2001** [122] | Retrospective | 1976-…. | N=1389 | >18 years | 65 vs 72‡ (p=0.001) | 5.8 vs 4.7 years‡ (no p-value) | Multivariable adjusted 10-year survival | Valve type was not a significant predictor. |
| **Petersheim et al, 1999** [123] | Retrospective | 1976-1996 | N=841 | >18 years | 62 vs 64 (p=NS) | Not provided | Multivariable adjusted 10-year survival | Valve type was not a significant predictor (p=0.4). |
| **Jamieson et al, 1995** [124] | Retrospective | 1982-1993 | N=1929 | None | 59 vs 67§ (no p-value) | 2.9 vs 5 years‡ (no p-value) | Multivariable adjusted 8-year survival | HR=1.32 (p=NS) |

*Read from Kaplan-Meier curve

†Median instead of mean

‡Unadjusted analysis

§Includes patients that underwent mitral valve replacement

CI = confidence interval; Biol = biological; HR = hazard ratio; Mech = mechanical; NS = not significant

sus bioprosthetic valves in a propensity-score adjusted analysis, although the difference was only marginal (HR associated with bioprosthesis = 1.04, 95% CI 1.01-1.07). There was, however, a significant interaction between age and prosthesis type that showed a stepwise increase in the risk of mortality associated with a bioprosthesis in younger age groups. The hazard ratio associated with a bioprosthesis was 1.23 (95% CI 1.16-1.31) in patients aged 65-69, 1.04 (95% CI 0.99-1.09) in patients aged 70-74, and 0.95 (95% CI 0.90-0.99) in patients aged 75-79.

It should be noted that none of the analyses reported a significantly improved survival rate with bioprosthetic over mechanical prostheses. However, there were several studies, specifically those that included younger patients, which found a significant benefit of mechanical over bioprosthetic valves. Based on the currently available data, there does not seem to be sufficient evidence to support lowering the age cut-off for implanting bioprosthetic valves below the age of 60 years to improve long-term survival. In terms of quality of life, numerous studies have reported comparable scores with mechanical and bioprosthetic valves, although results have also been conflicting.[32-37]



## SELECTED PATIENT COHORTS

The presence of specific comorbidities or risk factors may alter the decision-making process between mechanical and bioprosthetic valves. These patient characteristics should be considered when determining which prosthesis should be favoured (Table 2). Nevertheless, no single factor should be decisive and the risk/benefit of both valves should be established for each particular patient to select the most appropriate prosthesis.

### Atrial Fibrillation or Other Conditions Requiring Anticoagulation Therapy

There are no studies that evaluated outcomes explicitly of patients already on oral anticoagulation because of AF or other vascular conditions, but in theory the benefit of bioprostheses in such patients may be diminished. For patients on vitamin K antagonist anticoagulation, the recommended INR range for a mechanical prosthesis is similar or even lower than for AF (2.0-3.0 versus 2.0-3.0 or higher, respectively) and thus a mechanical prosthesis does not increase the risk of bleeding events. Surgeons should therefore consider implanting a mechanical valve irrespective of the patients' age. However, an argument for bioprostheses is that patients on non-vitamin K antagonist anticoagulation (NOAC) agents can continue this treatment that is recommended over vitamin K antagonists for stroke prevention in AF but is not recommended as anticoagulation for mechanical prostheses.[38]

### End-stage Renal Disease Including Dialysis

Patients with end-stage renal disease have long been considered not to be candidates for bioprostheses because of assumed progression of calcification causing SVD. Indeed,

**Table 2. Considerations for implanting a mechanical or bioprosthetic aortic valve**

| Patient characteristic | Consider favouring mechanical valve | Consider favouring bioprosthetic valve |
|---|---|---|
| Age <60 | X | |
| Age 60-70 | Unclear | Unclear |
| Age >70 years | | X |
| Age <60 but life expectancy <10 years | | X |
| Age <60 but pregnancy wish | | X |
| Age <60 but hazardous occupation (e.g. sports, mining, stunt(wo)man, etc) | | X |
| Preoperative lifelong anticoagulation indication (e.g. AF, PVD, hypercoagulable state) | X | |
| Reoperations for valve thrombosis because of compliance failure or inadequate INR regulation | | X |
| High bleeding risk | | X |
| Contra-indication for anticoagulation treatment | | X |
| End-stage renal failure on dialysis | | X |
| Metabolic syndrome | X | |
| Hyperparathyroidism | X | |
| Small aortic annulus | X | |

These factors should be weighted and could potentially lean towards performing mechanical or bioprosthetic valve implantation. Presence of any of these factors does not exclude the opportunity to perform valve replacement with another type of valve.
AF = atrial fibrillation; INR = International Normalized Ratio; PVD = peripheral vascular disease; TAVI = transcatheter aortic valve implantation

a meta-analysis of early studies reported a trend towards improved survival with mechanical over bioprosthetic valves (HR = 1.34, 95% CI 0.96-1.86; p=0.086), although this analysis consisted mainly of small studies and did not selectively include patients undergoing AVR.[39] The largest study to date from Herzog and coauthors included 5858 dialysis patients undergoing heart valve replacement of whom 3415 underwent isolated AVR; survival was only 39% at 2-year follow-up without a difference between mechanical and bioprosthetic valves.[40] Even in more recent reports, survival of patients on dialysis was generally short and therefore patients are not expected to outlive their bioprosthesis.[41] As a result, a bioprosthesis may be favoured to avoid the use of anticoagulation. No data exists on differences between valve types in patients with mild or moderate renal failure who also have increased calcium metabolism but a longer life-expectancy.

### Atherosclerotic Risk

Although contradictory results have been reported, evidence supporting accelerated bioprosthetic SVD in patients with a less healthy lifestyle prone to atherosclerotic risk is available from numerous studies: (i) smoking has been identified as an independent

predictor of reoperation for SVD [42, 43]; (ii) different measures of cholesterol have been linked with valve calcification[44] and failure[45]; (iii) an Italian multicenter study reported that diabetes was the strongest predictor of bioprosthetic valve degeneration in a propensity-matched study including 2226 patients[46]; and (iv) metabolic syndrome accelerated SVD during annual echocardiographic follow-up of 217 patients who underwent AVR in a study by Briand and coauthors.[47] Because of the increased risk of SVD, a mechanical valve may be favoured in patients at high risk of atherosclerosis.



### Coronary Artery Disease

Approximately 40% of patients who undergo AVR require concomitant CABG, which has a significant impact on long-term prognosis.[48] Only little evidence is available from studies comparing valve types in patients undergoing combined procedures. In a microsimulation study, differences in life-expectancy and event-free life-expectancy between mechanical and bioprosthetic valves were comparable whether male patients underwent isolated AVR or AVR+CABG, with a cut-off for implanting a bioprosthesis around 60 years of age.[49] The decision to opt for a mechanical or bioprosthetic valve in patients requiring a combined AVR+CABG procedure should not be different than for patients undergoing isolated AVR.

### Small Aortic Annulus

Prosthesis-patient mismatch (PPM) occurs when the effective orifice area (EAO) of a prosthetic valve is too small for the body surface area of the patient.[50] Although its impact on long-term outcomes has long been debated, a meta-analysis found that survival was significantly improved in patients with no PPM as compared with moderate PPM (HR = 1.19, 95% CI 1.07-1.33) or severe PPM (HR = 1.84, 95% CI 1.38-2.45).[51] For patients with a small aortic annulus the EOA is crucial to optimize hemodynamic performance of the valve and thus avoid PPM. Small-size mechanical valves generally have larger EOAs than small-size bioprosthetic valves.[52] In some instances, patients with a small annulus may therefore benefit from a mechanical valve. However, a root enlargement to allow implantation of a larger bioprosthesis may also be an option to avoid PPM.[53, 54]

### Root Replacement Procedures

A number of studies have compared outcomes after bioprosthetic and mechanical composite grafts among patients requiring AVR with root replacement because of bicuspid valves or root aneurysms.[55] Conflicting results have been reported from studies applying varies methods of adjustment for baseline differences, although generally a small number of patients were included in single-center studies and thus the generalizability is limited.[55-58] Therefore, if valve-sparing operations cannot be performed[58], the indica-

tion for a bioprosthetic or mechanical composite graft is similar to that of isolated AVR procedures with respect to age cut-offs.

### Aortic and Mitral Valve Replacement/Repair

In patients with a mechanical mitral valve already in place, implanting a mechanical aortic valve that has a lower INR target range than the mitral valve (2.0-3.0 versus 2.5-3.5, respectively) would not add significant long-term risks. However, for the 5-10% of patients that require combined aortic and mitral valve operations, the most appropriate strategy remains a matter of debate. Studies have been controversial on whether mitral valve repair should be preferred over valve replacement in combination with AVR.[59, 60] Leavitt and coauthors reported that survival of patients younger than 70 years was comparable between those with two mechanical valves and those with a bioprosthetic aortic valve and mitral repair but significantly lower among those with two bioprosthetic valves.[61] These studies and the differences in oral anticoagulation regimens after valve procedures impact on the decision to use a mechanical or bioprosthetic valve in the aortic position: (i) no long-term oral anticoagulation is mandatory after mitral valve repair and thus the choice of valve in the aortic position should depend on recommendations for isolated AVR; (ii) if the mitral valve requires replacement, clinical guidelines recommend the use of a mechanical valve in the mitral position up to the age of 65 and thus a mechanical aortic valve is advisable; (iii) a mechanical aortic valve is recommended if primary a mechanical mitral valve is chosen because of the INR target ranges.

### Endocarditis

The presence of active infection poses the risk of early recurrent endocarditis because a foreign body is implanted in an infected area. It has been suggested that a bioprosthesis may be favoured because it is less susceptible to reinfection and better to treat when reinfection does occur.[62] Indeed, the use of bioprostheses has increased also in active endocarditis.[63] However, mechanical valves have shown excellent performance and low rates of recurrent endocarditis  similar to that of bioprosheses.[64, 65] In fact, adjusted 5-year mortality has been found to be significantly lower with mechanical valves among patients younger than 65 years old with active endocarditis (HR = 4.14, 95% CI 1.27-13.45), while survival was similar in patients older than 65 years (HR = 1.45, 95% CI 0.35-5.97).[66] Most recent date from the International Collaboration on Endocarditis Prospective Cohort Study (ICE-PCS) reported that implantation of a bioprosthesis independently predicted one-year mortality.[67] Therefore, there is no evidence to specifically support use of bioprostheses in patients with active endocarditis irrespective of age.

## DEVELOPMENTS IN FAVOUR OF MECHANICAL VALVES

### Non-vitamin K Antagonist Anticoagulation with Mechanical Valves

Numerous NOAC agents have been developed to replace vitamin K antagonists. In studies of patients with atrial fibrillation, rivaroxaban, apixaban, edoxaban, and dabigatran showed to be noninferior for stroke prevention with significantly lower rates of bleeding.[38] Translation of these results to NOAC use in patients with a mechanical prosthesis would show a drastic improvement in outcomes. In the RE-ALIGN trial, however, the use of dabigatran as compared with warfarin was associated with an increase in the composite of death, stroke, systemic embolism, and myocardial infarction (8% versus 2%, respectively; *P*=0.11), as well as bleeding complications (27% versus 12%, respectively; *P*=0.01), which is why the trial was stopped prematurely.[68] The small, pilot, phase 2 CATHAR trial investigated the safety and efficacy of rivaroxaban use in mechanical prostheses but had to suspend enrollment (clinicaltrials.gov number: NCT02128841). No large randomized trials on the use of NOACs in mechanical valves are currently ongoing.



### Lower INR Ranges and Self-control and Self-management with Mechanical Valves

Before positive results from NOAC trials are available, patients are still sentenced to vitamin K antagonist anticoagulation therapy, which has several disadvantages that result in INR values outside the targeted range: (i) food interactions, (ii) drug interactions, and (iii) regular laboratory monitoring. However, the risk of bleeding events can be significantly reduced with vitamin K antagonists if the targeted INR could be lowered. Koertke and coauthors performed a randomized trial in which 2673 patients undergoing AVR were randomized to anticoagulation with a target INR of 1.8-2.8 versus 2.5-4.5.[69] After 2-year follow-up, the rate of thromboembolic events in the low-dose versus conventional dose groups was not significantly different at 0.24 versus 0.46% per patient-year, respectively, while the rate of bleeding was 1.42 versus 1.78% per patient-year, respectively. In a more recent randomized trial among 33 centers in North America investigating the On-X mechanical valve (On-X Life Technologies, Austin, Texas, United States), 375 high-risk patients were randomized at 3 months post-AVR to receive aspirin with anticoagulation for a targeted INR of 1.5-2.0 or 2.0-3.0.[70] Over the course of 5-year follow-up, rates of bleeding were significantly lower for patients in the low INR group (*P*=0.002), without significant increases in thromboembolic events (*P*=0.13). Although it is evident that lower INR ranges are beneficial in terms of bleeding events, it remains unclear to what extend the INR target can be lowered to be considered safe for the prevention of valve thrombosis and stroke.

Even if vitamin K antagonists remain necessary, the inconvenience associated with regular outpatient INR checks can safely be avoided. In a meta-analysis of 11 random-

ized trials comparing self-monitoring and self-management of anticoagulation with outpatient management in primary care or anticoagulation clinics found that among 6417 participants with 12800 patient-years of follow-up, there was a significant decline in the self-monitoring group in the rate of thromboembolic events (HR = 0.51, 95% CI 0.31-0.85; *P*=0.01) with similar rates of bleeding (HR = 0.88, 95% CI 0.74-1.06; *P*=0.18) and death (HR = 0.82, 95% CI 0.62-1.09; *P*=0.18).[71] Subgroup analyses found that the reduction of thromboembolic events with self-monitoring was seen particularly in patients with a mechanical valve as opposed to those with atrial fibrillation (*P* for interaction = 0.032), and in patients that not only self-tested but also self-managed anticoagulation dosing (*P* for interaction = 0.002).

A recent randomized trial attempted to combine the benefits of low-dose INR and self-management, by randomizing 1571 patients, of which 1304 had AVR, to low-dose INR self-control with a target range of 1.8-2.8 and weekly INR checks, very low-dose INR with a target range of 1.5-2.1 and weekly INR checks, and very low-dose INR with a target range of 1.5-2.1 and twice weekly INR checks over the course of 2 years.[13] Even though patients in the very low-dose INR groups were significantly longer outside the targeted INR range, a risk-adjusted analysis with the low-dose INR group as reference showed that major bleeding rates were significantly lower in patients in the very low-dose twice-weekly INR check (HR=0.27, 95% CI 0.09-0.84; *P*=0.02) as well as for those with a very low-dose weekly INR check (HR=0.38, 95% CI 0.15-0.99; *P*=0.046). There were comparable rates of major thrombotic events in the very low-dose INR twice-weekly (HR=1.22, 95% CI 0.32-4.61; *P*=0.77) and weekly checks (HR=0.24, 95% CI 0.03-2.18; *P*=0.21). Remarkably, even though death rates were low in all groups (range 97.1-98.9%), as compared with the low-dose INR group there was a significantly higher risk-adjusted mortality rate in the very low-dose INR group with twice-weekly checks (HR=3.15, 95% CI 1.20-8.29; *P*=0.02) but not in the very low-dose INR group with weekly checks (HR=1.36, 95% CI 0.46-4.12; *P*=0.58). These data still need to be replicated since the trial was stopped prematurely.

### Mechanical Valve Design

At the moment, 3-D printed mechanical valves are being used to test new valve designs in prototypes to optimize design and materials associated with less thrombogenicity and better flow patterns. Studies with the use of a 3-D printed mechanical valve found a much lower thrombogenicity potential index when compared with other mechanical valves and which was similar to that of bioprosthetic valves.[72] In theory, such valves would be able to function without the need for anticoagulation. To our knowledge, currently no 3-D valve is being developed for use in the near future.

The On-X valve was designed to be safe with only antiplatelet therapy in some low-risk patients.[70] Its design with a smoother surface of pure carbon without silicon, 90-degree

opening leaflets, a flared valve inlet, and stasis-free pivots reduce turbulence and thrombogenicity. Data on the use of aspirin and/or clopidogrel instead of anticoagulation treatment with the On-X valve are underway from the PROACT trial (clinicaltrials.gov number: NCT00291525).

The Lapeyre-Triflo FURTIVA valve (Triflo Medical Switzerland, Neuchâtel, Switzerland) is a trileaflet instead of bileaflet mechanical valve which combines the hemodynamic excellence of trileaflet native or bioprosthetic aortic valves but with mechanical valve durability. Oral anticoagulation may potentially be omitted because the design reduces high-velocity backflow jets that damage blood and activate thrombus formation, eliminates low flow areas, and lowers shear stress and turbulence through pivots.[73]



**Anticoagulation with Bioprosthetic Valves**

The incidence of leaflet thrombosis with surgical bioprostheses regained interest after findings of reduced leaflet motion on MSCT following transcatheter aortic valve implantation (TAVI).[19, 74] These data have triggered further analyses of bioprosthetic valve thrombosis.[75] Although it is not easy to derive the true incidence from these small studies, the risk factors they had in common were no or inadequate anticoagulation therapy, while initiation of anticoagulation resolved valve thrombosis in the majority of cases. Indeed, evidence supporting a recommendation for routine anticoagulation therapy after AVR with a bioprosthesis has been conflicting.[76, 77] Early reports have reported no difference between warfarin and aspirin treatment.[78] However, two recent studies found an indication for warfarin treatment. In elderly patients, Brennan and coauthors showed in a propensity-score adjusted analysis that warfarin in addition to aspirin treatment within the first 3 months after receiving a bioprosthesis significantly reduced rates of death (RR=0.80, 95% CI 0.66-0.96) and embolic events (RR=0.52, 95% CI 0.35-0.76) when compared to aspirin treatment alone, although at the cost of higher rates of bleeding (RR=2.80, 95% CI 2.18-3.60).[79] A Danish nation-wide study investigated whether anticoagulation beyond the first 3 months was associated with improved outcomes by identifying 4075 patients that underwent AVR between 1997 and 2009 and were discharged with warfarin treatment. Continuing warfarin during follow-up produced favourable outcomes of stroke and cardiovascular death. Remarkably, rates of bleeding events were also reduced significantly; although from the data it is not clear whether patients discontinued warfarin before bleeding occurred or as a result of bleeding, and therefore these results should be interpreted with caution.[80]

At the moment there is not enough evidence to support recommendations for routine anticoagulation therapy after bioprosthetic valve implantation, but future studies on this topic may significantly alter the debate on mechanical versus bioprosthetic valves. It will be crucial to determine whether (i) anticoagulation indeed improves outcomes with bioprosthetic valves, (ii) the duration that anticoagulation therapy is necessary, and

(iii) how outcomes of bioprosthetic valves with concomitant anticoagulation therapy compare with patients with a mechanical valve.

## DEVELOPMENTS IN FAVOUR OF BIOLOGICAL VALVES

### Bovine or Pericardial Bioprosthetic Surgical Valves

At short-term, several small randomized trials and prospective studies have found bovine valves to have significantly better hemodynamic results with lower valve gradients and larger aortic valve areas.[81-84] Whether these results translate into improved survival remains conflicted. The largest study to date from Hickey and coauthors included nearly 40000 patients and found that the 10-year survival rate was comparable between the bovine and porcine valves (49.0% versus 50.3%, respectively; *P*=0.77), which was confirmed by several recent smaller studies.[85-88] Moreover, the authors of an overview on porcine versus bovine studies clearly summarized that "variability between valve manufacturers, study designs, study period and patient population in studies impose limitations to the comparisons of valve types."[84]

Because of the assumed improved outcomes with bovine pericardial valves, newer bioprostheses generally contain bovine tissue leaflets. Newer bioprostheses may lead to improved outcomes because of improved designs with better hemodynamic performance.[3] For example, the Trifecta valve (St. Jude Medical, Saint Paul, Minnesota, United States) established superiority over Objective Performance Criteria (OPC) and showed excellent hemodynamic performance with lower gradients and higher aortic valve areas.[89-92] Registry data on the Perigon (Medtronic Inc, Minneapolis, Minnesota, United States, clinicaltrials.gov number: NCT02088554) and Resilia (Edwards Lifesciences, Irvine, California, United States, clinicaltrials.gov number: NCT01757665) valves are currently underway. Before these valves lead to even more implantation of bioprosthetic valves in younger patients, they should be compared to mechanical prostheses.

### Transcatheter Valves

Over the last decade since the introduction of transcatheter heart valves (THVs), numerous randomized trials have shown TAVI to be non-inferior if not superior to AVR in selected patients that are at intermediate- or high-risk for surgical mortality or morbidity.[93-97] Numerous THVs have been produced, all of which are bioprosthetic valves; there is a need to crimp the valve to fit a sheath for a predominant transfemoral approach of implantation. Some concerns have been raised about crimping, since this can damage the leaflet tissue.

Although TAVI is currently mostly reserved for elderly patients, the low complication rate of the procedure opens the door to implanting THVs in younger patients. The

reduced invasiveness and faster recovery time as compared with AVR could tip the scale in favour of TAVI with a bioprosthetic valve as opposed to AVR with a mechanical valve, if long-term results are at least non-inferior.[98] Especially now that valve-in-valve procedures have emerged as a valuable option in patients with degenerated (surgical) bioprostheses.[99, 100] Particularly in patients aged 60-70 in which both mechanical and bioprosthetic valves are valuable options according to clinical guidelines, implanting a bioprosthesis with a subsequent valve-in-valve in prospect may alter the decision in this particular age group. However, experience with valve-in-valve procedures remains relatively limited, is selectively used in high-risk patients, and long-term follow-up is scarce.[101] Moreover, PPM is not infrequent after valve-in-valve procedures and has a detrimental impact on long-term outcomes.[51, 101, 102]



### Sutureless Valves

Transcatheter heart valve technology has been paralleled by similar developments in surgical AVR with the advent of sutureless, also named rapid-deployment valves. Comparable to THVs, sutureless technology includes only bioprosthetic valves as these are compressed to a certain degree, although attempts have been made to develop sutureless mechanical valves that were tested in pigs.[103] The patient population that can benefit from sutureless valves is yet unclear, particularly considering the excellent results with TAVI in the intermediate- to high-risk patient population and its expansion to an all-comers population that includes those at low-risk.[104] However, with a growing interest in minimally invasive procedures, sutureless technology could be adopted more now that such procedures are considerably less technically challenging with a sutureless technique. Upcoming trials randomizing patients between sutureless or conventional AVR, like the PERSIST-AVR trial (clinicaltrials.gov number: NCT02673697), are underway.

## TISSUE-ENGINEERED VALVES

The need for mechanical and bioprosthetic valves could potentially be omitted in the future with the development of tissue-engineered heart valves. Constructed valves disrupt, although only marginally, the native size and shape of the aortic annulus, alternate hemodynamic flow, and are susceptible to cloth formation and endocarditis due to the presence of a foreign body. In contrast, tissue-engineered valves mimic natural blood flow through the left ventricular outflow tract and coronary arteries due to their natural structure, may have the possibility for self-repair and remodeling as opposed to degeneration of bioprosthetic valves, and provide no additional risk related to a triggered reaction as the result of a foreign body. Moreover, tissue-engineered valves have

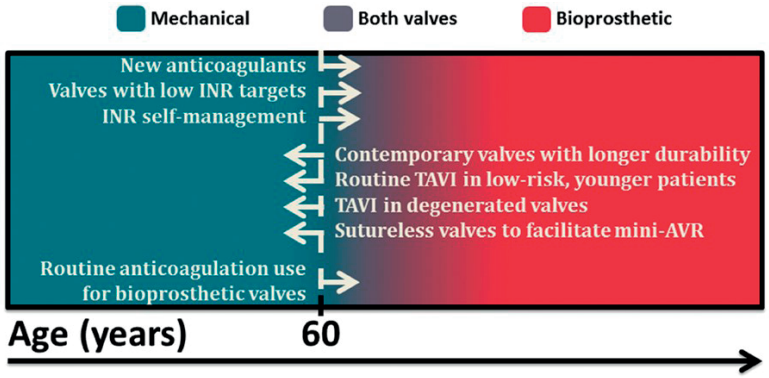


**Figure 4. Advancements in therapy related to mechanical and bioprosthetic valves that may change the cut-off for implanting a bioprosthesis.** Adapted from Head and coauthors.[59]

the potential to grow, allowing them to be implanted in pediatric patients without the obvious need for a reoperation when they would have outgrown their prosthesis.

Early concepts of tissue-engineering technology have focused on developing valves with the use of a matrix that is in-vitro seeded with harvested cells. Since then, many methods have been tested to overcome technical, logistical and financial hurdles and potentially introduce an 'off-the-shelf' valve for routine use.[105] At the moment, these different concepts are being tested in sheep.[106, 107] Their clinical application still requires additional feasibility studies and a first-in-man application, but it remains a promising prospect.[108]

## HEART TEAM

Multidisciplinary Heart Team decision-making is becoming more important for the treatment of aortic valve disease because of an increasing overlap of indications for AVR and TAVI. Clinical guidelines therefore recommended regular, formal Heart Team meetings. If a patient is a better candidate for AVR, these meetings furthermore provide the opportunity to discuss in a Heart Team whether a mechanical or bioprosthetic valve should be preferred based on the patient profile. Given the complex decision-making that relies on numerous comorbidities, expected hemodynamic performance of a prosthetic valve, and long-term secondary prevention that is directed by the cardiologist, these decisions may be more appropriate than when made by surgeons alone.

## CONCLUSIONS

The main reason to opt for a bioprosthesis is to avoid the indication for lifelong anticoagulation, which has resulted in a clear increase in the use of bioprosthetic as opposed to mechanical aortic valve replacement, particularly in middle-aged patients of 50-70 years old. However, there is currently no evidence to support lowering the age threshold below 60 years for implanting a bioprosthesis. New developments in the field of anticoagulation therapy and management and in both mechanical and bioprosthetic valve design and indications can potentially significantly alter the risk/benefit ratio associated with either prosthesis and change the decision-making process (Figure 4). Future randomized studies should investigate these developments. Until then, physicians and patients should be cautious in pursuing more bioprosthetic valve use until its benefit is clearly proven in middle-aged patients.

## REFERENCES


1. Edwards WS and Smith L. Aortic valve replacement with a subcoronary ball valve. *Surg Forum*. 1958;9:309-13.
2. Gott VL, Alejo DE and Cameron DE. Mechanical heart valves: 50 years of evolution. *Ann Thorac Surg*. 2003;76:S2230-9.
3. Pibarot P and Dumesnil JG. Prosthetic heart valves: selection of the optimal prosthesis and long-term management. *Circulation*. 2009;119:1034-48.
4. Ross DN. Homograft replacement of the aortic valve. *Lancet*. 1962;2:487.
5. Mokhles MM, Kortke H, Stierle U, Wagner O, Charitos EI, Bogers AJ, Gummert J, Sievers HH and Takkenberg JJ. Survival comparison of the Ross procedure and mechanical valve replacement with optimal self-management anticoagulation therapy: propensity-matched cohort study. *Circulation*. 2011;123:31-8.
6. David TE and Feindel CM. An aortic valve-sparing operation for patients with aortic incompetence and aneurysm of the ascending aorta. *J Thorac Cardiovasc Surg*. 1992;103:617-21; discussion 622.
7. Yacoub MH, Gehle P, Chandrasekaran V, Birks EJ, Child A and Radley-Smith R. Late results of a valve-preserving operation in patients with aneurysms of the ascending aorta and root. *J Thorac Cardiovasc Surg*. 1998;115:1080-90.
8. Badiu CC, Bleiziffer S, Eichinger WB, Zaimova I, Hutter A, Mazzitelli D, Voss B and Lange R. Are bicuspid aortic valves a limitation for aortic valve repair? *Eur J Cardiothorac Surg*. 2011;40:1097-104.
9. Beckmann A, Funkat AK, Lewandowski J, Frie M, Ernst M, Hekmat K, Schiller W, Gummert JF and Welz A. German Heart Surgery Report 2015: The Annual Updated Registry of the German Society for Thoracic and Cardiovascular Surgery. *Thorac Cardiovasc Surg*. 2016;64:462-74.
10. Head SJ and Kappetein AP. Aortic valve replacement in younger adults: a biological valve is not the logical choice. *Eur Heart J*. 2016;37:2668-70.
11. Chikwe J, Egorova NN and Adams DH. Age cutoffs for bioprosthetic vs mechanical aortic valve replacement--reply. *JAMA*. 2015;313:523-4.
12. Butchart EG, Payne N, Li HH, Buchan K, Mandana K and Grunkemeier GL. Better anticoagulation control improves survival after valve replacement. *J Thorac Cardiovasc Surg*. 2002;123:715-23.
13. Koertke H, Zittermann A, Wagner O, Secer S, Christ of H, Sciangula A, Saggau W, Sack FU, Ennker J, Cremer J, Musumeci F and Gummert JF. Telemedicine-guided, very low-dose international normalized ratio self-control in patients with mechanical heart valve implants. *Eur Heart J*. 2015;36:1297-305.
14. Bottio T, Casarotto D, Thiene G, Caprili L, Angelini A and Gerosa G. Leaflet escape in a new bileaflet mechanical valve: TRI technologies. *Circulation*. 2003;107:2303-6.
15. Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL, Takkenberg JJ, David TE, Butchart EG, Adams DH, Shahian DM, Hagl S, Mayer JE and Lytle BW. Guidelines for reporting mortality and morbidity after cardiac valve interventions. *Eur J Cardiothorac Surg*. 2008;33:523-8.
16. Jamieson WR, Ling H, Burr LH, Fradet GJ, Miyagishima RT, Janusz MT and Lichtenstein SV. Carpentier-Edwards supraannular porcine bioprosthesis evaluation over 15 years. *Ann Thorac Surg*. 1998;66:S49-52.
17. Siddiqui RF, Abraham JR and Butany J. Bioprosthetic heart valves: modes of failure. *Histopathology*. 2009;55:135-44.

18. Schoen FJ and Levy RJ. Calcification of tissue heart valve substitutes: progress toward understanding and prevention. *Ann Thorac Surg*. 2005;79:1072-80.
19. Makkar RR, Fontana G, Jilaihawi H, Chakravarty T, Kofoed KF, de Backer O, Asch FM, Ruiz CE, Olsen NT, Trento A, Friedman J, Berman D, Cheng W, Kashif M, Jelnin V, Kliger CA, Guo H, Pichard AD, Weissman NJ, Kapadia S, Manasse E, Bhatt DL, Leon MB and Sondergaard L. Possible Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves. *N Engl J Med*. 2015;373:2015-24.
20. Joint Task Force on the Management of Valvular Heart Disease of the European Society of C, European Association for Cardio-Thoracic S, Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL and Zembala M. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J*. 2012;33:2451-96.
21. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM, 3rd, Thomas JD and Members AATF. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:e521-643.
22. Dunning J, Gao H, Chambers J, Moat N, Murphy G, Pagano D, Ray S, Roxburgh J and Bridgewater B. Aortic valve surgery: marked increases in volume and significant decreases in mechanical valve use--an analysis of 41,227 patients over 5 years from the Society for Cardiothoracic Surgery in Great Britain and Ireland National database. *J Thorac Cardiovasc Surg*. 2011;142:776-782 e3.
23. Siregar S, de Heer F, Groenwold RH, Versteegh MI, Bekkers JA, Brinkman ES, Bots ML, van der Graaf Y and van Herwerden LA. Trends and outcomes of valve surgery: 16-year results of Netherlands Cardiac Surgery National Database. *Eur J Cardiothorac Surg*. 2014;46:386-97; discussion 397.
24. Isaacs AJ, Shuhaiber J, Salemi A, Isom OW and Sedrakyan A. National trends in utilization and in-hospital outcomes of mechanical versus bioprosthetic aortic valve replacements. *J Thorac Cardiovasc Surg*. 2015;149:1262-9 e3.
25. Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C and Rahimtoola SH. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. *J Am Coll Cardiol*. 2000;36:1152-8.
26. Oxenham H, Bloomfield P, Wheatley DJ, Lee RJ, Cunningham J, Prescott RJ and Miller HC. Twenty year comparison of a Bjork-Shiley mechanical heart valve with porcine bioprostheses. *Heart*. 2003;89:715-21.
27. Stassano P, Di Tommaso L, Monaco M, Iorio F, Pepino P, Spampinato N and Vosa C. Aortic valve replacement: a prospective randomized evaluation of mechanical versus biological valves in patients ages 55 to 70 years. *J Am Coll Cardiol*. 2009;54:1862-8.
28. Chiang YP, Chikwe J, Moskowitz AJ, Itagaki S, Adams DH and Egorova NN. Survival and long-term outcomes following bioprosthetic vs mechanical aortic valve replacement in patients aged 50 to 69 years. *JAMA*. 2014;312:1323-9.
29. Glaser N, Jackson V, Holzmann MJ, Franco-Cereceda A and Sartipy U. Aortic valve replacement with mechanical vs. biological prostheses in patients aged 50-69 years. *Eur Heart J*. 2016;37:2658-67.
30. Head SJ, Osnabrugge RL and Kappetein AP. Age cutoffs for bioprosthetic vs mechanical aortic valve replacement. *JAMA*. 2015;313:522-3.
31. Brennan JM, Edwards FH, Zhao Y, O'Brien S, Booth ME, Dokholyan RS, Douglas PS, Peterson ED and Team DEAR. Long-term safety and effectiveness of mechanical versus biologic aortic valve

prostheses in older patients: results from the Society of Thoracic Surgeons Adult Cardiac Surgery National Database. *Circulation*. 2013;127:1647-55.

32. Perchinsky M, Henderson C, Jamieson WR, Anderson WN, Jr., Lamy A, Lowe N and de Guzman S. Quality of life in patients with bioprostheses and mechanical prostheses. Evaluation of cohorts of patients aged 51 to 65 years at implantation. *Circulation*. 1998;98:II81-6; discussion II86-7.
33. Repack A, Ziganshin BA, Elefteriades JA and Mukherjee SK. Comparison of Quality of Life Perceived by Patients with Bioprosthetic versus Mechanical Valves after Composite Aortic Root Replacement. *Cardiology*. 2016;133:3-9.
34. Ruel M, Kulik A, Lam BK, Rubens FD, Hendry PJ, Masters RG, Bedard P and Mesana TG. Long-term outcomes of valve replacement with modern prostheses in young adults. *Eur J Cardiothorac Surg*. 2005;27:425-33; discussion 433.
35. Sedrakyan A, Hebert P, Vaccarino V, Paltiel AD, Elefteriades JA, Mattera J, Lin Z, Roumanis SA and Krumholz HM. Quality of life after aortic valve replacement with tissue and mechanical implants. *J Thorac Cardiovasc Surg*. 2004;128:266-72.
36. Florath I, Albert A, Rosendahl U, Alexander T, Ennker IC and Ennker J. Mid term outcome and quality of life after aortic valve replacement in elderly people: mechanical versus stentless biological valves. *Heart*. 2005;91:1023-9.
37. Aboud A, Breuer M, Bossert T and Gummert JF. Quality of life after mechanical vs. biological aortic valve replacement. *Asian Cardiovasc Thorac Ann*. 2009;17:35-8.
38. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GY, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL and Zeppenfeld K. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893-2962.
39. Chan V, Chen L, Mesana L, Mesana TG and Ruel M. Heart valve prosthesis selection in patients with end-stage renal disease requiring dialysis: a systematic review and meta-analysis. *Heart*. 2011;97:2033-7.
40. Herzog CA, Ma JZ and Collins AJ. Long-term survival of dialysis patients in the United States with prosthetic heart valves: should ACC/AHA practice guidelines on valve selection be modified? *Circulation*. 2002;105:1336-41.
41. Williams ML, Bavaria JE, Acker MA, Desai ND, Vallabhajosyula P, Hargrove WC, Atluri P and Szeto WY. Valve Selection in End-Stage Renal Disease: Should It Always Be Biological? *Ann Thorac Surg*. 2016;102:1531-1535.
42. Ruel M, Kulik A, Rubens FD, Bedard P, Masters RG, Pipe AL and Mesana TG. Late incidence and determinants of reoperation in patients with prosthetic heart valves. *Eur J Cardiothorac Surg*. 2004;25:364-70.
43. Nollert G, Miksch J, Kreuzer E and Reichart B. Risk factors for atherosclerosis and the degeneration of pericardial valves after aortic valve replacement. *J Thorac Cardiovasc Surg*. 2003;126:965-8.
44. Farivar RS and Cohn LH. Hypercholesterolemia is a risk factor for bioprosthetic valve calcification and explantation. *J Thorac Cardiovasc Surg*. 2003;126:969-75.
45. Mahjoub H, Mathieu P, Senechal M, Larose E, Dumesnil J, Despres JP and Pibarot P. ApoB/ApoA-I ratio is associated with increased risk of bioprosthetic valve degeneration. *J Am Coll Cardiol*. 2013;61:752-61.

46. Lorusso R, Gelsomino S, Luca F, De Cicco G, Bille G, Carella R, Villa E, Troise G, Vigano M, Banfi C, Gazzaruso C, Gagliardotto P, Menicanti L, Formica F, Paolini G, Benussi S, Alfieri O, Pastore M, Ferrarese S, Mariscalco G, Di Credico G, Leva C, Russo C, Cannata A, Trevisan R, Livi U, Scrofani R, Antona C, Sala A, Gensini GF, Maessen J and Giustina A. Type 2 diabetes mellitus is associated with faster degeneration of bioprosthetic valve: results from a propensity score-matched Italian multicenter study. *Circulation*. 2012;125:604-14.
47. Briand M, Pibarot P, Despres JP, Voisine P, Dumesnil JG, Dagenais F and Mathieu P. Metabolic syndrome is associated with faster degeneration of bioprosthetic valves. *Circulation*. 2006;114:I512-7.
48. Shahian DM, He X, Jacobs JP, Kurlansky PA, Badhwar V, Cleveland JC, Jr., Fazzalari FL, Filardo G, Normand SL, Furnary AP, Magee MJ, Rankin JS, Welke KF, Han J and O'Brien SM. The Society of Thoracic Surgeons Composite Measure of Individual Surgeon Performance for Adult Cardiac Surgery: A Report of The Society of Thoracic Surgeons Quality Measurement Task Force. *Ann Thorac Surg*. 2015;100:1315-24; discussion 1324-5.
49. Puvimanasinghe JP, Takkenberg JJ, Eijkemans MJ, Steyerberg EW, van Herwerden LA, Grunkemeier GL, Habbema JD and Bogers AJ. Choice of a mechanical valve or a bioprosthesis for AVR: does CABG matter? *Eur J Cardiothorac Surg*. 2003;23:688-95; discussion 695.
50. Rahimtoola SH. The problem of valve prosthesis-patient mismatch. *Circulation*. 1978;58:20-4.
51. Head SJ, Mokhles MM, Osnabrugge RL, Pibarot P, Mack MJ, Takkenberg JJ, Bogers AJ and Kappetein AP. The impact of prosthesis-patient mismatch on long-term survival after aortic valve replacement: a systematic review and meta-analysis of 34 observational studies comprising 27 186 patients with 133 141 patient-years. *Eur Heart J*. 2012;33:1518-29.
52. Pibarot P and Dumesnil JG. Prosthesis-patient mismatch: definition, clinical impact, and prevention. *Heart*. 2006;92:1022-9.
53. Castro LJ, Arcidi JM, Jr., Fisher AL and Gaudiani VA. Routine enlargement of the small aortic root: a preventive strategy to minimize mismatch. *Ann Thorac Surg*. 2002;74:31-6; discussion 36.
54. Coutinho GF, Correia PM, Pauperio G, de Oliveira F and Antunes MJ. Aortic root enlargement does not increase the surgical risk and short-term patient outcome? *Eur J Cardiothorac Surg*. 2011;40:441-7.
55. Svensson LG, Pillai ST, Rajeswaran J, Desai MY, Griffin B, Grimm R, Hammer DF, Thamilarasan M, Roselli EE, Pettersson GB, Gillinov AM, Navia JL, Smedira NG, Sabik JF, 3rd, Lytle BW and Blackstone EH. Long-term survival, valve durability, and reoperation for 4 aortic root procedures combined with ascending aorta replacement. *J Thorac Cardiovasc Surg*. 2016;151:764-71 e1-4.
56. Etz CD, Girrbach FF, von Aspern K, Battellini R, Dohmen P, Hoyer A, Luehr M, Misfeld M, Borger MA and Mohr FW. Longevity after aortic root replacement: is the mechanically valved conduit really the gold standard for quinquagenarians? *Circulation*. 2013;128:S253-62.
57. Gaudino M, Lau C, Munjal M, Avgerinos D and Girardi LN. Contemporary outcomes of surgery for aortic root aneurysms: A propensity-matched comparison of valve-sparing and composite valve graft replacement. *J Thorac Cardiovasc Surg*. 2015;150:1120-9 e1.
58. Badiu CC, Deutsch MA, Sideris C, Krane M, Hettich I, Voss B, Mazzitelli D and Lange R. Aortic root replacement: comparison of clinical outcome between different surgical techniques. *Eur J Cardiothorac Surg*. 2014;46:685-92; discussion 692.
59. Gillinov AM, Blackstone EH, Cosgrove DM, 3rd, White J, Kerr P, Marullo A, McCarthy PM and Lytle BW. Mitral valve repair with aortic valve replacement is superior to double valve replacement. *J Thorac Cardiovasc Surg*. 2003;125:1372-87.

60. Hamamoto M, Bando K, Kobayashi J, Satoh T, Sasako Y, Niwaya K, Tagusari O, Yagihara T and Kitamura S. Durability and outcome of aortic valve replacement with mitral valve repair versus double valve replacement. *Ann Thorac Surg*. 2003;75:28-33; discussion 33-4.
61. Leavitt BJ, Baribeau YR, DiScipio AW, Ross CS, Quinn RD, Olmstead EM, Sisto D, Likosky DS, Cochran RP, Clough RA, Boss RA, Jr., Kramer RS, O'Connor GT and Northern New England Cardiovascular Disease Study G. Outcomes of patients undergoing concomitant aortic and mitral valve surgery in northern new England. *Circulation*. 2009;120:S155-62.
62. Rouze S, Flecher E, Revest M, Anselmi A, Aymami M, Roisne A, Guihaire J and Verhoye JP. Infective Endocarditis With Paravalvular Extension: 35-Year Experience. *Ann Thorac Surg*. 2016;102:549-55.
63. Savage EB, Saha-Chaudhuri P, Asher CR, Brennan JM and Gammie JS. Outcomes and prosthesis choice for active aortic valve infective endocarditis: analysis of the Society of Thoracic Surgeons Adult Cardiac Surgery Database. *Ann Thorac Surg*. 2014;98:806-14.
64. Klieverik LM, Yacoub MH, Edwards S, Bekkers JA, Roos-Hesselink JW, Kappetein AP, Takkenberg JJ and Bogers AJ. Surgical treatment of active native aortic valve endocarditis with allografts and mechanical prostheses. *Ann Thorac Surg*. 2009;88:1814-21.
65. Langley SM, Alexiou C, Stafford HM, Dalrymple-Hay MJ, Haw MP, Livesey SA and Monro JL. Aortic valve replacement for endocarditis: determinants of early and late outcome. *J Heart Valve Dis*. 2000;9:697-704.
66. Nguyen DT, Delahaye F, Obadia JF, Duval X, Selton-Suty C, Carteaux JP, Hoen B, Alla F and group As. Aortic valve replacement for active infective endocarditis: 5-year survival comparison of bioprostheses, homografts and mechanical prostheses. *Eur J Cardiothorac Surg*. 2010;37:1025-32.
67. Delahaye F, Chu VH, Altclas J, Barsic B, Delahaye A, Freiberger T, Gordon DL, Hannan MM, Hoen B, Kanj SS, Lejko-Zupanc T, Mestres CA, Pachirat O, Pappas P, Lamas C, Selton-Suty C, Tan R, Tattevin P, Wang A and International Collaboration on Endocarditis Prospective Cohort Study I. One-year outcome following biological or mechanical valve replacement for infective endocarditis. *Int J Cardiol*. 2015;178:117-23.
68. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, Blatchford J, Devenny K, Friedman J, Guiver K, Harper R, Khder Y, Lobmeyer MT, Maas H, Voigt JU, Simoons ML, Van de Werf F and Investigators R-A. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med*. 2013;369:1206-14.
69. Koertke H, Zittermann A, Tenderich G, Wagner O, El-Arousy M, Krian A, Ennker J, Taborski U, Klovekorn WP, Moosdorf R, Saggau W and Koerfer R. Low-dose oral anticoagulation in patients with mechanical heart valve prostheses: final report from the early self-management anticoagulation trial II. *Eur Heart J*. 2007;28:2479-84.
70. Puskas J, Gerdisch M, Nichols D, Quinn R, Anderson C, Rhenman B, Fermin L, McGrath M, Kong B, Hughes C, Sethi G, Wait M, Martin T, Graeve A and Investigators P. Reduced anticoagulation after mechanical aortic valve replacement: interim results from the prospective randomized on-X valve anticoagulation clinical trial randomized Food and Drug Administration investigational device exemption trial. *J Thorac Cardiovasc Surg*. 2014;147:1202-1210; discussion 1210-1.
71. Heneghan C, Ward A, Perera R, Self-Monitoring Trialist C, Bankhead C, Fuller A, Stevens R, Bradford K, Tyndel S, Alonso-Coello P, Ansell J, Beyth R, Bernardo A, Christensen TD, Cromheecke ME, Edson RG, Fitzmaurice D, Gadisseur AP, Garcia-Alamino JM, Gardiner C, Hasenkam JM, Jacobson A, Kaatz S, Kamali F, Khan TI, Knight E, Kortke H, Levi M, Matchar D, Menendez-Jandula B, Rakovac I, Schaefer C, Siebenhofer A, Souto JC, Sunderji R, Gin K, Shalansky K, Voller H, Wagner O and Zittermann A. Self-monitoring of oral anticoagulation: systematic review and meta-analysis of individual patient data. *Lancet*. 2012;379:322-34.

72. Scotten LN and Siegel R. Are anticoagulant independent mechanical valves within reach-fast prototype fabrication and in vitro testing of innovative bi-leaflet valve models. *Ann Transl Med*. 2015;3:197.
73. www.triflomedical.com.
74. Pache G, Schoechlin S, Blanke P, Dorfs S, Jander N, Arepalli CD, Gick M, Buettner HJ, Leipsic J, Langer M, Neumann FJ and Ruile P. Early hypo-attenuated leaflet thickening in balloon-expandable transcatheter aortic heart valves. *Eur Heart J*. 2016;37:2263-71.
75. Egbe AC, Pislaru SV, Pellikka PA, Poterucha JT, Schaff HV, Maleszewski JJ and Connolly HM. Bioprosthetic Valve Thrombosis Versus Structural Failure: Clinical and Echocardiographic Predictors. *J Am Coll Cardiol*. 2015;66:2285-94.
76. Iung B and Rodes-Cabau J. The optimal management of anti-thrombotic therapy after valve replacement: certainties and uncertainties. *Eur Heart J*. 2014;35:2942-9.
77. Aramendi JI, Mestres CA, Martinez-Leon J, Campos V, Munoz G and Navas C. Triflusal versus oral anticoagulation for primary prevention of thromboembolism after bioprosthetic valve replacement (trac): prospective, randomized, co-operative trial. *Eur J Cardiothorac Surg*. 2005;27:854-60.
78. Gherli T, Colli A, Fragnito C, Nicolini F, Borrello B, Saccani S, D'Amico R and Beghi C. Comparing warfarin with aspirin after biological aortic valve replacement: a prospective study. *Circulation*. 2004;110:496-500.
79. Brennan JM, Edwards FH, Zhao Y, O'Brien S, Booth ME, Dokholyan RS, Douglas PS, Peterson ED and Team DEAR. Early anticoagulation of bioprosthetic aortic valves in older patients: results from the Society of Thoracic Surgeons Adult Cardiac Surgery National Database. *J Am Coll Cardiol*. 2012;60:971-7.
80. Merie C, Kober L, Skov Olsen P, Andersson C, Gislason G, Skov Jensen J and Torp-Pedersen C. Association of warfarin therapy duration after bioprosthetic aortic valve replacement with risk of mortality, thromboembolic complications, and bleeding. *JAMA*. 2012;308:2118-25.
81. Suri RM, Zehr KJ, Sundt TM, 3rd, Dearani JA, Daly RC, Oh JK and Schaff HV. Left ventricular mass regression after porcine versus bovine aortic valve replacement: a randomized comparison. *Ann Thorac Surg*. 2009;88:1232-7.
82. Chambers JB, Rajani R, Parkin D, Rimington HM, Blauth CI, Venn GE, Young CP and Roxburgh JC. Bovine pericardial versus porcine stented replacement aortic valves: early results of a randomized comparison of the Perimount and the Mosaic valves. *J Thorac Cardiovasc Surg*. 2008;136:1142-8.
83. Ruzicka DJ, Hettich I, Hutter A, Bleiziffer S, Badiu CC, Bauernschmitt R, Lange R and Eichinger WB. The complete supraannular concept: in vivo hemodynamics of bovine and porcine aortic bioprostheses. *Circulation*. 2009;120:S139-45.
84. Yap KH, Murphy R, Devbhandari M and Venkateswaran R. Aortic valve replacement: is porcine or bovine valve better? *Interact Cardiovasc Thorac Surg*. 2013;16:361-73.
85. Ganapathi AM, Englum BR, Keenan JE, Schechter MA, Wang H, Smith PK, Glower DD and Hughes GC. Long-Term Survival After Bovine Pericardial Versus Porcine Stented Bioprosthetic Aortic Valve Replacement: Does Valve Choice Matter? *Ann Thorac Surg*. 2015;100:550-9.
86. Hickey GL, Grant SW, Bridgewater B, Kendall S, Bryan AJ, Kuo J and Dunning J. A comparison of outcomes between bovine pericardial and porcine valves in 38,040 patients in England and Wales over 10 years. *Eur J Cardiothorac Surg*. 2015;47:1067-74.
87. Andreas M, Wallner S, Ruetzler K, Wiedemann D, Ehrlich M, Heinze G, Binder T, Moritz A, Hiesmayr MJ, Kocher A and Laufer G. Comparable long-term results for porcine and pericardial prostheses after isolated aortic valve replacement. *Eur J Cardiothorac Surg*. 2015;48:557-61.

88. Grunkemeier GL, Furnary AP, Wu Y, Wang L and Starr A. Durability of pericardial versus porcine bioprosthetic heart valves. *J Thorac Cardiovasc Surg*. 2012;144:1381-6.
89. Bavaria JE, Desai ND, Cheung A, Petracek MR, Groh MA, Borger MA and Schaff HV. The St Jude Medical Trifecta aortic pericardial valve: results from a global, multicenter, prospective clinical study. *J Thorac Cardiovasc Surg*. 2014;147:590-7.
90. Head SJ, Mylotte D, Mack MJ, Piazza N, van Mieghem NM, Leon MB, Kappetein AP and Holmes DR, Jr. Considerations and Recommendations for the Introduction of Objective Performance Criteria for Transcatheter Aortic Heart Valve Device Approval. *Circulation*. 2016;133:2086-93.
91. Anselmi A, Ruggieri VG, Lelong B, Flecher E, Corbineau H, Langanay T, Verhoye JP and Leguerrier A. Mid-term durability of the trifecta bioprosthesis for aortic valve replacement. *J Thorac Cardiovasc Surg*. 2016.
92. Colli A, Marchetto G, Salizzoni S, Rinaldi M, Di Marco L, Pacini D, Di Bartolomeo R, Nicolini F, Gherli T, Agrifoglio M, Borghetti V, Khoury G, De Paolis M, Zoffoli G, Mangino D, Amorim MJ, Manzan E, Zucchetta F, Balduzzi S and Gerosa G. The TRIBECA study: (TRI)fecta (B)ioprosthesis (E)valuation versus (C)arpentier Magna-Ease in (A)ortic position. *Eur J Cardiothorac Surg*. 2016;49:478-85.
93. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG and Investigators P. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. *N Engl J Med*. 2016;374:1609-20.
94. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, Webb JG, Douglas PS, Anderson WN, Blackstone EH, Kodali SK, Makkar RR, Fontana GP, Kapadia S, Bavaria J, Hahn RT, Thourani VH, Babaliaros V, Pichard A, Herrmann HC, Brown DL, Williams M, Akin J, Davidson MJ, Svensson LG and investigators Pt. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015;385:2477-84.
95. Thourani VH, Kodali S, Makkar RR, Herrmann HC, Williams M, Babaliaros V, Smalling R, Lim S, Malaisrie SC, Kapadia S, Szeto WY, Greason KL, Kereiakes D, Ailawadi G, Whisenant BK, Devireddy C, Leipsic J, Hahn RT, Pibarot P, Weissman NJ, Jaber WA, Cohen DJ, Suri R, Tuzcu EM, Svensson LG, Webb JG, Moses JW, Mack MJ, Miller DC, Smith CR, Alu MC, Parvataneni R, D'Agostino RB, Jr. and Leon MB. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. *Lancet*. 2016;387:2218-25.
96. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J, Jr., Kleiman NS, Chetcuti S, Heiser J, Merhi W, Zorn G, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte J, Maini B, Mumtaz M, Chenoweth S, Oh JK and Investigators USCC. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med*. 2014;370:1790-8.
97. Thyregod HG, Steinbruchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, Chang Y, Franzen OW, Engstrom T, Clemmensen P, Hansen PB, Andersen LW, Olsen PS and Sondergaard L. Transcatheter Versus Surgical Aortic Valve Replacement in Patients With Severe Aortic Valve Stenosis: 1-Year Results From the All-Comers NOTION Randomized Clinical Trial. *J Am Coll Cardiol*. 2015;65:2184-94.
98. Head SJ, Kaul S, Bogers AJ and Kappetein AP. Non-inferiority study design: lessons to be learned from cardiovascular trials. *Eur Heart J*. 2012;33:1318-24.

99. Dvir D, Webb JG, Bleiziffer S, Pasic M, Waksman R, Kodali S, Barbanti M, Latib A, Schaefer U, Rodes-Cabau J, Treede H, Piazza N, Hildick-Smith D, Himbert D, Walther T, Hengstenberg C, Nissen H, Bekeredjian R, Presbitero P, Ferrari E, Segev A, de Weger A, Windecker S, Moat NE, Napodano M, Wilbring M, Cerillo AG, Brecker S, Tchetche D, Lefevre T, De Marco F, Fiorina C, Petronio AS, Teles RC, Testa L, Laborde JC, Leon MB, Kornowski R and Valve-in-Valve International Data Registry I. Transcatheter aortic valve implantation in failed bioprosthetic surgical valves. *JAMA*. 2014;312:162-70.
100. Mylotte D, Andalib A, Theriault-Lauzier P, Dorfmeister M, Girgis M, Alharbi W, Chetrit M, Galatas C, Mamane S, Sebag I, Buithieu J, Bilodeau L, de Varennes B, Lachapelle K, Lange R, Martucci G, Virmani R and Piazza N. Transcatheter heart valve failure: a systematic review. *Eur Heart J*. 2015;36:1306-27.
101. Ye J, Cheung A, Yamashita M, Wood D, Peng D, Gao M, Thompson CR, Munt B, Moss RR, Blanke P, Leipsic J, Dvir D and Webb JG. Transcatheter Aortic and Mitral Valve-in-Valve Implantation for Failed Surgical Bioprosthetic Valves: An 8-Year Single-Center Experience. *JACC Cardiovasc Interv*. 2015;8:1735-44.
102. Seiffert M, Conradi L, Baldus S, Knap M, Schirmer J, Franzen O, Koschyk D, Meinertz T, Reichenspurner H and Treede H. Impact of patient-prosthesis mismatch after transcatheter aortic valve-in-valve implantation in degenerated bioprostheses. *J Thorac Cardiovasc Surg*. 2012;143:617-24.
103. Berreklouw E, Koene B, De Somer F, Bouchez S, Chiers K, Taeymans Y and Van Nooten GJ. Sutureless replacement of aortic valves with St Jude Medical mechanical valve prostheses and Nitinol attachment rings: feasibility in long-term (90-day) pig experiments. *J Thorac Cardiovasc Surg*. 2011;141:1231-7 e1.
104. Sondergaard L, Steinbruchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, Ngo AT, Olsen NT, Chang Y, Franzen OW, Engstrom T, Clemmensen P, Olsen PS and Thyregod HG. Two-Year Outcomes in Patients With Severe Aortic Valve Stenosis Randomized to Transcatheter Versus Surgical Aortic Valve Replacement: The All-Comers Nordic Aortic Valve Intervention Randomized Clinical Trial. *Circ Cardiovasc Interv*. 2016;9.
105. Emmert MY and Hoerstrup SP. Tissue engineered heart valves: moving towards clinical translation. *Expert Rev Med Devices*. 2016;13:417-9.
106. Driessen-Mol A, Emmert MY, Dijkman PE, Frese L, Sanders B, Weber B, Cesarovic N, Sidler M, Leenders J, Jenni R, Grunenfelder J, Falk V, Baaijens FP and Hoerstrup SP. Transcatheter implantation of homologous "off-the-shelf" tissue-engineered heart valves with self-repair capacity: long-term functionality and rapid in vivo remodeling in sheep. *J Am Coll Cardiol*. 2014;63:1320-9.
107. Weber B, Scherman J, Emmert MY, Gruenenfelder J, Verbeek R, Bracher M, Black M, Kortsmit J, Franz T, Schoenauer R, Baumgartner L, Brokopp C, Agarkova I, Wolint P, Zund G, Falk V, Zilla P and Hoerstrup SP. Injectable living marrow stromal cell-based autologous tissue engineered heart valves: first experiences with a one-step intervention in primates. *Eur Heart J*. 2011;32:2830-40.
108. Yacoub MH and Takkenberg JJ. Will heart valve tissue engineering change the world? *Nat Clin Pract Cardiovasc Med*. 2005;2:60-1.
109. Sakamoto Y, Yoshitake M, Matsumura Y, Naruse H, Bando K and Hashimoto K. Choice of Aortic Valve Prosthesis in a Rapidly Aging and Long-Living Society. *Ann Thorac Cardiovasc Surg*. 2016.
110. Okamoto Y, Yamamoto K and Yoshii S. Early and Late Outcomes of Aortic Valve Replacement Using Bioprosthetic Versus Mechanical Valve in Elderly Patients: A Propensity Analysis. *J Card Surg*. 2016;31:195-202.

111. Wang Y, Chen S, Shi J, Li G and Dong N. Mid- to long-term outcome comparison of the Medtronic Hancock II and bi-leaflet mechanical aortic valve replacement in patients younger than 60 years of age: a propensity-matched analysis. *Interact Cardiovasc Thorac Surg*. 2016;22:280-6.
112. Roumieh M, Ius F, Tudorache I, Ismail I, Fleissner F, Haverich A and Cebotari S. Comparison between biological and mechanical aortic valve prostheses in middle-aged patients matched through propensity score analysis: long-term results. *Eur J Cardiothorac Surg*. 2015;48:129-36.
113. McClure RS, McGurk S, Cevasco M, Maloney A, Gosev I, Wiegerinck EM, Salvio G, Tokmaji G, Borstlap W, Nauta F and Cohn LH. Late outcomes comparison of nonelderly patients with stented bioprosthetic and mechanical valves in the aortic position: a propensity-matched analysis. *J Thorac Cardiovasc Surg*. 2014;148:1931-9.
114. Badhwar V, Ofenloch JC, Rovin JD, van Gelder HM and Jacobs JP. Noninferiority of closely monitored mechanical valves to bioprostheses overshadowed by early mortality benefit in younger patients. *Ann Thorac Surg*. 2012;93:748-53.
115. Weber A, Noureddine H, Englberger L, Dick F, Gahl B, Aymard T, Czerny M, Tevaearai H, Stalder M and Carrel TP. Ten-year comparison of pericardial tissue valves versus mechanical prostheses for aortic valve replacement in patients younger than 60 years of age. *J Thorac Cardiovasc Surg*. 2012;144:1075-83.
116. Ashikhmina EA, Schaff HV, Dearani JA, Sundt TM, 3rd, Suri RM, Park SJ, Burkhart HM, Li Z and Daly RC. Aortic valve replacement in the elderly: determinants of late outcome. *Circulation*. 2011;124:1070-8.
117. Brown ML, Schaff HV, Lahr BD, Mullany CJ, Sundt TM, Dearani JA, McGregor CG and Orszulak TA. Aortic valve replacement in patients aged 50 to 70 years: improved outcome with mechanical versus biologic prostheses. *J Thorac Cardiovasc Surg*. 2008;135:878-84; discussion 884.
118. Polomsky M, Kilgo PD, Puskas JD, Halkos ME, Thourani VH, Kelli HM, Guyton RA and Lattouf OM. Long-term survival for patients with metabolic syndrome after bioprosthetic or mechanical valve replacement. *J Card Surg*. 2014;29:26-34.
119. Gaca JG, Clare RM, Rankin JS, Daneshmand MA, Milano CA, Hughes GC, Wolfe WG, Glower DD and Smith PK. Risk-adjusted survival after tissue versus mechanical aortic valve replacement: a 23-year assessment. *J Heart Valve Dis*. 2013;22:810-6.
120. Ruel M, Chan V, Bedard P, Kulik A, Ressler L, Lam BK, Rubens FD, Goldstein W, Hendry PJ, Masters RG and Mesana TG. Very long-term survival implications of heart valve replacement with tissue versus mechanical prostheses in adults <60 years of age. *Circulation*. 2007;116:I294-300.
121. Carrier M, Pellerin M, Perrault LP, Page P, Hebert Y, Cartier R, Dyrda I and Pelletier LC. Aortic valve replacement with mechanical and biologic prosthesis in middle-aged patients. *Ann Thorac Surg*. 2001;71:S253-6.
122. Khan SS, Trento A, DeRobertis M, Kass RM, Sandhu M, Czer LS, Blanche C, Raissi S, Fontana GP, Cheng W, Chaux A and Matloff JM. Twenty-year comparison of tissue and mechanical valve replacement. *J Thorac Cardiovasc Surg*. 2001;122:257-69.
123. Peterseim DS, Cen YY, Cheruvu S, Landolfo K, Bashore TM, Lowe JE, Wolfe WG and Glower DD. Long-term outcome after biologic versus mechanical aortic valve replacement in 841 patients. *J Thorac Cardiovasc Surg*. 1999;117:890-7.
124. Jamieson WR, Munro AI, Burr LH, Germann E, Miyagishima RT and Ling H. Influence of coronary artery bypass and age on clinical performance after aortic and mitral valve replacement with biological and mechanical prostheses. *Circulation*. 1995;92:II101-6.

## APPENDIX

### PubMed search

"aortic valve replacement AND mechanical [tiab] AND (biologic [tiab] OR biological [tiab] OR bioprosthetic [tiab] OR bioprosthesis [tiab] OR tissue [tiab]) AND (propensity [tiab] OR multivariate [tiab] OR multivariable [tiab] OR random* [tiab] OR adjust* [tiab] OR independent [tiab])"

# 5 Anticoagulation after mechanical aortic valve implantation: Is it time to act after PROACT?

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Anticoagulation management after mechanical prosthetic heart valve (PHV) implantation should find the delicate balance between effectively preventing valve-related thromboembolic events while not substantially increasing the risk of bleeding.[1] Mechanical PHVs traditionally require lifelong anticoagulation with vitamin K antagonists (VKAs). VKAs have a narrow therapeutic range, a delayed on- and offset of action, and their effect is influenced by dietary vitamin K intake and numerous drug interactions, which necessitates high patient compliance and lifelong monitoring of the International Normalized Ratio (INR).[2] Moreover, there is a considerable life-time bleeding risk associated with VKAs, especially considering that the time spent in the therapeutic range (TTR) might be as low as 50% in some cases.[3] The wish to avoid long-term anticoagulation is reflected in the recent trends of PHV utilization, favoring biological over mechanical valves despite their inferior long-term durability.[4] However, efforts are made to reduce the intensity and burden of anticoagulation after mechanical heart valve implantation[5-7] or to completely replace VKAs with alternative antithrombotic therapy in patients that do require a mechanical valve.[8] Another potential advancement that could completely eliminate the use of VKAs would be the development of novel mechanical heart valves not requiring anticoagulation.[9,10] The On-X valve (Cryolife, Kennesaw, GA, US) is designed with the intention to promote physiological blood flow and low thrombogenicity after mechanical PHV implantation by using a silicon-free pyrolytic carbon and allowing for 90-degrees leaflet opening.[11]



In a recent article, Puskas and colleagues reported long-term follow-up of the PROACT (Prospective Randomized On-X Anticoagulation Clinical Trial) study, which investigated the non-inferiority of a lowered target INR (range 1.5 to 2.0) combined with low-dose acetylsalicylic acid ("high-risk arm") or dual antiplatelet therapy (DAPT, "low-risk arm") over standard anticoagulation with warfarin in patients undergoing mechanical aortic valve replacement (AVR) with the On-X valve.[11] The investigational therapy commenced 3 months after surgery, following a period of formal anticoagulation. PROACT enrolled 576 participants (n=375 in the high-risk arm and n=201 in the low-risk arm) and the primary endpoint of the study was the composite of major and minor bleeding, thromboembolic events, and valve thrombosis. Interim results of the PROACT high-risk arm were already published in 2014[5], and played a major role in the regulatory approval of the lowered target INR range labeling claim by On-X. These results were also incorporated in the most recent American clinical practice guidelines on the management of valvular heart disease.[12] This final report includes extended follow-up of the high-risk patients, and reports outcomes of the low-risk arm.

In the high-risk arm, the incidence of the combined primary endpoint was 5.50% per patient-year (%/py) versus 9.35%/py (p=0.002) in patients receiving reduced and standard intensity anticoagulation, respectively. The incidence of bleeding was lower with reduced versus standard intensity warfarin (2.86%/py versus 7.43%/py, respec-

tively; p<0.001), without affecting the incidences of valve thrombosis (0.21%/py versus 0.18%/py; p=0.90), stroke (0.74%/py versus 0.64%/py; p=0.80), transient ischemic attack (1.27%/py versus 1.01%/py; p=0.60), peripheral thromboembolism (0.42%/py versus 0.09%/py; p=0.20) or all cause-mortality (1.38%/py versus 1.56%/py; p=0.70) in patients with reduced and standard anticoagulation, respectively. We performed additional analyses to calculate the incidence rate and rate ratio of all the thromboembolic events (neurological events, peripheral thromboembolic events, and valve thrombosis combined) in the high-risk arm: the incidence of thromboembolic events was 2.64%/py versus 1.92%/py (rate ratio: 1.37, 95% CI 0.77-2.45; p=0.28) in patients receiving reduced and standard intensity anticoagulation, respectively. In the low-risk arm, the incidence of thromboembolic events was significantly higher in patients receiving DAPT versus standard anticoagulation (4.86%/py versus 0.29%/py, respectively; p=0.02), while no difference in the incidence of bleeding between the two groups was noted (3.82%/py versus 3.49%/py, respectively; p=0.80).

This report reinforces the safety of lowered INR ranges after mechanical AVR with the On-X valve. However, we cannot exclude the possibility that the safety of a lowered INR range after mechanical AVR might also apply to other modern bileaflet mechanical PHVs. Indeed, there are no studies comparing thromboembolic risk between different modern bileaflet mechanical PHVs. Nevertheless, several studies have been published supporting this notion.[6,7,13,14] Recently, a post-hoc analysis of the LOWERING-IT (LOWERing the INtensity of oral anticoaGulant Therapy in patients with bileaflet mechanical aortic valve replacement) trial that focused on 292 patients receiving LivaNova Bicarbon mechanical aortic valves (LivaNova, London, United Kingdom) concluded that a lowered INR target (range 1.5–2.5 n=148) was equally safe in terms of thromboembolic complications when compared to standard anticoagulation (range INR 2.0–3.0; n=144), while significantly less bleeding events occurred in the low INR group.[13] In the ESCAT III (Early Self-Controlled Anticoagulation Trial) study, a lower INR target (range 1.6-2.1) with self-management was found to be superior when compared to standard anticoagulation (INR target 1.8-2.8) in terms of bleeding risk, and comparable in terms of thrombotic risk in a large cohort undergoing mechanical AVR, mostly receiving St Jude valves (Abbott, Chicago, IL, US).[7]

Despite these positive findings in the high-risk arm, the results for the low-risk arm were less assuring. Although previous data suggested that thromboembolic events after mechanical PHV implantation are linked to platelet activation[15] and might be prevented with the use of DAPT[16], the PROACT low-risk arm that investigated DAPT versus standard anticoagulation had to be terminated due to an excess in thromboembolic events in the DAPT group without a benefit in terms of bleeding rates. Of note, the previous CAPTA (Clopidogrel and Aspirin in the Prevention of Thromboembolic Complications After Mechanical Aortic Valve Replacement) study, enrolling 200 patients to compare DAPT with

warfarin in mechanical AVR, was stopped prematurely due to similar reasons.[17] Even though the design of the On-X valve is believed to be less thrombogenic as compared with many other valves used in the CAPTA trial[11], exclusive antiplatelet therapy with aspirin and clopidogrel still does not appear to be safe after mechanical AVR with the On-X valve. Of note, novel antiplatelet drugs – ticagrelor and prasugrel – have proven to be more effective when compared to clopidogrel in patients with coronary artery disease[18,19], and it needs to be determined whether these more potent P2Y12-inhibitors in combination with aspirin may potentially have a role as antithrombotic therapy in a population of patients with mechanical PHVs.

The PROACT study has some aspects to consider when interpreting the result. Firstly, due to the relatively low number of participants and the choice of the composite endpoint (grouping two clinical events that move in opposite directions, e.g. bleeding and thrombosis), the design and statistical power of the study have been questioned.[5] Secondly, in the high-risk arm, 22 patients (12%) in the lowered INR group suffered a thromboembolic event that required cross-over to standard anticoagulation. In real-world clinical practice, it will be imperative to identify which patients are at risk of a thromboembolic event with a lower INR range before reducing the intensity of anticoagulation. Thirdly, in the PROACT high-risk arm, a combination of warfarin and aspirin was tested and not a lowered dose of warfarin alone. Therefore, it is unclear whether the findings of PROACT would also be applicable for lowered warfarin dosage alone. Finally, all patients assigned to receive warfarin in the PROACT study received an INR testing device for weekly self-monitoring.[7,20] This set-up is ideal to optimize INR control and increase patient comfort[21], but makes it difficult to extrapolate the study results to a population that does not monitor INR at home since self-monitoring might have an additional protective effect by increasing patients' consciousness and compliance with the anticoagulation therapy.

In conclusion, the PROACT study adds to the growing body of evidence of the feasibility of a lowered INR range in high-risk patients undergoing mechanical AVR with the On-X valve. However, these lower INR targets are safe in a strategy with concomitant aspirin therapy and with self-monitoring INR values, and it is imperative to note that new studies are required before the 1.5-2.0 INR range can be adopted without aspirin therapy or with less rigorous INR-monitoring. Further studies will add to the growing knowledge of the feasibility of a lowered target INR range after mechanical AVR other than the On-X valve (clinicaltrials.gov identifier: NCT03636295). However, it appears that eliminating anticoagulation completely is not safe and is not an acceptable strategy, even in low-risk patients.

## REFERENCES


1. Head SJ, Celik M, Kappetein AP. Mechanical versus bioprosthetic aortic valve replacement. Eur Heart J. 2017;38(28):2183-91.
2. Shameem R, Ansell J. Disadvantages of VKA and requirements for novel anticoagulants. Best Pract Res Clin Haematol. 2013;26(2):103-14.
3. Poli D, Antonucci E, Pengo V, Migliaccio L, Testa S, Lodigiani C, et al. Mechanical prosthetic heart valves: Quality of anticoagulation and thromboembolic risk. The observational multicenter PLECTRUM study. Int J Cardiol. 2018;267:68-73.
4. Isaacs AJ, Shuhaiber J, Salemi A, Isom OW, Sedrakyan A. National trends in utilization and in-hospital outcomes of mechanical versus bioprosthetic aortic valve replacements. The Journal of thoracic and cardiovascular surgery. 2015;149(5):1262-9 e3.
5. Puskas J, Gerdisch M, Nichols D, Quinn R, Anderson C, Rhenman B, et al. Reduced anticoagulation after mechanical aortic valve replacement: interim results from the prospective randomized on-X valve anticoagulation clinical trial randomized Food and Drug Administration investigational device exemption trial. The Journal of thoracic and cardiovascular surgery. 2014;147(4):1202-10; discussion 10-1.
6. Koertke H, Zittermann A, Tenderich G, Wagner O, El-Arousy M, Krian A, et al. Low-dose oral anticoagulation in patients with mechanical heart valve prostheses: final report from the early self-management anticoagulation trial II. Eur Heart J. 2007;28(20):2479-84.
7. Koertke H, Zittermann A, Wagner O, Secer S, Christ of H, Sciangula A, et al. Telemedicine-guided, very low-dose international normalized ratio self-control in patients with mechanical heart valve implants. Eur Heart J. 2015;36(21):1297-305.
8. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, et al. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med. 2013;369(13):1206-14.
9. Triflo Medical. www.novostia.com (16 August 2018) [Internet].
10. Scotten LN, Siegel R. Are anticoagulant independent mechanical valves within reach-fast prototype fabrication and in vitro testing of innovative bi-leaflet valve models. Ann Transl Med. 2015;3(14):197.
11. CryoLife. www.cryolife.com (16 August 2018) [Internet].
12. Puskas JD, Gerdisch M, Nichols D, Fermin L, Rhenman B, Kapoor D, et al. Anticoagulation and Antiplatelet Strategies After On-X Mechanical Aortic Valve Replacement. J Am Coll Cardiol. 2018;71(24):2717-26.
13. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017.
14. Torella M, Aquila I, Chiodini P, Amarelli C, Romano G, Della Ratta EE, et al. Low-dose anticoagulation after isolated mechanical aortic valve replacement with Liva Nova Bicarbon prosthesis: A post hoc analysis of LOWERING-IT Trial. Sci Rep. 2018;8(1):8405.
15. Torella M, Torella D, Chiodini P, Franciulli M, Romano G, De Santo L, et al. LOWERing the INtensity of oral anticoaGulant Therapy in patients with bileaflet mechanical aortic valve replacement: results from the "LOWERING-IT" Trial. Am Heart J. 2010;160(1):171-8.
16. Becker RC, Eisenberg P, Turpie AG. Pathobiologic features and prevention of thrombotic complications associated with prosthetic heart valves: fundamental principles and the contribution of platelets and thrombin. Am Heart J. 2001;141(6):1025-37.

17. Garcia-Rinaldi R. Antiplatelet therapy as sole anticoagulant in patients with aortic mechanical prostheses. The Journal of thoracic and cardiovascular surgery. 2014;148(6):3255-6.
18. Schlitt A, von Bardeleben RS, Ehrlich A, Eimermacher A, Peetz D, Dahm M, et al. Clopidogrel and aspirin in the prevention of thromboembolic complications after mechanical aortic valve replacement (CAPTA). Thrombosis research. 2003;109(2-3):131-5.
19. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361(11):1045-57.
20. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357(20):2001-15.
21. Matchar DB, Love SR, Jacobson AK, Edson R, Uyeda L, Phibbs CS, et al. The impact of frequency of patient self-testing of prothrombin time on time in target range within VA Cooperative Study #481: The Home INR Study (THINRS), a randomized, controlled trial. J Thromb Thrombolysis. 2015;40(1):17-25.
22. Sawicki PT. A structured teaching and self-management program for patients receiving oral anticoagulation: a randomized controlled trial. Working Group for the Study of Patient Self-Management of Oral Anticoagulation. JAMA. 1999;281(2):145-50.

# 6 Mortality in low-risk patients with aortic stenosis undergoing transcatheter or surgical aortic valve replacement: a reconstructed individual patient data meta-analysis

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## GRAPHICAL ABSTRACT

**Key question:** compare the incidence of all-cause mortality after transcatheter and surgical aortic valve replacement.
**Key findings:** transcatheter aortic valve replacement has higher incidence of all-cause mortality during long-term follow-up.
**Take-home message:** SAVR should be considered in all low-risk patients with severe AS.

## ABSTRACT

**Objectives:** Although the standard of care for patients with severe aortic stenosis (AS) at low surgical risk has included surgical aortic valve replacement (SAVR) since the mid-1960s, many clinical studies have investigated whether transcatheter aortic valve implantation (TAVI) might be a better approach in these patients. Because no individual study has been powered to detect the difference in mortality between these two treatment strategies, we did a reconstructive individual patient data analysis to study the long-term difference of all-cause mortality.
**Methods:** Randomized clinical trials (RCTs) and propensity score matched (PSM) studies that included low-risk adult patients with severe AS undergoing either SAVR or TAVI and with reports on the mortality rates during follow-up were considered. The primary outcome was all-cause mortality up to 5 years.
**Results:** In the reconstructed individual patient data analysis, there was no statistically significant difference in all-cause mortality between TAVI and SAVR at 5-year of follow-up (30.7% versus 21.4%, HR 1.19, 95% CI 0.96-1.48, P=0.104). However, landmark analyses in patients surviving up to 1-year of follow-up show significant higher all-cause mortality at 5-years of follow-up (27.5% vs 17.3%, HR 1.77, 95% CI 1.29-2.43, P<0.001), in patients undergoing TAVI compared to patients undergoing SAVR, respectively.
**Conclusions:** This reconstructed individual patient data analysis in low-risk patients with severe AS demonstrates that 5-year all-cause mortality rates are higher after TAVI compared with SAVR, driven by markedly higher mortality rates between 1- and 5-years of follow-up in the TAVI group. The present results call for caution in expanding TAVI procedure as the treatment of choice for the majority of all low-risk patients until long-term data from contemporary RCTs are available.

## INTRODUCTION

Since the mid-1960s, surgical aortic valve replacement (SAVR) is the gold standard of care for treatment of patients with severe symptomatic aortic stenosis (AS) who are at low-risk for surgical mortality with year-by-year improvements in both short- and long-term outcomes.[1] In 2002, the first successful transcatheter aortic valve implantation (TAVI) was performed in an inoperable patient with calcified AS presenting with cardiogenic shock.[2] Rapidly, the beneficiary results of TAVI over medical therapy in inoperable patients[3] led toward the expansion of TAVI approach to high-risk patients.[4,5] Comparable results from randomized controlled trials (RCTs) and prospective registries in those at high-risk led to further expansion of TAVI toward patients who are at intermediate-risk for surgical mortality.[6,7] Moreover, this interventional approach is now widely indicated in the European and American Guidelines for the management of symptomatic AS as class I for high-risk and class IIa for intermediate risk patients.[8,9]

Recently published up to 2 years of follow-up results from the two large multicenter RCTs have enraged the debate of conducting TAVI as the first line treatment procedure in the majority of patients with severe AS irrespective of surgical risk.[10,11] Controversy exists whether available data is robust enough to justify further TAVI expansion to the low-risk population, which represents the vast majority of all AS cases (75-80%).[12] To date, the evidence is inconclusive on hard clinical outcomes, including all-cause mortality, due to the fact that all published studies lacked statistical power to detect differences in individual outcomes between TAVI and SAVR. Therefore, we performed a reconstructed individual patient data meta-analysis of RCTs and propensity-score matched (PSM) studies to compare the risk of all-cause mortality up to 5 years after TAVI and SAVR in low-risk symptomatic patients with severe AS.

## METHODS

The reporting of this study complies with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA-P) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Guidelines (Table S1).[13,14]

### Search strategy and study inclusion

The MEDLINE, Embase and Cochrane databases were searched from their inception to March 13th, 2020, for full-length, English-language, RCTs or PSM cohort studies that reported on low-risk patients with severe AS who were treated with either SAVR or transfemoral TAVI. The search strategy is provided in the Supplementary Material, Table

S2. Because the data sharing statements indicate confidentiality, the authors were not contacted for studies if data was unclear.

Two investigators (M.C. and A.P.D.) independently screened the search result in duplicate for eligibility. In case of disagreement, consensus was reached through discussion. Firstly, the title and abstract were reviewed, after which the remaining articles were reviewed in-depth. Relevant articles identified by cross-referencing were added manually to ensure no relevant studies were missed.

Study inclusion consisted of the following criteria: i) comparison of TAVI to SAVR, ii) inclusion of adult patients with severe AS quantified by at least an aortic valve area (AVA) of <1.0 $cm^2$ or an indexed AVA (iAVA) <0.6 $cm^2/m^2$, a jet velocity of >4.0 m/s, or a mean gradient of >40 mmHg; iii) inclusion of patients with low-risk, defined as the mean society of thoracic surgery [STS] score <4% or the logistic European System for Cardiac Operative Risk Evaluation [EuroSCORE] <10%; and iv) reporting at least the event based on valve replacement approach during follow-up .

**Data extraction**

After relevant articles were identified, two investigators (M.C. and A.P.D.) independently extracted clinically relevant data and those necessary for inclusion of the study in the present meta-analysis. Consensus was reached through discussion, in case of any disagreements. Study description data that was extracted included the location of the study, design of the study, the number of included patients, time span of patient inclusion, used transcatheter system, TAVI approach, whether the study used the VARC-II definition, and the primary objective of each study. As baseline characteristics data was extracted consisted of age, gender, left ventricular ejection fraction (LVEF) and used risk scores to assess the risk of surgical mortality was extracted as patient characteristics. Further, we did extract the amount of patients with diabetes mellitus, coronary artery disease, previous CVA, previous MI, peripheral vascular disease, atrial fibrillation, pre-existing pacemaker and proportion of patients in NYHA III/IV. Given the primary endpoint for the present analysis we extracted the total follow-up time, mean or median time of follow-up, and the number of events that occurred during this follow-up for our endpoint of interest. Furthermore, hazard ratios (HRs) with 95% confidence intervals (CI) were estimated from Kaplan-Meier (KM) survival curves. Risk of bias assessment was independently performed by two investigators (M.C. and M.M.M). Consensus was reached through discussion, in case of any disagreements. The Revised Cochrane Risk of Bias Tool for Randomized Controlled Trials versions 2.0 was used to assess the bias in the randomized trials[15], and the ROBIN-1 Risk of Bias Tool for Non-Randomized Controlled trials was used to assess the bias in observational studies.[16]

### Statistical analyses

Descriptive statistics were summarized as mean ± SD or crude numbers with percentages, where appropriate. The primary endpoint of this study was all-cause mortality at 5 years of follow-up. Due to the fact that the two largest RCTs used a 'modified intention-to-treat' principle in their study design which was virtually equal to 'as-treated' principle, the analysis was performed on an "as-treated" basis, whenever possible.

All-cause mortality following TAVI versus SAVR was compared using aggregated reconstructed individual patient data. Kaplan-Meier survival data was extracted per study with DigitizeIt (http://digitizeit.de). Per study extracted data was then reconstructed and visually compared with the original published data and the estimated KM curves did not demonstrate major graphical differences. If possible, reconstructed HRs were compared with the originally published estimates and their corresponding 95% CI.

Data was then reconstructed from the published Kaplan-Meier curves as previously described.[17,18] The reconstructed data was then used to obtain pooled cumulative incidences of all-cause mortality and Cox regression HRs with its corresponding 95% CI. Visual inspection of the Kaplan-Meier curves suggested a violation of the proportionality assumption. The proportional hazard assumption for the overall group was assessed based on the scaled Schoenfeld residuals, which was violated (p=0.042). Therefore, landmark analyses was used to describe the occurrence of all-cause mortality in time, within 1 year, and through 1 to 5-years. The hazards proportionality was further tested in the landmark subgroups, within the first year (p=0.017), and between 1- and 5-years (0.83). Further, a fully parametric model was used to obtain time-dependent HR (Royston-Parmar). In addition, a study level meta-analysis was performed using a random-effects model. Data analyses were performed using Stata (version 16.1, StataCorp, College Station, Texas, USA) and R software, version 3.5 (R Foundation, Vienna, Austria).



## RESULTS

### Description of included studies

We screened 2029 studies, of which 14 were judged potentially eligible during screening of titles and abstracts (Figure 1). The search strategy is added in the Supplementary Material, Table S2. Six studies met our inclusion criteria[10,11,19-22], including, 3 RCTs, and 3 PSM cohort studies. One study was evaluated per intention-to-treat basis[21], whereas the other 5 studies were analyzed per as-treated basis.[10,11,19,20,22] An overview of quality assessment is presented in Table S2 and S3. Most patients were male (60.5%) and aged above 70 years (Table 2). The transfemoral access was the most frequently used approach for TAVI. All RCTs reported perioperative procedural risk of mortality using STS-PROM at 30 days and in addition, 2 studies reported the logistic EuroSCORE (LES). The mean STS-PROM scores ranged from 1.9% to 3.0%.

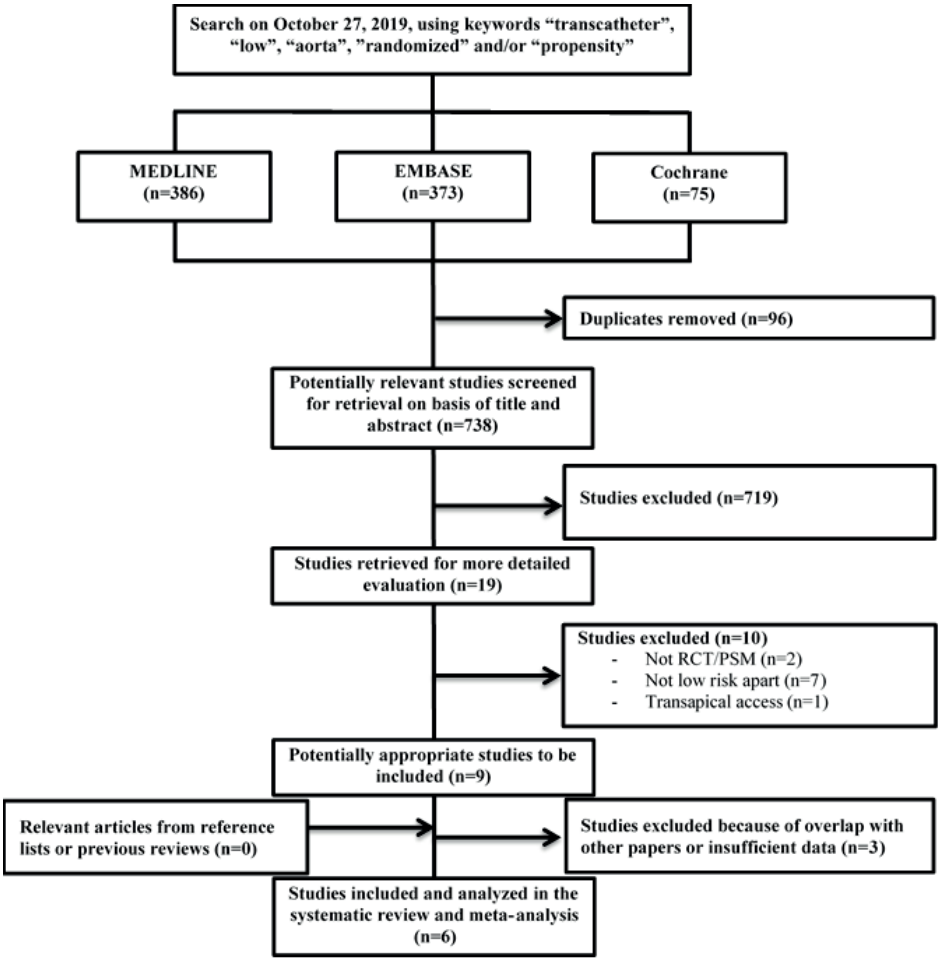


**Figure 1. Flow-chart of systematic literature search and study inclusion.**
A total of 2029 potentially relevant articles were screened of which 6 were finally eligible for this study. PSM, propensity score matched; RCTs, randomized controlled trials.

**Table 1. Characteristics of included studies**

| Study, year | No. patients | Period | Age (mean±SD) | STS risk score (mean±SD) | Design | Follow-up | Transcatheter system used | Type of approach for TAVI | VARC-II definition used | Primary Objective |
|---|---|---|---|---|---|---|---|---|---|---|
| **Schaefer, 2019** | 218 | 2009-2014 | 75.2±8.0 | 2.0±0.8* | PSM | 60m | N/A | Transfemoral 100% | Yes | All-cause mortality; 30-days |
| **Virtanen, 2019** | 608 | 2008-2017 | 78±5.4 | 2.1±0.7 | PSM | 36m | 3rd generation | Transfemoral 100% | No | All-cause mortality; 30-days and 3-year |
| **PARTNER 3, 2019** | 950 | 2016-2017 | 73.4±5.9 | 1.9±0.7 | RCT | 12m | SAPIEN 3 | Transfemoral 100% | Yes | Composite of all-cause mortality, stroke or rehospitalization; 1-year |
| **EVOLUT, 2019** | 1403 | 2016-2018 | 73.9±6.0 | 1.9±0.7 | RCT | 24m | CoreValve, Evolut R, Evolut PRO | Transfemoral 99.0%; direct aortic 0.4%, and subclavian 0.6% | Yes | Composite of all-cause mortality or stroke; 2-years |
| **NOTION, 2019** | 280 | 2009-2013 | 79.1±4.8 | 3.0±1.7 | RCT | 60m | CoreValve | Transfemoral 96.5%, subclavian 3.5% | Yes | Composite of all-cause mortality, stroke or MI; 1-year |
| **Rosato, 2016** | 710 | 2010-2012 | 80.1±5.8 | <4%* | PSM | 36m | SAPIEN XT, CoreValve | Transfemoral 91.1%, transapical 8.9% | No | All-cause mortality; 3-years |

*EuroSCORE II

**EuroSCORE**, European system for cardiac operative risk evaluation; **N/A**, not assessed; **PSM,** propensity score matching; **RCT** randomized controlled trial; **SD**, standard deviation; **VARC**, valve academic research consortium.

**Table 2. Baseline patients' characteristics***

| Study | | Number of patients | Mean age | Male (%) | STS (±SD) | Diabetes (%) | Left ventricular ejection fraction (±SD) | Coronary disease (N, %) | Previous CVA (N, %) | Previous MI (N, %) | Peripheral vascular disease (N, %) | Atrial Fibrillation (N, %) | Pre-existing pacemaker (N, %) | NYHA III or IV (N, %) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Schaefer, 2019** | **SAVR** | 109 | 74.4±7.5 | 46 (50) | 2.0±0.8 | 22 (24) | N/A | 29 (32) | 9 (10) | 5 (5) | N/A | N/A | N/A | 57 (62) |
| | **TAVI** | 109 | 75.9±8.4 | 46 (50) | 2.0±0.8 | 16 (17) | N/A | 30 (33) | 12 (13) | 4 (4) | N/A | N/A | N/A | 68 (74) |
| **Virtanen, 2019** | **SAVR** | 304 | 78.1±4.8 | 151 (49.7) | 2.1±0.5 | 68 (22.4) | N/A | 57 (18.8) | 24 (7.9) | N/A | N/A | 105 (34.5) | 15 (4.9) | N/A |
| | **TAVI** | 304 | 77.9±6.0 | 143 (47.0) | 2.1±0.9 | 68 (22.4) | N/A | 57 (18.8) | 26 (8.6) | N/A | N/A | 107 (35.2) | 21 (6.9) | N/A |
| **PARTNER 3, 2019** | **SAVR** | 454 | 73.6±6.1 | 323 (71.1) | 1.9±0.6 | 137/453 (30.2) | 66.2±8.6 | 127 (28.0) | 23/453 (5.1) | 26/452 (5.8) | 33/453 (7.3) | 85/453 (18.8) | 13 (2.9) | 108 (23.8) |
| | **TAVI** | 496 | 73.3±5.8 | 335 (67.5) | 1.9±0.7 | 155 (31.2) | 65.7±9.0 | 137/494 (27.7) | 17 (3.4) | 28/495 (5.7) | 34/494 (6.9) | 78 (15.7) | 12 (2.4) | 155 (31.2) |
| **EVOLUT, 2019** | **SAVR** | 678 | 73.6±5.9 | 449 (66.2) | 1.9±0.7 | 207 (30.5) | 61.9±7.7 | N/A | 80 (11.8) | 33 (4.9) | 56 (8.3) | N/A | 26 (3.8) | 193 (28.4) |
| | **TAVI** | 725 | 74.1±5.8 | 464 (64.0) | 1.9±0.7 | 228 (31.4) | 61.7±7.9 | N/A | 74 (10.2) | 48 (6.6) | 54/718 (7.5) | N/A | 23 (3.2) | 182 (25.1) |
| **NOTION, 2019** | **SAVR** | 135 | 79.0±4.7 | 71 (52.6) | 3.1±1.7 | 28 (20.7) | N/A | N/A | 22 (16.3) | 6 (4.4) | 9 (6.7) | N/A | 6 (4.4) | 61/134 (45.5) |
| | **TAVI** | 145 | 79.2±4.9 | 78 (53.8) | 2.9±1.6 | 26 (17.9) | N/A | N/A | 24 (16.6) | 8 (5.5) | 6 (4.1) | N/A | 5 (3.4) | 70/144 (48.6) |
| **Rosato, 2016** | **SAVR** | 355 | 80.0±5.1 | 209 (58.9) | N/A | 57 (16.1) | 304 (85.6) ‡ | 45 (12.7) | N/A | 29 (8.2) | 31 (8.7) | N/A | N/A | 182 (51.3) |
| | **TAVI** | 355 | 80.1±6.4 | 206 (58.0) | N/A | 53 (14.9) | 304 (85.6) ‡ | 56 (15.8) | N/A | 26 (7.3) | 36 (10.1) | N/A | N/A | 180 (50.7) |
| **Pooled** | **SAVR** | 2035 | 75.8±5.7 | 1249 (61.4) | 2.1±0.8 | 519 (25.5) | 63.6±8.1 | 258 (21.1) | 158 (9.4) | 99 (5.7) | 129 (8.0) | 190 (25.1) | 60 (3.8) | 601 (34.7) |
| | **TAVI** | 2134 | 75.9±6.0 | 1272 (59.6) | 2.0±0.8 | 546 (25.6) | 63.3±8.4 | 280 (22.2) | 153 (8.6) | 114 (6.2) | 130 (7.6) | 185 (23.1) | 61 (3.7) | 655 (35.8) |

*Plus-minus values are means ± SD

‡ ≥50% (n, %)

**CVA**, cerebrovascular accident; **MI** myocardial infarction; **N/A**, not applicable; **NYHA**, New York Heart Association; **SAVR**, surgical aortic valve replacement; **SD**, standard deviation; **STS**, society of thoracic surgeons; **TAVI**, transcatheter aortic valve implantation.

## Mortality

Our secondary pooled Kaplan-Meier analyses for the all-cause mortality showed significant difference in the rate of all-cause mortality at 30 days (1.1% vs. 1.8%, HR 0.59, 95% CI 0.35-0.99, P=0.048) in favour of TAVI. However no significant difference in the rate of all-cause mortality between TAVI and SAVR were noted at 1-year of follow-up (4.4% vs. 5.0%, HR 0.85, 95% CI 0.64-1.14, P=0.28), at 3-years of follow-up (18.7% vs. 12.4%, HR 1.17 95% CI 0.91-1.43, P=0.26), and at 5-year of follow-up (30.7% vs. 21.4%, HR 1.19, 95% CI 0.96-1.48, P=0.10) (Figure 2, respectively). At landmark analyses with patients surviving up to 1 year, the 5-year mortality was significantly higher after TAVI vs. SAVR (HR 1.77, 95% CI 1.29-2.43, P<0.001) (Figure 2). The early hazard was in favor of TAVI,

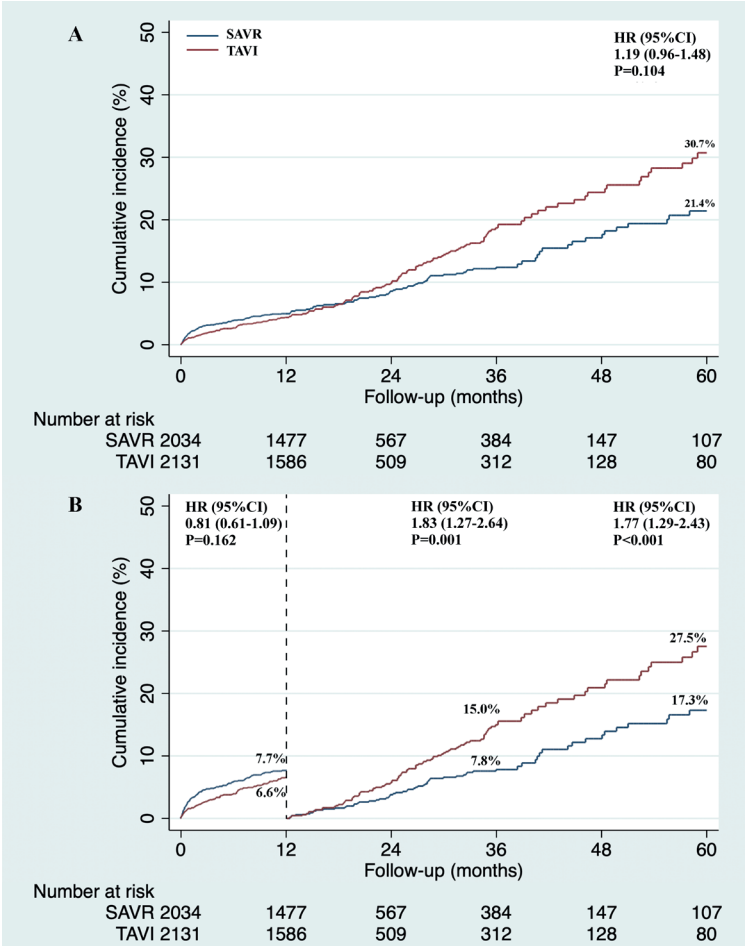


**Figure 2. A reconstructed pooled individual patient cumulative incidence of all-cause mortality in patients with low surgical risk undergoing either TAVI or SAVR.** A) shows the overall curve, B) shows a landmark analysis, HRs are given for 1-year, 3-year, and 5-year.

while over time this favor diminished and mortality was higher in TAVI. The crossover starts at approximately the first half year, significantly favoring SAVR after 24 months (Figure 3). In addition, a study-level meta-analysis on all-cause mortality was performed. Early mortality showed a trend in favour of TAVR (HR 0.73, 95% CI 0.37-1.44), while there was a trend in favour of SAVR at 5-years of follow-up (HR 1.53, 95% CI 0.89-2.62)

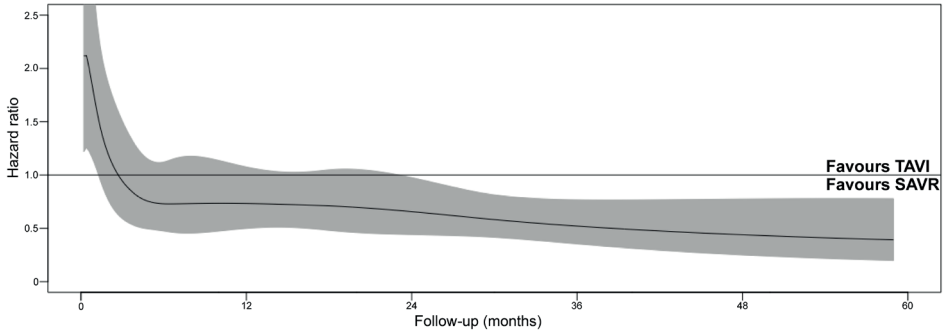


**Figure 3. Time-varying hazard ratio for all-cause mortality with a fully parametric generalized survival model.** HR is given as all-cause mortality after index procedure. HR below 1.0 is in favor of SAVR, while an HR above 1.0 is in favor of TAVI. Abbreviations as in Figure 2.

## DISCUSSION

This reconstructed individual patient data analyses from 3 RCTs randomized and 3 PSM cohort studies is the first large-scale study performed to estimate the long-term all-cause mortality following TAVI and SAVR in low-risk patients. The main findings of the present study are as follows: (1) all-cause mortality at 30-days tends to be lower in patients treated with TAVI compared to SAVR, (2) comparable outcome is seen at 1-year, and (3) at 5-year follow-up, the incidence of mortality is markedly higher after TAVI compared to SAVR.

The initial comparable outcomes between TAVI and SAVR in patients at intermediate-to-high surgical risks led to further expansion of the TAVI approach across the risk spectrum of patient population. The Food and Drug Administration (FDA) approved certain TAVI devices to be used in the low risk patient in November 2019. It is expected that this will increase the use of TAVI irrespective of surgical risk worldwide, given the fact that already 10% of European TAVI centers has performed routine TAVI in the low-risk patient even before the FDA announcement.[23]

Our results confirm the benefit of TAVI over SAVR in the early post-procedural phase. While the in-hospital outcomes after SAVR are linked to the need for more invasive treatment with cardiopulmonary bypass and general anesthesia, it carries a natural higher likelihood of early interventional hazard compared with TAVI itself.[24,25] On the other

hand, the less invasive character of TAVI and continuous improvements such as treatment under analgo-sedation only and with shorter hospital stay, certainly lowers the complications rates and subsequent early mortality.[26] With increasing operator[27], hospital[28], and international experience, very low hospital mortality rates are achieved.[29,30] Moreover, the newer generation devices used in contemporary practice showing in-hospital mortality at historically low levels.[31,32]

The early favorable nature of TAVI is reflected by low post-procedural mortality rates, while this might not fully reflect the difference of treatment effect in the long-term. Again, SAVR is linked to a natural higher likelihood of early interventional hazard compared to TAVI due to its nature. To avoid this early bias, the non-proportionality of the effects of the treatment, we did use an approach, wherein patients surviving up to 1-year were selected in a landmark approach. However, using an additional landmark approach might inherently i) lead to omission of events which could be important and occur early on, and ii) loss of power.[33] However, choosing an early point for landmarking minimizes these risks.

Recently published results of the meta-analysis summarizing the mortality rates of available RCTs irrespective of surgical risk up to 2-years, shows a significant reduction of all-cause mortality with TAVI over SAVR.[34] However, additional analyses accounting for the non-proportionality across the studies nullifies this assumption. A divergence in all-cause mortality favoring SAVR during long-term follow-up is noted. There is an earlier onset of this divergence when climbing down the risk ladder. The 5-year results in high-risk patients show similar survival rates with nearly equal or even a crossover of survival rates after 60 months favoring SAVR in the long-term[35], while in the intermediate-risk patients this crossover is expected with an earlier onset.[7]

There are a number of concerns for extrapolating the favorable TAVI results to the younger population. Firstly, the global average life expectancy (LE) increased by 5.5 years between 2000 and 2016, and continues to increase markedly, leading to substantially higher risk for re-intervention during life-span. Secondly, low-risk does not automatically mean "younger", since the mean age of our analyses were 76 years of age. As younger age is associated with less mortality[36], one expects a multiplier effect for the TAVI in the young low-risk patient, for its non-invasive character. Thirdly, a high need for pacemaker implantation is likely to impair quality of life in active patients. Finally, given the unknown long-term mortality results and durability of these valves, caution is necessary offering TAVI to the younger low-risk patients with LE exceeding 10 years. Especially, after noting an earlier onset of crossover and divergence of mortality in favor of SAVR while climbing down the risk ladder. We therefore await the long-term data from the younger population with bicuspid morphology (NCT02701283) and the three RCTs (PARTNER 3, Evolut R Low Risk and NOTION 2) in younger low-risk patients, which are recently completed and will be presenting follow-up up to 10 years.[10,11]

### Future outlook

Given the data from recently published RCTs, surgical risk is not anymore, the single determinant for eligibility of patients and other important variables, including anatomy and comorbidities should lead patient allocation. Multidisciplinary Heart Team decision-making is becoming more important for the treatment of aortic valve disease because of an increasing overlap of indications for SAVR and TAVI. Formal Heart Team meetings are recommended to assess patients and allocate patients accordingly. Nevertheless, we need to be cautious and await long-term data from RCTs before changing the current standards of care.

### Limitations

It is important to emphasize that this study has several limitations. Firstly, this meta-analysis includes both RCTs and PSM cohort studies. While, both types of studies account for baseline characteristics, a difference in magnitude of effect size can be noted.[37] However, differences in effect estimates are not significantly different and consistency is shown.[37,38] Secondly, for the definition of surgical risk, we were very strict on risk adopting only the STS surgical risk score. The STS score accurately predicts SAVR outcomes[39,40], yet overestimates 30-day mortality in TAVI patients. The lack of TAVI risk scores need to be issued in the future.[41] Thirdly, it was impossible to perform a network meta-analysis to indirectly compare transfemoral and transapical approach because of the low number of studies comparing SAVR to transapical TAVI procedure, which will become the procedure of choice only for highly selected patients. Finally, the most important limitation of the present study is the limited follow-up period of the two largest RCTs.

## CONCLUSIONS

In this reconstructed individual patient data analyses of studies comparing AS patients at low surgical risk who had undergone either a surgical or an interventional procedure, the present data showed that 5-year mortality did not significantly differ in patients receiving either TAVI and SAVR. In particular, the benefit of SAVR over TAVI was shown in patients surviving up to 1 year after the index procedure. Longer follow-up from well-conducted RCTs and large national registries are warranted to better define mortality differences between these two complementary procedures.

**ACKNOWLEDGEMENTS**

The authors thank Wichor M. Bramer from the Medical Library department of the Erasmus Medical Center for designing and executing the search strategies.

## REFERENCES


1. Brennan JM, Edwards FH, Zhao Y, O'Brien SM, Douglas PS, Peterson ED, et al. Long-term survival after aortic valve replacement among high-risk elderly patients in the United States: insights from the Society of Thoracic Surgeons Adult Cardiac Surgery Database, 1991 to 2007. Circulation. 2012;126(13):1621-9.
2. Cribier A, Eltchaninoff H, Bash A, Borenstein N, Tron C, Bauer F, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. Circulation. 2002;106(24):3006-8.
3. Kapadia SR, Tuzcu EM, Makkar RR, Svensson LG, Agarwal S, Kodali S, et al. Long-term outcomes of inoperable patients with aortic stenosis randomly assigned to transcatheter aortic valve replacement or standard therapy. Circulation. 2014;130(17):1483-92.
4. Gleason TG, Reardon MJ, Popma JJ, Deeb GM, Yakubov SJ, Lee JS, et al. 5-Year Outcomes of Self-Expanding Transcatheter Versus Surgical Aortic Valve Replacement in High-Risk Patients. J Am Coll Cardiol. 2018;72(22):2687-96.
5. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet. 2015;385(9986):2477-84.
6. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med. 2016;374(17):1609-20.
7. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Sondergaard L, Mumtaz M, et al. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med. 2017;376(14):1321-31.
8. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Fleisher LA, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017;70(2):252-89.
9. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739-91.
10. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. N Engl J Med. 2019.
11. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. N Engl J Med. 2019.
12. Thourani VH, Suri RM, Gunter RL, Sheng S, O'Brien SM, Ailawadi G, et al. Contemporary real-world outcomes of surgical aortic valve replacement in 141,905 low-risk, intermediate-risk, and high-risk patients. Ann Thorac Surg. 2015;99(1):55-61.
13. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;350:g7647.
14. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283(15):2008-12.
15. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
16. Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.

17. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012;12:9.
18. Wei Y, Royston P. Reconstructing time-to-event data from published Kaplan-Meier curves. Stata J. 2017;17(4):786-802.
19. Rosato S, Santini F, Barbanti M, Biancari F, D'Errigo P, Onorati F, et al. Transcatheter Aortic Valve Implantation Compared With Surgical Aortic Valve Replacement in Low-Risk Patients. Circ Cardiovasc Interv. 2016;9(5):e003326.
20. Schaefer A, Schofer N, Gossling A, Seiffert M, Schirmer J, Deuschl F, et al. Transcatheter aortic valve implantation versus surgical aortic valve replacement in low-risk patients: a propensity score-matched analysis. Eur J Cardiothorac Surg. 2019;56(6):1131-9.
21. Thyregod HGH, Ihlemann N, Jorgensen TH, Nissen H, Kjeldsen BJ, Petursson P, et al. Five-Year Clinical and Echocardiographic Outcomes from the Nordic Aortic Valve Intervention (NOTION) Randomized Clinical Trial in Lower Surgical Risk Patients. Circulation. 2019.
22. Virtanen MPO, Eskola M, Jalava MP, Husso A, Laakso T, Niemela M, et al. Comparison of Outcomes After Transcatheter Aortic Valve Replacement vs Surgical Aortic Valve Replacement Among Patients With Aortic Stenosis at Low Operative Risk. JAMA Netw Open. 2019;2(6):e195742.
23. Petronio AS, Capranzano P, Barbato E, Piazza N, Baumbach A, Haude M, et al. Current status of transcatheter valve therapy in Europe: results from an EAPCI survey. EuroIntervention. 2016;12(7):890-5.
24. Cockburn J, Dooley M, de Belder A, Trivedi U, Hildick-Smith D. A comparison between surgical risk scores for predicting outcome in patients undergoing transcatheter aortic valve implantation. J Cardiovasc Surg (Torino). 2017;58(3):467-72.
25. Butchart EG, Gohlke-Barwolf C, Antunes MJ, Tornos P, De Caterina R, Cormier B, et al. Recommendations for the management of patients after heart valve surgery. Eur Heart J. 2005;26(22):2463-71.
26. Hyman MC, Vemulapalli S, Szeto WY, Stebbins A, Patel PA, Matsouaka RA, et al. Conscious Sedation Versus General Anesthesia for Transcatheter Aortic Valve Replacement: Insights from the National Cardiovascular Data Registry Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. Circulation. 2017;136(22):2132-40.
27. Vemulapalli S, Carroll JD, Mack MJ, Li Z, Dai D, Kosinski AS, et al. Procedural Volume and Outcomes for Transcatheter Aortic-Valve Replacement. N Engl J Med. 2019;380(26):2541-50.
28. Carroll JD, Vemulapalli S, Dai D, Matsouaka R, Blackstone E, Edwards F, et al. Procedural Experience for Transcatheter Aortic Valve Replacement and Relation to Outcomes: The STS/ACC TVT Registry. J Am Coll Cardiol. 2017;70(1):29-41.
29. Auffret V, Lefevre T, Van Belle E, Eltchaninoff H, Iung B, Koning R, et al. Temporal Trends in Transcatheter Aortic Valve Replacement in France: FRANCE 2 to FRANCE TAVI. J Am Coll Cardiol. 2017;70(1):42-55.
30. Gaede L, Blumenstein J, Kim WK, Liebetrau C, Dorr O, Nef H, et al. Trends in aortic valve replacement in Germany in 2015: transcatheter versus isolated surgical aortic valve repair. Clin Res Cardiol. 2017;106(6):411-9.
31. Waksman R, Rogers T, Torguson R, Gordon P, Ehsan A, Wilson SR, et al. Transcatheter Aortic Valve Replacement in Low-Risk Patients With Symptomatic Severe Aortic Stenosis. J Am Coll Cardiol. 2018;72(18):2095-105.

32. Ando T, Takagi H, Telila T, Afonso L. Comparison of outcomes in new-generation versus early-generation heart valve in transcatheter aortic valve implantation: A systematic review and meta-analysis. Cardiovasc Revasc Med. 2018;19(2):186-91.
33. Dafni U. Landmark analysis at the 25-year landmark point. Circ Cardiovasc Qual Outcomes. 2011;4(3):363-71.
34. Siontis GCM, Overtchouk P, Cahill TJ, Modine T, Prendergast B, Praz F, et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of symptomatic severe aortic stenosis: an updated meta-analysis. Eur Heart J. 2019;40(38):3143-53.
35. Kapadia SR, Leon MB, Makkar RR, Tuzcu EM, Svensson LG, Kodali S, et al. 5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet. 2015;385(9986):2485-91.
36. Navarese EP, Andreotti F, Kolodziejczak M, Wanha W, Lauten A, Veulemans V, et al. Age-Related 2-Year Mortality After Transcatheter Aortic Valve Replacement: the YOUNG TAVR Registry. Mayo Clin Proc. 2019;94(8):1457-66.
37. Dahabreh IJ, Sheldrick RC, Paulus JK, Chung M, Varvarigou V, Jafri H, et al. Do observational studies using propensity score methods agree with randomized trials? A systematic comparison of studies on acute coronary syndromes. Eur Heart J. 2012;33(15):1893-901.
38. Anglemyer A, Horvath HT, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. Cochrane Database Syst Rev. 2014(4):MR000034.
39. Ferguson TB, Jr., Dziuban SW, Jr., Edwards FH, Eiken MC, Shroyer AL, Pairolero PC, et al. The STS National Database: current changes and challenges for the new millennium. Committee to Establish a National Database in Cardiothoracic Surgery, The Society of Thoracic Surgeons. Ann Thorac Surg. 2000;69(3):680-91.
40. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg. 1999;16(1):9-13.
41. Debonnaire P, Fusini L, Wolterbeek R, Kamperidis V, van Rosendael P, van der Kley F, et al. Value of the "TAVI2-SCORe" versus surgical risk scores for prediction of one year mortality in 511 patients who underwent transcatheter aortic valve implantation. Am J Cardiol. 2015;115(2):234-42.

## SUPPLEMENTARY MATERIAL

**Table S1 - PRISMA-P Checklist 2015** [1,2]

| Section/topic | # | Checklist item | Information reported Yes | No | Line number(s) |
|---|---|---|---|---|---|
| **ADMINISTRATIVE INFORMATION** | | | | | |
| **Title** | | | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | | | |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | | | |
| **Registration** | 2 | If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract | | | |
| **Authors** | | | | | |
| Contact | 3a | Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author | | | 1-23 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | | | Noted within Editorial Manager under: "Order of Authors (with Contributor Roles):" |
| **Amendments** | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | | | |
| **Support** | | | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | | | 11 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | | | 11 |
| Role of sponsor/funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | | | 11 |
| **INTRODUCTION** | | | | | |
| **Rationale** | 6 | Describe the rationale for the review in the context of what is already known | | | 81-105 |
| **Objectives** | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | | | 94-105 |

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|---|---|---|---|---|---|
| | | | Yes | No | |
| **METHODS** | | | | | |
| **Eligibility criteria** | 8 | Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review | | | 111-117 |
| **Information sources** | 9 | Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage | | | 111-117 |
| **Search strategy** | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | | | Table S2. |
| **STUDY RECORDS** | | | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | | | 111-117 |
| Selection process | 11b | State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis) | | | 118-120 and 132-135 |
| Data collection process | 11c | Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | | | 118-122 and 132-148 |
| **Data items** | 12 | List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications | | | 132-148 |
| **Outcomes and prioritization** | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | | | 132-148 |
| **Risk of bias in individual studies** | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | | | 148-153; Supplementary tables 3-4 |

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|---|---|---|---|---|---|
| | | | Yes | No | |
| **DATA** | | | | | |
| **Synthesis** | 15a | Describe criteria under which study data will be quantitatively synthesized | | | 155-161 |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., $I^2$, Kendall's tau) | | | 155-182 |
| | 15c | Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression) | | | 169-182 |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | | | 169-182 |
| **Meta-bias(es)** | 16 | Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies) | | | |
| **Confidence in cumulative evidence** | 17 | Describe how the strength of the body of evidence will be assessed (e.g., GRADE) | | | |

**Table S2 – search strategy**

| | | |
|---|---|---|
| embase.com (1971-) | 1396 | 1365 |
| Medline ALL Ovid (1946-) | 1536 | 540 |
| Cchrane CENTRAL register of trials (1992-) | 293 | 124 |
| **Total** | **3225** | **2029** |

**embase.com (1971-March 13, 2020) 1396**

('transcatheter aortic valve implantation'/exp OR (((transcatheter* OR trans-catheter* OR percutan* OR per-cutan* OR trans-femoral* OR transfemoral*) NEAR/3 aortic-valv* NEAR/3 (implantat* OR replace*)) OR tavr OR tavi):ab,ti) AND (surgery/de OR 'open heart surgery'/de OR 'open surgery'/de OR 'heart surgery'/de OR 'heart valve surgery'/de OR 'heart valve replacement'/de OR 'surgical aortic valve replacement'/de OR 'aortic stenosis'/dm_su OR 'surgical approach'/de OR 'surgical risk'/de OR (((open OR replace* OR approach*) NEAR/6 (surger* OR surgical*)) OR conventional* OR savr):ab,ti) AND ('Controlled clinical trial'/exp OR 'Crossover procedure'/de OR 'Double-blind procedure'/de OR 'Single-blind procedure'/de OR ('propensity score'/de AND 'cohort analysis'/de) OR (random* OR factorial* OR crossover* OR (cross NEXT/1 over*) OR placebo* OR ((doubl* OR singl*) NEXT/1 blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups OR (propensity-score* AND cohort*)):ab,ti,kw) NOT ([animals]/lim NOT [humans]/lim) NOT ([Conference Abstract]/lim) NOT ('case report'/de OR 'case report':ab,ti) AND [english]/lim

**Medline ALL Ovid (1946- March 13, 2020) 1536**

(Transcatheter Aortic Valve Replacement / OR (((transcatheter* OR trans-catheter* OR percutan* OR per-cutan* OR trans-femoral* OR transfemoral*) ADJ3 aortic-valv* ADJ3 (implantat* OR replace*)) OR tavr OR tavi).ab,ti.) AND (Surgical Procedures, Operative/ OR Conversion to Open Surgery/ OR Thoracic Surgery/ OR Cardiac Surgical Procedures/ OR Aortic Valve Stenosis/su OR Heart Valves/su OR (((open OR replace* OR approach*) ADJ6 (surger* OR surgical*)) OR conventional* OR savr).ab,ti.) AND (Exp Controlled clinical trial/ OR "Double-Blind Method"/ OR "Single-Blind Method"/ OR "Random Allocation"/ OR (random* OR factorial* OR crossover* OR cross over* OR placebo* OR ((doubl* OR singl*) ADJ blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups).ab,ti,kf.) NOT (exp Animals/ NOT Humans/) NOT (news OR congres* OR abstract* OR book* OR chapter* OR dissertation abstract*).pt. NOT (case reports/ OR case report.ab,ti.) AND english.la.

**Cchrane CENTRAL register of trials (1992- March 13, 2020) 293**

((((transcatheter* OR trans-catheter* OR percutan* OR per-cutan* OR trans-femoral* OR transfemoral*) NEAR/3 aortic-valv* NEAR/3 (implantat* OR replace*)) OR tavr OR tavi):ab,ti) AND ((((open OR replace* OR approach*) NEAR/6 (surger* OR surgical*)) OR conventional* OR savr):ab,ti)

**Table S3 – Revised Cochrane Risk of Bias Tool for Randomized Controlled Trials 2.0** [3]

| Study | PARTNER 3 | EVOLUT | NOTION |
|---|---|---|---|
| Bias due to randomization process | SC | SC | SC |
| Bias due to deviations from intended interventions | SC | SC | LR |
| Missing outcome data | HR | LR | LR |
| Bias in measurement of the outcome | HR | LR | LR |
| Bias in selection of the reported result | LR | LR | LR |
| Overall | HR | SC | SC |

**LR**, low risk of bias; **SC**, some concerns of bias; **HR**, High risk of bias

**Table S4 – ROBIN-1 Risk of Bias Tool for Non-Randomized Controlled trials** [4]

| Study | Schaefer | Virtanen | Rosato |
|---|---|---|---|
| Bias due to confounding | SC | SC | SC |
| Bias in selection of participants into the study | HR | HR | SC |
| Bias in classification of interventions | LR | LR | LR |
| Bias due to deviations from intended interventions | SC | SC | SC |
| Bias due to missing data | SC | SC | SC |
| Bias in measurement of the outcome | LR | LR | LR |
| Bias in selection of the reported result | LR | LR | LR |
| Overall | HR | HR | SC |

**LR**, low risk of bias; **SC**, some concerns of bias; **HR**, High risk of bias

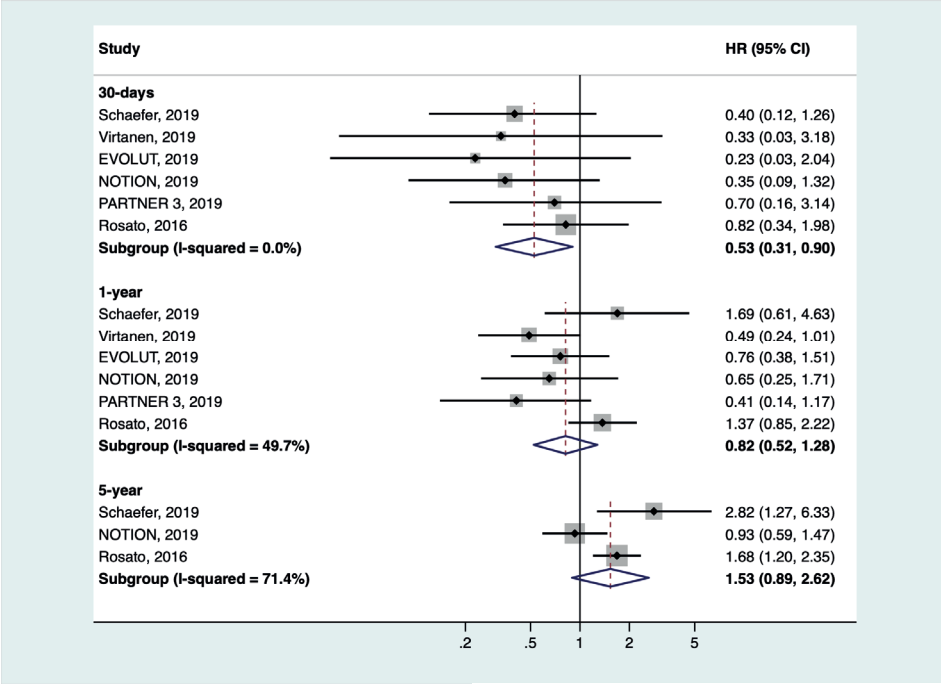


**Figure S1. Forest plot of all-cause death in patients undergoing TAVI or SAVR during 30-days, 1-year, and 5-years of follow-up.** HR below 1.0 is in favor of TAVI, while an HR above 1.0 is in favor of SAVR.

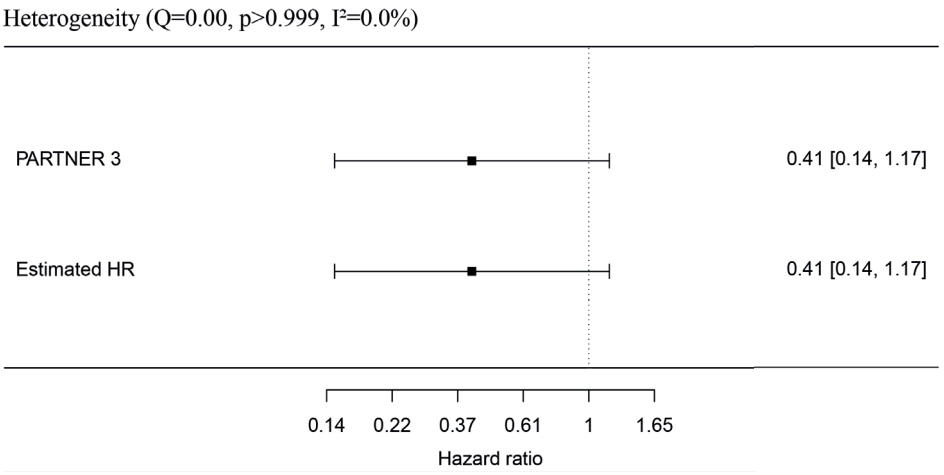


**Figure S2. Comparison of estimated data with reported data**
Data reported in the trial and data estimated data with individual patient data extractions

## SUPPLEMENTARY REFERENCES


1. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015;4:1.
2. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ.* 2015;350:g7647.
3. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019;366:l4898.
4. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ.* 2016;355:i4919.

# 7 Differences in Baseline Characteristics and Outcomes of Bicuspid and Tricuspid Aortic Valve in Surgical Aortic Valve Replacement

Çelik M, Milojevic M, Durko AP, Oei FBS,
Bogers AJJC, Mahtab EAF.

**European Journal of CardioThoracic Surgery. 2021.**

## ABSTRACT

**Background:** Patients with bicuspid aortic valve (BAV) encompass a substantial portion of patients undergoing surgical aortic valve replacement (SAVR). To quantify the prevalence of BAV in the current SAVR ± CABG population, assess differences in cardiovascular risk profiles and assess differences in long-term survival in patients with BAV compared to patients with tricuspid aortic valve (TAV), this study was performed.
**Methods:** Patients who underwent SAVR with or without concomitant CABG and having a surgical report denoting the valvular anatomy were eligible and included. Prevalence, predictors and outcomes for patients with BAV were analyzed and compared to patients with TAV. Matched patients with BAV and TAV were compared using a propensity score matching strategy and an age-matching strategy.
**Results**: A total of 3723 patients of whom 3145 (mean age 66.6 ± 11.4 years, 37.4% female) had an operative report describing the aortic valvular morphology, underwent SAVR ± CABG between 1987 and 2016. The overall prevalence of patients with BAV was 19.3% (607). Patients with BAV were younger compared to patients with TAV (60.6 ± 12.1 versus 68.0 ± 10.7, respectively). In the age-matched cohort patients with BAV were less likely to have comorbidities, amongst others diabetes (p=0.001), hypertension (p<0.001), and hypercholesterolemia (p=0.003), compared to patients with TAV. Twenty-year survival following the index procedure was higher in patients with BAV (14.8%) compared to TAV (12.9%) in the age-matched cohort, p=0.015.
**Conclusions:** Substantial differences in cardiovascular risk profile exist in patients with BAV and TAV. Long-term survival after SAVR in patients with BAV is satisfactory.


## GRAPHICAL ABSTRACT

**Key question:** What are the long-term outcomes of patients with bicuspid aortic valve undergoing surgical aortic valve replacement?
**Key findings:** BAV patients have better survival in an age-matched cohort, p=0.008
**Take-home message:** These satisfactory long-term results reinforce the role of surgical aortic valve replacement (SAVR) in the bicuspid aortic valve population

## INTRODUCTION

Bicuspid aortic valve (BAV) disease is the most prevalent congenital heart defect, with a prevalence between 0.5 and 2.0% in the general population.[1,2] Compared to the patients with tricuspid aortic valve (TAV), patients with BAV are younger at the time of surgery.[3] Patients with a BAV present with a different cardiovascular risk profile than patients with a TAV and have a higher incidence of aortic stenosis, aortic regurgitation, aortopathy and related complications.[4] BAV and TAV both have anatomical and procedural differences at the time of surgical intervention.[5]

Studies comparing the clinical profiles and outcomes of patients with BAV and TAV undergoing surgical aortic valve replacement (SAVR) are scarce, especially in an era where indications for transcatheter aortic valve implantation (TAVI) are expanding and becoming an alternative treatment for younger patients with low surgical risk and even for asymptomatic patients.[6] Therefore, the purpose of this study was to (1) describe the prevalence of BAV in the current SAVR population, (2) describe similarities and differences in patients with BAV and TAV and (3) compare the long-term survival and predictors of survival in patients with BAV and TAV.



## METHODS

### Study design

Adult (≥18 years) patients who underwent SAVR with or without a coronary artery bypass graft (CABG) between 1987 and 2016 at the Erasmus Medical Centre, Rotterdam, The Netherlands were included. Patients with concomitant surgical procedures other than CABG were excluded. Patients who did not receive a biological or mechanical aorta valve prosthesis were excluded. Patients with previous aortic valve replacement were likewise excluded. Baseline patient and procedural characteristics were collected from electronic medical records. Survival status was obtained through the National Civil Registry. Patients were classified according to the number of cusps treated during the operation. Valvular morphology was defined by the surgeon in the operative report. Functional BAV, such as having an obstructed or incomplete commissure in an originally tricuspid valve, was classified as TAV.

This study was conducted according to the privacy policy of the Erasmus Medical Centre and the Erasmus Medical Centre regulations for the appropriate use of data in patient-oriented research, which are based on international regulations, including the Declaration of Helsinki (MEC-2020-0454). All the authors vouch for the validity of the data and adherence to the protocol.

### End points and definitions

The primary end point was to assess the prevalence of BAV and the differences in patient characteristics between BAV and TAV in the SAVR population. An additional end point was the difference in survival between patients with BAV and TAV. To assess for the prevalence of BAV within the surgical cohort, patients were classified across 6 age groups (group 1: patients younger than 40; group 2: patients between 40 and 49; group 3: patients between 50 and 59; group 4: patients between 60 and 69; group 5: patients between 70 and 79; and group 6: patients aged or older than 80). The primary indication for an operation (aortic stenosis [AS], aortic regurgitation [AR] or combined AS and AR) was determined based on the initial echocardiogram and on the clinical guidelines in use at the time of the operation, corresponding to the current European and American valvular guidelines.[7,8] In general, SAVR within 24 h of establishing the indication was classified as an emergency procedure. Renal failure was defined as a creatinine level ≥2.0 mg/dl. Left ventricular function was classified as normal if the left ventricular ejection fraction (LVEF) was >50%, as mildly reduced if the LVEF was 40-49%, as moderately reduced if the LVEF was 30-39% and as severely reduced if the LVEF was less than 30%, as assessed by a trained echocardiographer.[9]

### Statistical analyses

Discrete variables are presented as numbers, percentages or proportions and compared with either the $\chi^2$ test or the Fisher exact test, where appropriate. Continuous variables are presented as means ± standard deviation or median with the interquartile range if there was evidence of skewed data according to the Kolmogorov-Smirnov test and compared with either the two-sample *t*-test or the Wilcoxon rank-sum test, where appropriate.

Non-parsimonious logistic regression was used to estimate each patient's probability of being in the bicuspid aortic valve group. Propensity scores were calculated for each group with the following covariates: age, gender, previous cardiac operation, atrial fibrillation, diabetes mellitus, decompensation, hypercholesterolaemia, hypertension, myocardial infarction, previous percutaneous coronary intervention, chronic obstructive pulmonary disease, endocarditis, history of cancer, stroke/transient ischaemic attack, arterial disease, indication for surgery, concomitant CABG and size and type of valve implanted. The balance between treatment groups was assessed with the use of standardized mean differences. A standardized mean difference of 0.1 or less was deemed to be the ideal balance, and a standardized difference of 0.2 or less was deemed to be an acceptable balance.[10] The relative survival can be used as an estimate of cause-specific mortality. It is defined as the ratio between the observed survival rates and the expected survival rates in the general population.[11] Further, the proportional hazard assumption for the overall group was assessed with the corresponding test for correlation of the

Schoenfeld residuals over time. Nonetheless, the restricted mean survival time at 10 years of follow-up was calculated to substantiate the overall between-group treatment effect in the overall cohort, the propensity score matched cohort and the age-matched cohort.

The Human Mortality Database is used to obtain the age-, sex- and calendar year-matched expected survival data of the general population in the Netherlands.[12] The Human Mortality Database is continuously updated and includes mortality data from The Netherlands through 2016. Relative survival is estimated using the Ederer II method.[13,14] Predictors of mortality were identified in a Cox proportional hazards model. Significant variables on univariable analyses were included in a multivariable Cox proportional hazards model. Sensitivity analysis were performed for isolated SAVR. Two-sided p-values <0.05 were considered to be statistically significant. Data analyses were done using SPSS 25.0 (SPSS Inc, Chicago, IL USA) and R software, version 3.5 (R Foundation, Vienna, Austria). Figures were generated using Microsoft Excel (Microsoft, Redmond, WA USA) and R software, version 3.5 (R Foundation).



## RESULTS

### Characteristics of patients with bicuspid aortic valves

A total of 3723 patients underwent SAVR with or without CABG, 3145 of whom had a surgeon's report on the valvular anatomy, with 607 BAV (19.3%) and 2538 TAV (80.7%). A total of 48 patients with BAV were excluded due to concomitant aortic surgery; differences in characteristics between included and excluded patients are shown in Table S1. The prevalence of bicuspid aortic morphology according to age group was 36.2%, 35.0%, 28.0%, 19.3%, 10.1% and 3.2% in patients aged <40, 40-49, 50-59, 60-69, 70-79, and 80≥ years, respectively (Fig. 1). The prevalence of bicuspid aortic morphology for those operated after the year 2000 is shown in Figure S1. Patients with BAV were younger than patients with TAV at the time of the operation (mean age 60.6 ± 12.1 years vs 68.0 ± 10.7 years; p< 0.001) and were less often women (32.9% vs 38.5%; p=0.013). The prevalence of BAV decreased from 43.8% to 16.2% between 1987 and 2016. The prevalence of hypertension (24.7% vs 39.6%), hypercholesterolaemia (10.0% vs 18.6%) and diabetes (7.7% vs 17.2%) was lower in patients with BAV than in those with TAV (all p-values <0.001) (Table 1). These differences persisted after age matching. Further characteristics in the overall cohort, the propensity score matched cohort and the age-matched cohort are shown in Table 1. Subanalyses on the characteristics of patients operated on after 2000 are shown in Table S2 and Figure S2.

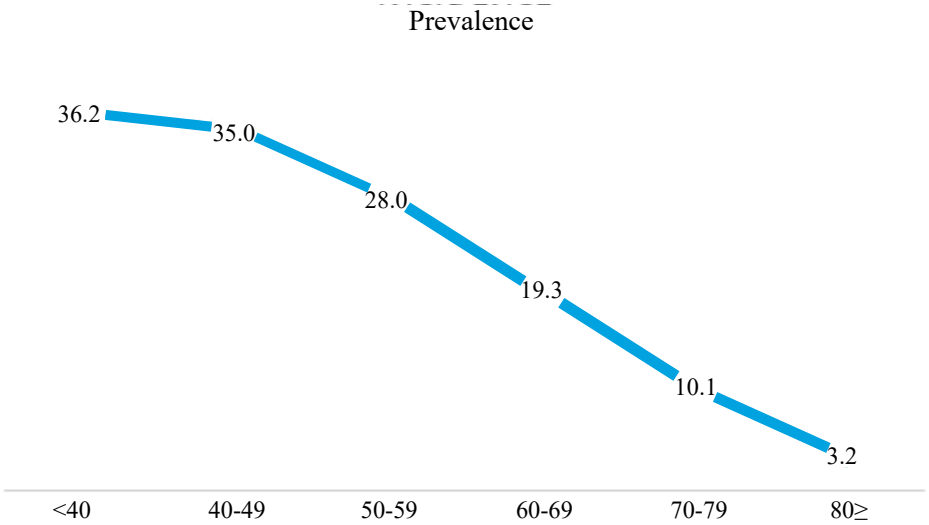


**Figure 1. Prevalence of bicuspid aortic valve.**
The percentage of patients with bicuspid aortic valves decreases considerably with increasing age. Results are reported as percentages.

## Procedural characteristics

The indication for surgery was mainly AS (75.0%), followed by AR (7.7%) or AS and AR combined (17.1%). Concomitant CABG surgery was performed in 21.9% of the patients, less often in patients with BAV compared to those with TAV ($p<0.001$); this difference persisted after age matching ($p=0.004$). The incidence of mechanical valve implantation was higher in the BAV group compared to the TAV group in the overall cohort (61.4% vs 39.2%; $p<0.001$) and in the age-matched cohort (63.1% vs 57.5%; $p=0.05$). The diameter of the implanted prosthesis was higher in patients with BAV than in those with TAV in the overall cohort ($24.4 \pm 2.4$ vs $23.4 \pm 2.3$; $p<0.001$) and in the age-matched cohort ($24.4 \pm 2.4$ vs $23.7 \pm 2.4$; $p<0.001$).

**Table 1. Baseline and procedural characteristics, stratified according to the overall cohort, propensity score matched cohort, and age-matched cohort.**

| | TAV (2538) | BAV (607) | p-value | SMD | PSM-TAV (593) | PSM-BAV (593) | p-value | SMD | AM-TAV (590) | AM-BAV (590) | p-value | SMD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Age at operation** | 68.0 ± 10.7 | 60.6 ± 12.1 | *<0.001* | 0.647 | 61.6 ± 12.5 | 61.0 ± 11.7 | *0.40* | 0.049 | 61.3 ± 11.5 | 61.3 ± 11.5 | >0.999 | <0.001 |
| **Gender (female)** | 977 (38.5) | 200 (32.9) | *0.01* | 0.116 | 193 (32.5) | 198 (33.4) | *0.81* | 0.018 | 188 (31.9) | 198 (33.6) | 0.58 | 0.036 |
| **Indication** | | | *0.02* | 0.149 | | | *0.77* | 0.062 | | | <0.001 | 0.353 |
| - **AS** | 1843 (72.6) | 455 (75.0) | *0.24* | 0.053 | 452 (76.2) | 445 (75.0) | *0.64* | 0.027 | 382 (64.7) | 447 (75.8) | <0.001 | 0.243 |
| - **AI** | 306 (12.1) | 47 (7.7) | *0.002* | 0.145 | 50 (8.4) | 47 (7.9) | *0.75* | 0.018 | 110 (18.6) | 42 (7.1) | <0.001 | 0.349 |
| - **Combined** | 385 (15.2) | 104 (17.1) | *0.23* | 0.053 | 89 (15.0) | 100 (16.9) | *0.38* | 0.051 | 97 (16.4) | 100 (16.9) | 0.81 | 0.014 |
| **Previous cardiac operation** | 161 (6.3) | 31 (5.1) | *0.29* | 0.053 | 29 (4.9) | 30 (5.1) | *>0.999* | 0.008 | 41 (6.9) | 29 (4.9) | 0.18 | 0.086 |
| **Creatinine** | 0.98 (0.84-1.16) 67 (2.7) | 0.95 (0.82-1.10) 10 (1.7) | *0.001* | 0.095 | 0.95 (0.81-1.10) 9 (1.5) | 0.95 (0.81-1.10) 9 (1.5) | *0.86* | 0.087 | 0.96 (0.83-1.13) 13 (2.2) | 0.95 (0.81-1.10) 9 (1.5) | *0.19* | 0.089 |
| - **≥2mg/dL** | | | *0.20* | 0.069 | | | *>0.999* | <0.001 | | | *0.51* | 0.051 |
| **Atrial fibrillation** | 350 (13.8) | 54 (8.9) | *0.002* | 0.155 | 61 (10.3) | 54 (9.1) | *0.56* | 0.040 | 66 (11.2) | 54 (9.2) | 0.29 | 0.067 |
| **Diabetes mellitus** | 436 (17.2) | 47 (7.7) | *<0.001* | 0.289 | 50 (8.4) | 47 (7.9) | *0.83* | 0.018 | 85 (14.4) | 47 (8.0) | 0.001 | 0.205 |
| **Decompensation cordis** | 397 (15.6) | 64 (10.5) | *0.002* | 0.152 | 54 (9.1) | 63 (10.6) | *0.44* | 0.051 | 97 (16.4) | 62 (10.5) | 0.004 | 0.174 |
| **Hypertension** | 1004 (39.6) | 150 (24.7) | *<0.001* | 0.322 | 158 (26.6) | 150 (25.3) | *0.64* | 0.031 | 213 (36.1) | 149 (25.3) | <0.001 | 0.237 |
| **Hypercholesterol-emia** | 473 (18.6) | 61 (10.0) | *<0.001* | 0.247 | 60 (10.1) | 61 (10.3) | *>0.999* | 0.006 | 97 (16.4) | 61 (10.3) | 0.003 | 0.180 |
| **Previous. myocardial infarction** | 312 (12.3) | 48 (7.9) | *0.003* | 0.146 | 54 (9.1) | 47 (7.9) | *0.53* | 0.042 | 68 (11.5) | 4 (8.1) | 0.06 | 0.114 |
| **Previous PCI** | 201 (7.9) | 21 (3.5) | *<0.001* | 0.193 | 25 (4.2) | 21 (3.5) | *0.65* | 0.035 | 40 (6.8) | 21 (3.6) | 0.018 | 0.146 |
| **COPD** | 292 (11.5) | 44 (7.2) | *0.003* | 0.146 | 37 (6.2) | 44 (7.4) | *0.49* | 0.047 | 67 (11.4) | 44 (7.5) | 0.028 | 0.134 |
| **Endocarditis** | 99 (3.9) | 26 (4.3) | *0.75* | 0.019 | 21 (3.5) | 23 (3.9) | *0.88* | 0.018 | 35 (5.9) | 24 (4.1) | 0.18 | 0.086 |
| **History of cancer** | 190 (7.5) | 26 (4.3) | *0.007* | 0.136 | 24 (4.0) | 26 (4.4) | *0.89* | 0.017 | 37 (6.3) | 26 (4.4) | 0.20 | 0.083 |

**Table 1. Baseline and procedural characteristics, stratified according to the overall cohort, propensity score matched cohort, and age-matched cohort.** (*continued*)

| | TAV (2538) | BAV (607) | p-value | SMD | PSM-TAV (593) | PSM-BAV (593) | p-value | SMD | AM-TAV (590) | AM-BAV (590) | p-value | SMD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Stroke/TIA** | 240 (9.5) | 35 (5.8) | *0.005* | 0.139 | 27 (4.6) | 35 (5.9) | *0.36* | 0.061 | 55 (9.3) | 35 (5.9) | 0.037 | 0.128 |
| - **Stroke** | 106 (4.2) | 17 (2.8) | *0.15* | 0.075 | 15 (2.5) | 17 (2.9) | *0.86* | 0.021 | 23 (3.9) | 17 (2.9) | 0.42 | 0.056 |
| - **TIA** | 155 (6.1) | 21 (3.5) | *0.014* | 0.124 | 13 (2.2) | 21 (3.5) | *0.22* | 0.081 | 35 (5.9) | 21 (3.6) | 0.08 | 0.112 |
| **Arterial disease** | 131 (5.2) | 14 (2.3) | *0.004* | 0.151 | 11 (1.9) | 14 (2.4) | *0.69* | 0.035 | 23 (3.9) | 14 (2.4) | 0.18 | 0.088 |
| - **Carotid** | 22 (0.9) | 1 (0.2) | *0.12* | 0.098 | 1 (0.2) | 1 (0.2) | *>0.999* | <0.001 | 5 (0.8) | 1 (0.2) | 0.22 | 0.095 |
| - **Peripheral** | 114 (4.5) | 13 (2.1) | *0.011* | 0.132 | 10 (1.7) | 13 (2.2) | *0.67* | 0.037 | 19 (3.2) | 13 (2.2) | 0.37 | 0.063 |
| **Concomitant CABG** | 914 (36.0) | 133 (21.9) | *<0.001* | 0.307 | 133 (22.4) | 132 (22.3) | *>0.999* | 0.004 | 177 (30.0) | 133 (22.5) | 0.004 | 0.170 |
| **Valve size** | 23.4 ± 2.3 | 24.4 ± 2.4 | *<0.001* | 0.466 | 24.4 ± 2.4 | 24.4 ± 2.4 | *0.86* | 0.010 | 23.7 ± 2.4 | 24.4 ± 2.4 | <0.001 | 0.296 |
| **Urgency** | | | *0.09* | 0.138 | | | *0.69* | 0.094 | | | 0.34 | 0.134 |
| **Emergent** | 28 (1.2) | 6 (1.2) | | | 4 (0.8) | 6 (1.2) | | | 7 (1.3) | 5 (1.0) | | |
| **Not emergent** | 2252 (98.8) | 490 (98.8) | | | 525 (99.2) | 478 (98.8) | | | 522 (98.7) | 475 (99.0) | | |
| **LVEF** | | | *0.65* | 0.062 | | | *0.78* | 0.063 | | | 0.09 | 0.156 |
| - **Preserved** | 1880 (79.9) | 445 (81.8) | | | 447 (82.2) | 437 (81.7) | | | 416 (76.3) | 433 (81.9) | | |
| - **Mildy reduced** | 164 (7.0) | 31 (5.7) | | | 25 (4.6) | 31 (5.8) | | | 43 (7.9) | 29 (5.5) | | |
| - **Moderately reduced** | 227 (9.6) | 48 (8.8) | | | 49 (9.0) | 48 (9.0) | | | 54 (9.9) | 48 (9.1) | | |
| - **Severely reduced** | 82 (3.5) | 20 (3.7) | | | 23 (4.2) | 19 (3.6) | | | 32 (5.9) | 19 (3.6) | | |
| **Valve (mechanical)** | 996 (39.2) | 389 (64.1) | *<0.001* | 0.513 | 356 (60.0) | 376 (63.4) | *0.26* | 0.069 | 339 (57.5) | 372 (63.1) | 0.050 | 0.114 |

AM, age-matched; AS, aortic stenosis; AR, aortic regurgitation, CI, confidence interval; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; TIA, transient ischemic attack; LVEF, left ventricular ejection fraction; PSM, propensity score matched; SMD= standardized mean difference

## Long-term outcomes after surgery

A total of 1728 patients died during the follow-up period (309 patients with BAV and 1419 patients with TAV; p=0.03). Survival was 75.1% versus 57.4% and 40.5% versus 17.8% at 10 and 20 years of follow-up in the overall cohort for patients with BAV and TAV, respectively (p<0.001) (Fig. 2A). The survival was 75.1% versus 69.9% and 40.0%

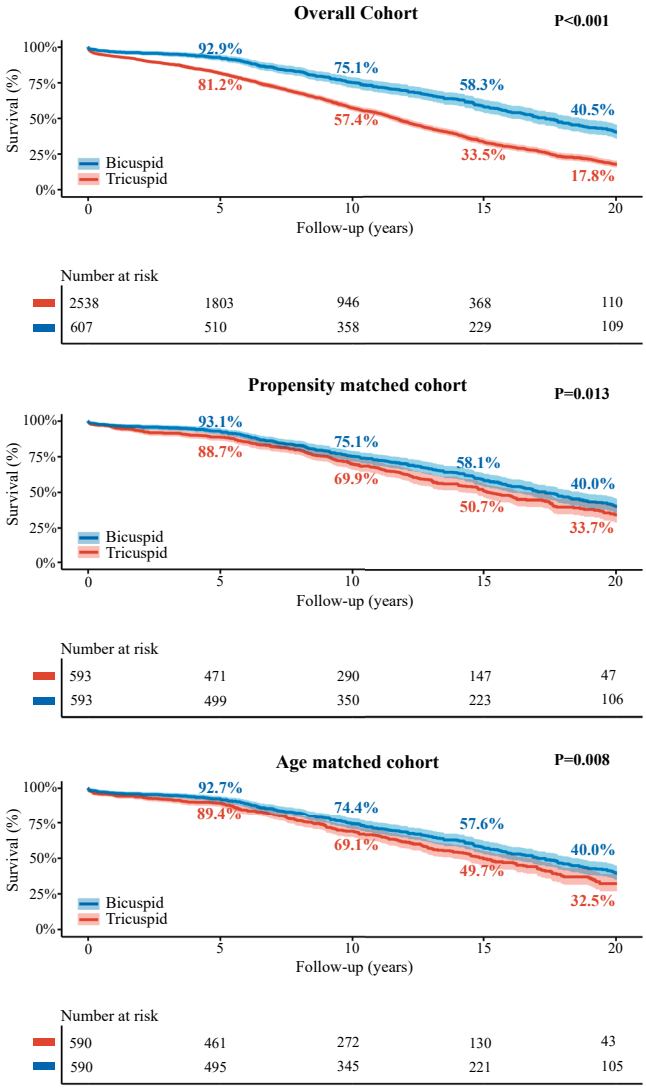


**Figure 2. Long term survival after SAVR ± CABG.**

Survival in overall cohort, B) Survival in propensity matched cohort. *Blue line represents patients with bicuspid aortic valve and red line represents patients with tricuspid aortic valve, C)* Survival in age-matched cohort. *Blue line represents patients with bicuspid aortic valve and red line represents patients with tricuspid aortic valve.*

versus 33.7% at 10 and 20 years of follow-up in the propensity score matched cohort for patients with BAV and TAV, respectively (p=0.02) (Fig. 2B). The survival was 74.4% versus 69.1% and 40.0% versus 32.5% at 10 and 20 years of follow-up in the age-matched cohort for patients with BAV and TAV, respectively (p=0.015) (Fig. 2C). Similar results have been noted for patients operated on after 2000 (Fig. S3). In age-, sex- and year-matched Dutch controls, the relative survival in patients with BAV was 102.6%, 98.6%, 95.5% and 89.0%, at 5, 10, 15 and 20 years of follow-up, respectively (Fig. 3A). The relative survival in patients with TAV was 97.0%, 87.5%, 70.2% and 52.9%, at 5, 10, 15 and 20 years of follow-up, respectively (Fig. 3B). Patients with BAV had 7 months survival benefit compared to those with TAV at 20 years of follow-up in the overall cohort (Table 2), which diminished after propensity score matching. Further survival benefits according to different matching methods and age groups are shown in Table 2.

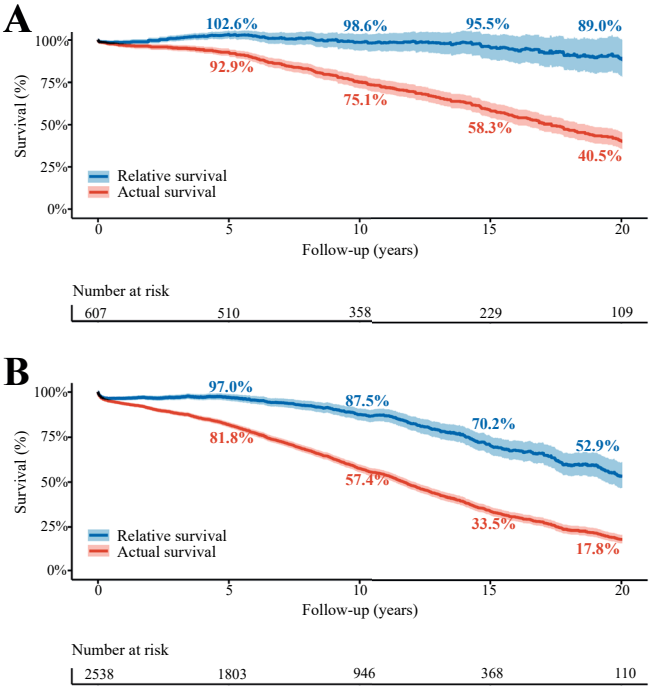


**Figure 3. Long term survival in overall cohort.**
A) Actual survival (red line) in the bicuspid aortic valve cohort and relative survival compared to the age-, gender-, and year-matched population (blue line), B) Actual survival (red line) in the tricuspid aortic valve cohort and relative survival compared to the age-, gender-, and year-matched population (blue line).

**Table 2. Between-group differences in survival among patients in the overall, propensity score matched, and age-matched cohort, divided by age at index procedure.**

| **Overall cohort** | | | |
|---|---|---|---|
| Restricted mean survival time at 10 year (95% CI) | years | 95% CI | p-value |
| Difference – years | 0.242 | 0.116-0.369 | <0.001 |
| Difference – years (50-59 years) | 0.168 | -0.036 – 0.373 | 0.11 |
| Difference – years (60-69 years) | 0.141 | 0.019-0.262 | 0.023 |
| Difference – years (70-79 years) | 0.210 | 0.082-0.339 | 0.001 |
| | | | |
| Restricted mean survival time at 20 year (95% CI) | | 95% CI | p-value |
| Difference – years | 0.592 | 0.305-0.880 | <0.001 |
| Difference – years (50-59 years) | 0.440 | -0.020-0.901 | 0.06 |
| Difference – years (60-69 years) | 0.343 | 0.060-0.627 | 0.018 |
| Difference – years (70-79 years) | 0.506 | 0.214-0.798 | 0.001 |
| | | | |
| **Propensity score matched cohort** | | | |
| Restricted mean survival time at 10 year (95% CI) | | 95% CI | p-value |
| Difference – years | 0.062 | -0.100-0.223 | 0.45 |
| Difference – years (50-59 years) | 0.067 | -0.163-0.298 | 0.57 |
| Difference – years (60-69 years) | 0.033 | -0.111-0.178 | 0.65 |
| Difference – years (70-79 years) | 0.070 | -0.096-0.236 | 0.41 |
| | | | |
| Restricted mean survival time at 20 year (95% CI) | | 95% CI | p-value |
| Difference – years | 0.212 | -0.156-0.579 | 0.26 |
| Difference – years (50-59 years) | 0.224 | -0.297-0.744 | 0.40 |
| Difference – years (60-69 years) | 0.141 | -0.199-0.480 | 0.42 |
| Difference – years (70-79 years) | 0.221 | -0.156-0.598 | 0.25 |
| | | | |
| **Age matched cohort** | | | |
| Restricted mean survival time at 10 year (95% CI) | | 95% CI | p-value |
| Difference – years | 0.127 | -0.045-0.298 | 0.15 |
| Difference – years (50-59 years) | 0.191 | -0.081-0.464 | 0.17 |
| Difference – years (60-69 years) | 0.188 | 0.011-0.365 | 0.037 |
| Difference – years (70-79 years) | 0.129 | -0.045-0.303 | 0.15 |
| | | | |
| Restricted mean survival time at 20 year (95% CI) | | 95% CI | p-value |
| Difference – years | 0.291 | -0.096-0.678 | 0.14 |
| Difference – years (50-59 years) | 0.451 | -0.155-1.057 | 0.14 |
| Difference – years (60-69 years) | 0.399 | -0.001-0.800 | 0.051 |
| Difference – years (70-79 years) | 0.281 | -0.111-0.673 | 0.16 |

## Factors associated with survival during follow-up in the age-matched population

In multivariable analyses, the presence of cardiovascular risk factors such as increasing age (p<0.001), atrial fibrillation (p<0.001), previous myocardial infarction (p=0.05) and concomitant CABG (p<0.001) were predictors of mortality in the age-matched BAV population (Table 3). In the age-matched TAV population, increasing age (p<0.001), diabetes (p=0.003), COPD (p=0.01) and concomitant CABG (p=0.01) were independent predictors of mortality (Table 3). Sensitivity analysis for patients with isolated SAVR is shown in Table S3.

**Table 3. predictors of survival after SAVR in overall age matched cohort of BAV and TAV.**

| | Age-matched BAV population | | Age-matched TAV population | |
|---|---|---|---|---|
| **Characteristics** | **Univariable HR (95% CI); p-value** | **Multivariable HR (95% CI); p-value** | **Univariable HR (95% CI); p-value** | **Multivariable HR (95% CI); p-value** |
| **Age** | 1.07 (1.06-1.09); p<0.001 | 1.07 (1.05-1.09); p<0.001 | 1.07 (1.05-1.08); p<0.001 | 1.05 (1.03-1.07); p<0.001 |
| **Sex (female)** | 1.0 (0.7-1.2); p=0.76 | | 1.0 (0.8-1.3); p=0.97 | |
| **AS** | 2.3 (1.3-4.2); p=0.007 | 1.0 (0.5-1.9); p=0.97 | 1.5 (1.1-2.2); p=0.014 | 1.1 (0.8-1.6); p=0.62 |
| **Hypertension** | 1.2 (0.9-1.6); p=0.16 | 1.1 (0.9-1.5); p=0.35 | 1.3 (1.0-1.6); p=0.08 | 1.0 (0.8-1.3); p=0.97 |
| **Hypercholesterol-emia** | 1.0 (0.8-1.1); p=0.29 | | 0.9 (0.6-1.3); p=0.54 | |
| **Diabetes mellitus** | 1.4 (0.9-2.1); p=0.14 | 0.9 (0.6-1.5); p=0.77 | 2.1 (1.5-3.0); p<0.001 | 1.7 (1.2-2.3); p=0.003 |
| **Arterial disease** | 1.4 (0.6-3.1); p=0.44 | | 2.3 (1.3-4.1); p=0.003 | 1.6 (0.9-2.8); p=0.13 |
| **Renal failure** | 1.3 (0.6-3.0); p=0.49 | | 3.4 (1.8-6.4); p<0.001 | 3.6 (1.8-7.1); p<0.001 |
| **Previous MI** | 1.6 (1.1-2.4); p=0.013 | 1.5 (1.0-2.2); p=0.05 | 1.8 (1.3-2.5); p=0.001 | 1.2 (0.8-1.7); p=0.34 |
| **Previous PCI** | 1.1 (0.6-2.1); p=0.74 | | 1.2 (0.8-2.0); p=0.41 | |
| **Decompensated heart failure** | 1.8 (1.3-2.5); p<0.001 | 1.5 (1.1-2.0); p=0.023 | 1.6 (1.2-2.1); p=0.003 | 1.3 (1.0-1.8); p=0.08 |
| **LVEF <50%** | 0.9 (0.5-1.8); p=0.86 | | 0.9 (0.5-1.5); p=0.56 | |
| **Atrial fibrillation** | 2.1 (1.5-3.0); p<0.001 | 2.0 (1.4-2.8); p<0.001 | 1.9 (1.3-2.6); p<0.001 | 1.4 (1.0-2.0); p=0.06 |
| **Previous stroke or TIA** | 1.2 (0.7-2.0); p=0.47 | | 1.3 (0.9-1.9); p=0.24 | |
| **COPD** | 1.9 (1.3-2.8); p=0.002 | 1.9 (1.3-2.9); p=0.002 | 1.7 (1.1-2.5); p=0.01 | 1.7 (1.1-2.5); p=0.01 |
| **Concomitant CABG** | 1.6 (1.3-2.1); p<0.001 | 1.4 (1.1-1.8); p=0.008 | 2.2 (1.7-2.8); p<0.001 | 1.5 (1.1-2.0); p=0.01 |
| **Emergent SAVR versus non-emergent** | 1.3 (0.4-4.0); p=0.67 | | 1.1 (0.3-4.5); p=0.87 | |
| **Mechanical prosthesis** | 0.5 (0.4-0.6); p<0.001 | 0.9 (0.7-1.3); p=0.67 | 1.7 (1.1-2.5); p=0.01 | 0.9 (0.6-1.2); p=0.40 |

AS, aortic stenosis; CABG, coronary artery bypass grafting; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio, MI, myocardial infarction; TIA, transient ischemic attack; LVEF, left ventricular ejection fraction; SAVR, surgical aortic valve replacement

## DISCUSSION

This study describes the association of aortic valve morphology, patient characteristics at the time of SAVR and the subsequent long-term survival. We found that (1) younger patients had a higher prevalence of BAV at the time of the index procedure; (2) patients with BAV had fewer cardiovascular risk factors; (3) this difference in cardiovascular risk factors remained after adjusting for age; (4) long-term survival is comparable in patients with BAV and TAV after adjusting for baseline characteristics and (5) the long-term survival after SAVR is exceptionally high in patients with BAV compared to the age, sex and calendar matched Dutch population.

In an era where TAVI indications are expanding and becoming an alternative treatment for younger patients with low surgical risk, the knowledge regarding the prevalence of bicuspid valvular morphology in the current SAVR population is of utmost importance. The prevalence of bicuspid morphology in patients undergoing SAVR is higher than that of the general population.[3,15] An echocardiographic evaluation of a Chinese population showed a negative correlation of age and prevalence of bicuspid aortic valves; increasing prevalence with decreasing age (1.16% in patients aged 0-20; 0.18% in patients aged 60-83).[15] A similar trend was noted in a Western cohort undergoing SAVR and reporting a prevalence of 76% for quinquagenarians, 60% for sexagenarians and 42% for septuagenarians[3], which was notably higher than in our cohort. The included patients underwent isolated SAVR and only had aortic valvular problems, whereas our cohort also included a proportion of patients with concomitant CABG. Of note, the currently observed prevalence of BAV in a surgical cohort is higher than the current incidence in the TAVI population, even after reviewing an age-matched TAVI population[16], reflecting the current relative contraindications for patients with BAV to undergo TAVR.

Patients with BAV more often have (pure) AS and fewer cardiovascular risk factors compared to patients with TAV. To account for the difference in age and the association of age with cardiovascular risk factors[17], we additionally analysed an age-matched group. Yet, the difference in systemic cardiovascular risk factors remained in the age-matched cohort, which reflects the congenital component in aberrant morphology in those with BAV.[18,19] This difference in AS is also partly explained by an accelerated calcification process compared to patients with TAV[20], whereas the calcification mechanism is the same.[21] Cardiovascular risk factors such as diabetes, hypertension and hypercholesterolaemia occur less frequently in patients with BAV compared to TAV, highlighting the difference in the disease process.[22] The aortic prosthesis was larger in patients with BAV (24.4 vs 23.4; $p<0.001$). This difference persisted in the age-adjusted population (24.4 vs 23.7; $p<0.001$). Bicuspid morphology is associated with increased prevalence of aortic root dilatation and ascending aortic aneurysms[19], even in patients without valvular dysfunction, such as or AR, due to BAV.[23] However, even after excluding patients with

concomitant procedures due to dilating annulopathy or ascending aorta, we might notice beginning dilating annulopathy.

In our population, patients with BAV had better survival even after propensity score matching; this difference did not disappear after adjusting for age only. This finding could be explained by the lower prevalence of the cardiovascular risk profile of those patients, again reflecting the systemic component of the disease, which could be related to factors not captured in our cohort, such as higher body mass index in patients with TAV[18], which might affect survival[24], especially because small prosthesis implants were more prevalent in those undergoing SAVR with TAV. Crude survival alone does not adjust for death due to other, nonintervention related causes. Relative survival is a comparison of the investigated population to the survival of the general population, proving an estimate of the disease-related risk.[25] In patients with BAV, the relative survival in the age-, sex- and calendar year-matched Dutch population was historically high after 20 years of follow-up (89.0%), which is close to that in the general population.

## Future outlook

Bicuspid valvular aortic disease has systematically been excluded from the pivotal TAVI trials.[26,27] Initial experience with early generation TAVR devices in bicuspid anatomy lead to high incidences of PVL and high PPM[28], which is decreasing with newer generation devices. Patients with BAV who have TAVI have a higher risk of short-term mortality and morbidity compared to patients with tricuspid AS.[29] Until long-term data from well-conducted randomized trials with new-generation TAVI devices in patients with bicuspid aortic valves are available, surgery remains a feasible and well-accepted strategy for those with bicuspid aortic valves.

## Limitations

Our study has multiple limitations. First, because our study is retrospective and single-centre, it has the inherent shortcomings related to data capture, changes in definitions of comorbidities and patients being lost to follow-up, especially with a 30-year follow-up. Second, we did not base the final decision of aortic valve morphology on echocardiographic or CT findings but on surgical reports, wherein the prevalence of BAV differs from that in population studies. Third, our study evaluated the patient characteristics and long-term mortality as outcomes. Other aspects of clinical outcome and specific valve-related outcomes, including symptom improvement, quality of life and structural valve dysfunction at long-term follow-up, were not assessed and should be studied in further trials.

## CONCLUSION

Patients with BAV compared to those with TAV have fewer cardiovascular risk factors and exhibit excellent survival rates after SAVR. Additional studies are needed to examine the exact effect of differing cardiovascular risk profiles on other end points such as quality of life and risk of structural valvular dysfunction and the relation to the expected burden of TAVR.

## REFERENCES


1. Nistri S, Basso C, Marzari C, Mormino P, Thiene G. Frequency of bicuspid aortic valve in young male conscripts by echocardiogram. Am J Cardiol. 2005;96(5):718-21.
2. Braverman AC, Guven H, Beardslee MA, Makan M, Kates AM, Moon MR. The bicuspid aortic valve. Curr Probl Cardiol. 2005;30(9):470-522.
3. Roberts WC, Ko JM. Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. Circulation. 2005;111(7):920-5.
4. Mordi I, Tzemos N. Bicuspid aortic valve disease: a comprehensive review. Cardiol Res Pract. 2012;2012:196037.
5. Cozijnsen L, van der Zaag-Loonen HJ, Cozijnsen MA, Braam RL, Heijmen RH, Bouma BJ, et al. Differences at surgery between patients with bicuspid and tricuspid aortic valves. Neth Heart J. 2019;27(2):93-9.
6. Gahl B, Celik M, Head SJ, Vanoverschelde JL, Pibarot P, Reardon MJ, et al. Natural History of Asymptomatic Severe Aortic Stenosis and the Association of Early Intervention With Outcomes: A Systematic Review and Meta-Analysis. JAMA Cardiol. 2020.
7. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739-91.
8. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Fleisher LA, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017;70(2):252-89.
9. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16(3):233-70.
10. Silber JH, Rosenbaum PR, Trudeau ME, Even-Shoshan O, Chen W, Zhang X, et al. Multivariate matching and bias reduction in the surgical outcomes study. Med Care. 2001;39(10):1048-64.
11. Perme MP, Pavlic K. Nonparametric Relative Survival Analysis with the R Package relsurv. 2018. 2018;87(8):27.
12. Database HM. 2019 [Available from: https://www.mortality.org/.
13. Pohar M, Stare J. Relative survival analysis in R. Comput Methods Programs Biomed. 2006;81(3):272-8.
14. Pohar M, Stare J. Making relative survival analysis relatively easy. Comput Biol Med. 2007;37(12):1741-9.
15. Li Y, Wei X, Zhao Z, Liao Y, He J, Xiong T, et al. Prevalence and Complications of Bicuspid Aortic Valve in Chinese According to Echocardiographic Database. Am J Cardiol. 2017;120(2):287-91.
16. Zhao ZG, Jilaihawi H, Feng Y, Chen M. Transcatheter aortic valve implantation in bicuspid anatomy. Nat Rev Cardiol. 2015;12(2):123-8.
17. Dhingra R, Vasan RS. Age as a risk factor. Med Clin North Am. 2012;96(1):87-91.
18. Huntley GD, Thaden JJ, Alsidawi S, Michelena HI, Maleszewski JJ, Edwards WD, et al. Comparative study of bicuspid vs. tricuspid aortic valve stenosis. Eur Heart J Cardiovasc Imaging. 2018;19(1):3-8.

19. Tadros TM, Klein MD, Shapira OM. Ascending aortic dilatation associated with bicuspid aortic valve: pathophysiology, molecular biology, and clinical implications. Circulation. 2009;119(6):880-90.
20. Wallby L, Janerot-Sjoberg B, Steffensen T, Broqvist M. T lymphocyte infiltration in non-rheumatic aortic stenosis: a comparative descriptive study between tricuspid and bicuspid aortic valves. Heart. 2002;88(4):348-51.
21. Lewin MB, Otto CM. The bicuspid aortic valve: adverse outcomes from infancy to old age. Circulation. 2005;111(7):832-4.
22. Yan AT, Koh M, Chan KK, Guo H, Alter DA, Austin PC, et al. Association Between Cardiovascular Risk Factors and Aortic Stenosis: The CANHEART Aortic Stenosis Study. J Am Coll Cardiol. 2017;69(12):1523-32.
23. Nkomo VT, Enriquez-Sarano M, Ammash NM, Melton LJ, 3rd, Bailey KR, Desjardins V, et al. Bicuspid aortic valve associated with aortic dilatation: a community-based study. Arterioscler Thromb Vasc Biol. 2003;23(2):351-6.
24. Wang B, Yang H, Wu S, Cao G, Yang H. Obesity and the risk of late mortality after aortic valve replacement with small prosthesis. J Cardiothorac Surg. 2013;8:174.
25. Sarfati D, Blakely T, Pearce N. Measuring cancer survival in populations: relative survival vs cancer-specific survival. Int J Epidemiol. 2010;39(2):598-610.
26. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. N Engl J Med. 2019;380(18):1695-705.
27. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. N Engl J Med. 2019;380(18):1706-15.
28. Yoon SH, Lefevre T, Ahn JM, Perlman GY, Dvir D, Latib A, et al. Transcatheter Aortic Valve Replacement With Early- and New-Generation Devices in Bicuspid Aortic Valve Stenosis. J Am Coll Cardiol. 2016;68(11):1195-205.
29. Makkar RR, Yoon SH, Leon MB, Chakravarty T, Rinaldi M, Shah PB, et al. Association Between Transcatheter Aortic Valve Replacement for Bicuspid vs Tricuspid Aortic Stenosis and Mortality or Stroke. JAMA. 2019;321(22):2193-202.

## SUPPLEMENTARY MATERIAL

**Table S1. Baseline and procedural characteristics stratified according to included BAV cohort and excluded BAV cohort due to aortic surgery.**

| | BAV with concomitant aortic surgery (n=48) | BAV without concomitant aortic surgery (n=607) | p-value | SMD |
|---|---|---|---|---|
| **Age at operation** | 58.7 ± 13.2 | 60.6 ± 12.1 | *0.29* | 0.152 |
| **Gender (female)** | 16 (33.3) | 200 (32.9) | *0.96* | 0.008 |
| **Indication** | | | *0.06* | 0.350 |
| - **AS** | 30 (62.5) | 455 (75.0) | *0.06* | 0.271 |
| - **AI** | 9 (18.8) | 47 (7.7) | *0.009* | 0.329 |
| - **Combined** | 9 (18.8) | 104 (17.1) | *0.78* | 0.042 |
| **Previous cardiac operation** | 6 (12.5) | 31 (5.1) | *0.033* | 0.263 |
| **Creatinine** | 0.93 (0.86-1.07) | 0.95 (0.82-1.10) | *0.69* | 0.095 |
| - **≥2mg/dL** | 0 | 10 (1.7) | *0.37* | 0.183 |
| **Atrial fibrillation** | 5 (10.4) | 54 (8.9) | *0.72* | 0.051 |
| **Diabetes mellitus** | 2 (4.2) | 47 (7.7) | *0.37* | 0.152 |
| **Decompensation cordis** | 4 (8.3) | 64 (10.5) | *0.63* | 0.076 |
| **Hypertension** | 15 (32.1) | 150 (24.7) | *0.32* | 0.146 |
| **Hypercholesterolemia** | 5 (10.4) | 61 (10.0) | *0.94* | 0.012 |
| **Previous.myocardial infarction** | 3 (6.2) | 48 (7.9) | *0.68* | 0.065 |
| **Previous PCI** | 1 (2.1) | 21 (3.5) | *0.61* | 0.084 |
| **COPD** | 1 (2.1) | 44 (7.2) | *0.17* | 0.247 |
| **Endocarditis** | 2 (4.2) | 26 (4.3) | *0.97* | 0.006 |
| **History of cancer** | 3 (6.2) | 26 (4.3) | *0.52* | 0.088 |
| **Stroke/TIA** | 2 (4.2) | 35 (5.8) | *0.64* | 0.074 |
| - **Stroke** | 1 (2.1) | 17 (2.8) | *0.77* | 0.046 |
| - **TIA** | 2 (4.2) | 21 (3.5) | *0.80* | 0.037 |
| **Arterial disease** | 3 (6.2) | 14 (2.3) | *0.10* | 0.196 |
| - **Carotid** | 1 (2.1) | 1 (0.2) | *0.02* | 0.183 |
| - **Peripheral** | 2 (4.2) | 13 (2.1) | *0.37* | 0.116 |
| **Concomitant CABG** | 8 (16.7) | 133 (21.9) | *0.40* | 0.133 |
| **Valve size** | 24.8 ± 2.3 | 24.4 ± 2.4 | *0.26* | 0.173 |
| **Urgency** | | | *0.003* | 0.563 |
| **Emergent** | 3 (6.6) | 6 (1.2) | | |
| **Not emergent** | 42 (93.4) | 490 (98.8) | | |
| **LVEF** | | | *0.78* | 0.151 |
| - **Preserved** | 35 (76.1) | 445 (81.8) | *0.34* | 0.141 |
| - **Mildy reduced** | 3 (6.5) | 31 (5.7) | *0.82* | 0.034 |
| - **Moderately reduced** | 6 (13.0) | 48 (8.8) | *0.34* | 0.136 |
| - **Severely reduced** | 2 (4.3) | 20 (3.7) | *0.82* | 0.034 |
| **Valve (mechanical)** | 29 (60.4) | 389 (64.1) | *0.61* | 0.076 |

AS, aortic stenosis; AR, aortic regurgitation, CI, confidence interval; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; TIA, transient ischemic attack; LVEF, left ventricular ejection fraction; SMD= standardized mean difference

**Table S2. Baseline characteristics, stratified according to the overall cohort, propensity score matched cohort, and age-matched cohort for patients undergoing index procedure after the year 2000.**

| | TAV (1832) | BAV (317) | P-value | SMD | PSM-TAV (311) | PSM-BAV (311) | P-value | SMD | A-TAV (301) | A-BAV (301) | P-value | SMD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Age at operation** | 68.1 ± 11.2 | 59.1 ± 13.2 | <0.001 | 0.736 | 60.1 ± 14.0 | 59.4 ± 12.9 | 0.53 | 0.050 | 60.3 ± 12.3 | 60.1 ± 12.4 | 0.86 | 0.014 |
| **Gender (female)** | 692 (37.8) | 102 (32.3) | 0.07 | 0.118 | 98 (31.5) | 100 (32.2) | 0.93 | 0.014 | 93 (30.9) | 97 (32.2) | 0.79 | 0.029 |
| **Indication** | | | 0.82 | 0.049 | | | 0.75 | 0.088 | | | 0.001 | 0.328 |
| - **AS** | 1402 (76.5) | 243 (76.7) | | 0.003 | 240 (77.2) | 238 (76.5) | 0.85 | 0.015 | 190 (63.1) | 233 (77.4) | <0.001 | 0.316 |
| - **AR** | 208 (11.4) | 34 (10.7) | | 0.020 | 30 (9.6) | 33 (10.6) | 0.69 | 0.032 | 56 (18.6) | 29 (9.6) | 0.002 | 0.260 |
| - **Combined** | 220 (12.0) | 39 (12.3) | | 0.009 | 41 (13.2) | 39 (12.5) | 0.81 | 0.010 | 54 (17.9) | 38 (12.6) | 0.07 | 0.148 |
| **Previous cardiac operation** | 108 (5.9) | 19 (6.0) | >0.999 | 0.004 | 21 (6.8) | 19 (6.1) | 0.87 | 0.026 | 25 (8.3) | 18 (6.0) | 0.34 | 0.090 |
| **Creatinine** | 0.97 (0.83-1.15) | 0.93 (0.79-1.06) | <0.001 | 0.193 | 0.95 (0.83-1.11) | 0.93 (0.79-1.06) | 0.16 | 0.116 | 0.96 (0.83-1.12) | 0.93 (0.80-1.06) | 0.048 | 0.165 |
| - **≥2mg/dL** | 51 (2.8) | 5 (1.6) | 0.29 | 0.083 | 5 (1.6) | 5 (1.6) | >0.999 | <0.001 | 9 (3.0) | 5 (1.7) | 0.42 | 0.088 |
| **Atrial fibrillation** | 240 (13.1) | 24 (7.6) | 0.007 | 0.182 | 24 (7.7) | 24 (7.7) | >0.999 | <0.001 | 29 (9.6) | 24 (8.0) | 0.57 | 0.059 |
| **Diabetes mellitus** | 360 (19.7) | 31 (9.8) | <0.001 | 0.281 | 22 (7.1) | 31 (10.0) | 0.25 | 0.104 | 57 (18.9) | 31 (10.3) | 0.004 | 0.246 |
| **Decompensation cordis** | 233 (12.7) | 24 (7.6) | 0.012 | 0.171 | 24 (7.7) | 24 (7.7) | >0.999 | <0.001 | 40 (13.3) | 24 (8.0) | 0.044 | 0.173 |
| **Hypertension** | 829 (45.3) | 92 (29.0) | <0.001 | 0.341 | 92 (29.6) | 92 (29.6) | >0.999 | <0.001 | 117 (38.9) | 89 (29.6) | 0.020 | 0.197 |
| **Hypercholesterolemia** | 417 (22.8) | 46 (14.5) | 0.001 | 0.213 | 51 (16.4) | 46 (14.8) | 0.66 | 0.044 | 54 (17.9) | 45 (15.0) | 0.38 | 0.081 |
| **Previous myocardial infarction** | 228 (12.4) | 28 (8.8) | 0.08 | 0.117 | 26 (8.4) | 27 (8.7) | >0.999 | 0.012 | 41 (13.6) | 27 (9.0) | 0.09 | 0.147 |
| **Previous PCI** | 173 (9.4) | 18 (5.7) | 0.039 | 0.143 | 14 (4.5) | 18 (5.8) | 0.59 | 0.058 | 30 (10.0) | 17 (5.6) | 0.07 | 0.162 |
| **COPD** | 235 (12.8) | 28 (8.8) | 0.06 | 0.129 | 28 (9.0) | 28 (9.0) | >0.999 | <0.001 | 29 (9.6) | 28 (9.3) | >0.999 | 0.011 |
| **Endocarditis** | 76 (4.1) | 17 (5.4) | 0.41 | 0.057 | 17 (5.5) | 15 (4.8) | 0.86 | 0.029 | 22 (7.3) | 15 (5.0) | 0.31 | 0.097 |
| **History of cancer** | 163 (8.9) | 18 (5.7) | 0.07 | 0.124 | 14 (4.5) | 18 (5.8) | 0.59 | 0.058 | 21 (7.0) | 17 (5.6) | 0.62 | 0.055 |

**Table S2. Baseline characteristics, stratified according to the overall cohort, propensity score matched cohort, and age-matched cohort for patients undergoing index procedure after the year 2000.** (*continued*)

| | TAV (1832) | BAV (317) | P-value | SMD | PSM-TAV (311) | PSM-BAV (311) | P-value | SMD | A-TAV (301) | A-BAV (301) | P-value | SMD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Stroke/TIA** | 198 (10.8) | 23 (7.3) | 0.07 | 0.124 | 22 (7.1) | 23 (7.4) | >0.999 | 0.012 | 24 (8.0) | 23 (7.6) | >0.999 | 0.012 |
| - **Stroke** | 83 (4.5) | 9 (2.8) | 0.22 | 0.090 | 8 (2.6) | 9 (2.9) | >0.999 | 0.020 | 11 (3.7) | 9 (3.0) | 0.82 | 0.037 |
| - **TIA** | 133 (7.3) | 16 (5.0) | 0.19 | 0.092 | 14 (4.5) | 16 (5.1) | 0.85 | 0.030 | 14 (4.70 | 16 (5.3) | 0.85 | 0.031 |
| **Arterial disease** | 102 (5.6) | 10 (3.2) | 0.099 | 0.118 | 11 (3.5) | 10 (3.2) | >0.999 | 0.018 | 17 (5.6) | 10 (3.3) | 0.24 | 0.113 |
| - **Carotid** | 19 (1.0) | 1 (0.3) | 0.36 | 0.088 | 4 (1.3) | 1 (0.3) | 0.37 | 0.108 | 2 (0.7) | 1 (0.3) | >0.999 | 0.047 |
| - **Peripheral** | 87 (4.7) | 9 (2.8) | 0.17 | 0.100 | 7 (2.3) | 9 (2.9) | 0.80 | 0.041 | 15 (5.0) | 9 (3.0) | 0.30 | 0.102 |
| **CABG** | 625 (34.1) | 67 (21.1) | <0.001 | 0.293 | 76 (24.4) | 66 (21.2) | 0.39 | 0.077 | 77 (25.6) | 66 (21.9) | 0.34 | 0.086 |
| **Valve size** | 23.2 ± 2.3 | 24.4 ± 2.4 | <0.001 | 0.515 | 24.3 ± 2.5 | 24.4 ± 2.4 | 0.90 | 0.011 | 23.6 ± 2.4 | 24.4 ± 2.4 | <0.001 | 0.352 |
| **Urgency** | | | 0.26 | 0.141 | | | 0.89 | 0.087 | | | 0.68 | 0.127 |
| - **Emergent** | 23 (1.3) | 3 (1.0) | | | 6 (2.0) | 5 (2.0) | | | 8 (2.7) | 3 (1.0) | | |
| - **Not emergent** | 1739 (98.7) | 299 (99.0) | | | 300 (98.0) | 298 (98.0) | | | 286 (97.3) | 284 (99.0) | | |
| **LVEF** | | | 0.72 | 0.074 | | | 0.66 | 0.105 | | | 0.12 | 0.204 |
| - **Preserved** | 1395 (80.0) | 248 (82.1) | | | 254 (83.0) | 261 (85.3) | | | 210 (74.5) | 235 (82.2) | | |
| - **Mildy reduced** | 146 (8.4) | 22 (7.3) | | | 23 (7.5) | 19 (6.2) | | | 30 (10.6) | 19 (6.6) | | |
| - **Moderately reduced** | 153 (8.8) | 22 (7.3) | | | 20 (6.5) | 21 (6.9) | | | 25 (8.9) | 22 (7.7) | | |
| - **Severely reduced** | 50 (2.9) | 10 (3.3) | | | 9 (2.9) | 8 (2.6) | | | 17 (6.0) | 10 (3.5) | | |
| **Valve (mechanical)** | 508 (27.7) | 160 (50.5) | <0.001 | 0.479 | 150 (48.2) | 156 (50.2) | 0.69 | 0.039 | 152 (50.5) | 147 (48.8) | 0.74 | |

AS, aortic stenosis; AR, aortic regurgitation; CABG, coronary artery bypass graft; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio, MI, myocardial infarction; TIA, transient ischemic attack; LVEF, left ventricular ejection fraction; SAVR, surgical aortic valve replacement

**Table S3. predictors of survival after SAVR in age matched cohort of BAV and TAV who underwent isolated SAVR.**

| | Age-matched BAV population | | Age-matched TAV population | |
|---|---|---|---|---|
| **Characteristics** | **Univariable HR (95% CI); p-value** | **Multivariable HR (95% CI); p-value** | **Univariable HR (95% CI); p-value** | **Multivariable HR (95% CI); p-value** |
| **Age** | 1.06 (1.05-1.08); p<0.001 | 1.06 (1.04-1.09); p<0.001 | 1.05 (1.03-1.07); p<0.001 | 1.05 (1.02-1.07); p<0.001 |
| **Sex (female)** | 1.0 (0.8-1.4); p=0.79 | | 1.0 (0.7-1.4); p=0.99 | |
| **AS** | 2.1 (1.0-4.6); p=0.05 | 1.3 (0.5-3.3); p=0.56 | 1.4 (0.9-2.1); p=0.15 | 1.0 (0.7-1.6); p=0.89 |
| **Hypertension** | 1.0 (0.7-1.5); p=0.86 | | 1.4 (1.0-1.9); p=0.07 | 1.0 (0.7-1.5); p=0.90 |
| **Hypercholesterolemia** | 1.0 (0.6-1.7); p=0.98 | | 0.7 (0.4-1.2); p=0.22 | |
| **Diabetes mellitus** | 1.0 (0.6-2.0); p=0.89 | | 1.6 (1.0-2.7); p=0.05 | 1.2 (0.7-2.1); p=0.42 |
| **Arterial disease** | 1.7 (0.6-4.6); p=0.29 | | 4.9 (2.5-9.6); p<0.001 | 4.0 (2.0-8.1); p<0.001 |
| **Renal failure** | 4.2 (1.0-17.3); p=0.04 | 4.1 (0.3-53.1); p=0.28 | 5.9 (2.6-13.6); p<0.001 | 6.1 (2.4-15.4); p<0.001 |
| **Previous MI** | 2.6 (1.3-5.1); p=0.006 | 2.6 (1.2-5.7); p=0.02 | 0.9 (0.4-2.2); p=0.89 | |
| **Previous PCI** | 2.0 (0.8-4.8); p=0.13 | 1.3 (0.5-3.8); p=0.58 | 0.9 (0.4-2.0); p=0.84 | |
| **Decompensated heart failure** | 2.6 (1.5-4.3); p<0.001 | 2.1 (1.2-3.6); p=0.008 | 1.4 (1.0-2.2); p=0.07 | 1.2 (0.7-1.9); 0.52 |
| **LVEF <50%** | 1.1 (0.7-1.8); p=0.55 | | 1.5 (1.0-2.1); p=0.04 | 1.4 (0.9-2.1); p=0.13 |
| **Atrial fibrillation** | 2.4 (1.5-3.9); p<0.001 | 1.7 (1.1-2.9); p=0.03 | 2.2 (1.4-3.4); p<0.001 | 1.5 (1.0-2.5); p=0.07 |
| **Previous stroke or TIA** | 1.6 (0.9-2.9); p=0.12 | | 0.9 (0.4-1.8); p=0.87 | |
| **COPD** | 2.5 (1.4-4.5); p=0.003 | 2.4 (1.3-4.4); p=0.007 | 1.7 (1.0-3.3); p=0.06 | 2.0 (1.1-3.6); p=0.017 |
| **Emergent SAVR versus not emergent** | 4.5 (1.1-18.5); p=0.04 | 2.0 (0.2-25.7); p=0.60 | 0.7 (0.1-5.3); p=0.77 | |
| **Mechanical prosthesis** | 0.5 (0.4-0.7); p<0.001 | 1.0 (0.7-1.5); p=0.94 | 0.6 (0.4-0.8); p=0.002 | 1.0 (0.6-1.5); p=0.85 |

AS, aortic stenosis; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio, MI, myocardial infarction; TIA, transient ischemic attack; LVEF, left ventricular ejection fraction; SAVR, surgical aortic valve replacement

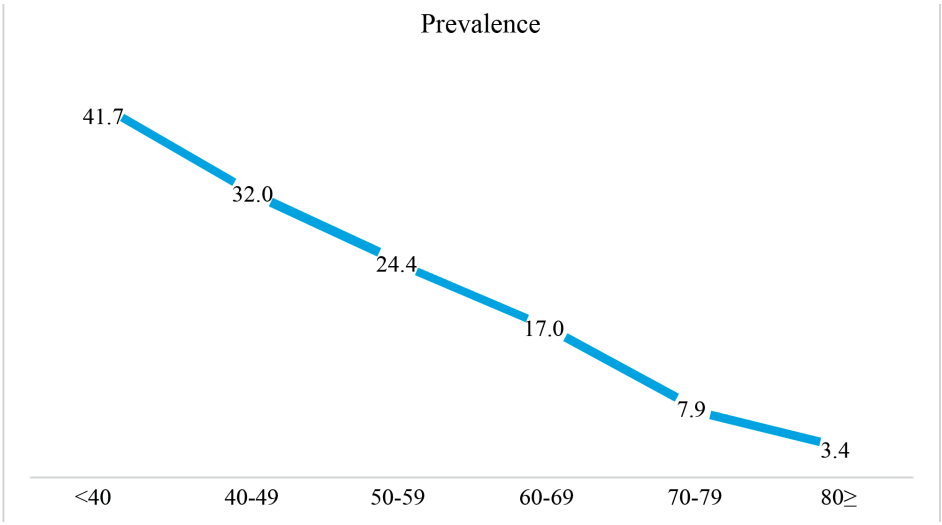


**Figure S1. Prevalence of bicuspid aortic valve in patients operated after 2000.**

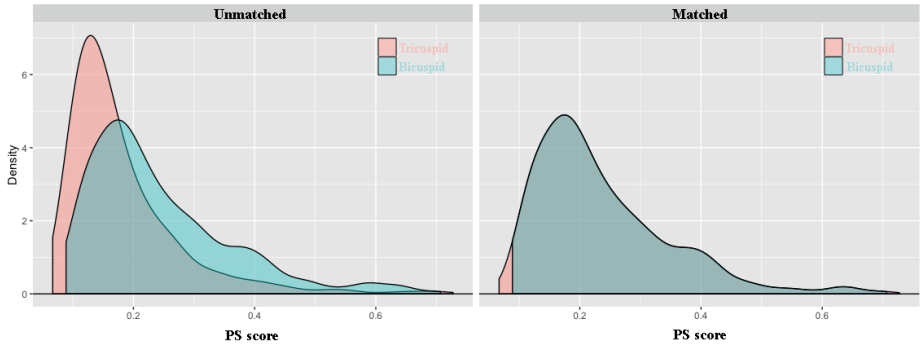


**Figure S2. Density of propensity scores in (A) unmatched and (B) matched cohort in patients operated after 2000.**

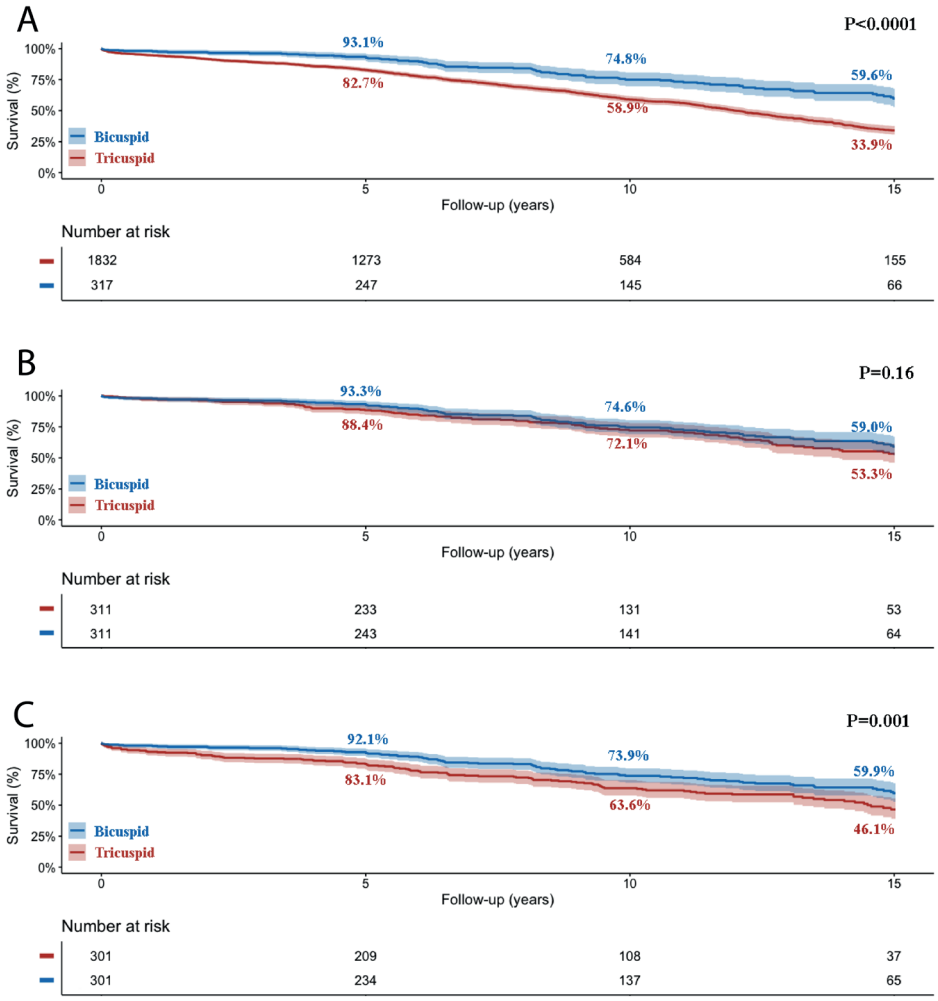


**Figure S3. Survival in patients operated after 2000.**
Survival in the overall cohort, B) propensity score matched cohort, C) age-matched cohort

# 8 Surgical Aortic Valve Replacement with Concomitant Aortic Surgery in Patients with Purely Bicuspid Aortic Valve and Associated Aortopathy

Çelik M, Mahtab EAF, Bogers AJJC.

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## ABSTRACT

**Background:** Bicuspid aortic valve (BAV) is the most common congenital cardiac malformation associated with aortopathy. The current study provides surgical clinical data on patient characteristics and long-term survival of this less common adult purely BAV population undergoing surgical aortic valve replacement (SAVR) with concomitant aortic surgery.

**Methods:** Adult patients with purely BAV who underwent SAVR and concomitant aortic surgery were included. Prevalence, predictors of survival, and outcomes for this patient population were analyzed.

**Results:** A total of 48 patients (mean age 58.7 ± 13.2 years, 33% female) with purely BAV underwent SAVR and concomitant aortic surgery between 1987 and 2016. The majority (62%) of the patients had pure aortic stenosis (AS). A total of 12 patients died. Survival was 92%, 73%, and 69% at 1-, 5- and 20-years of follow-up. At 15 years of follow-up, the survival is close to that of the Dutch population, with a relative survival of 77%.

**Conclusions:** Adult patients with a purely bicuspid aortic valve morphology undergoing SAVR and concomitant aortic root and/or ascending aorta present with excellent survival.

## INTRODUCTION

Bicuspid aortic valve (BAV) disease is the most prevalent congenital heart defect with a prevalence of approximately 1% in the general population.[1,2] A classification system for BAV from 304 surgical specimens, shows an incidence of only 7% purely BAV in an autopsied population.[3] Although much data is present in patients with BAV and a raphe, data in patients with the less common purely bicuspid aortic valves,is still relatively limited.[3]

BAV is associated with aortopathies that lead to clinical manifestations such as aortic dilation, aneurysm, and dissection.[4] In the adult population, BAV patients undergoing aortic valve surgery are younger compared to the tricuspid aortic valve population. Patients with BAV present earlier with aortic stenosis (AS) and tend to undergo more frequent concomitant aortic surgery due to aortopathy.[5]

Studies assessing the clinical profiles of BAV patients with a purely bicuspid aortic valve undergoing surgical aortic valve replacement (SAVR) and concomitant aortic surgery remain scarce. Therefore, the purpose of this study is to (i) describe the clinical characteristics of the purely BAV patientsundergoing SAVR with concomitant aortic surgery and (ii) assess the long-term survival and predictors of survival in this subpopulation of BAV patients.



## METHODS

### Study design

Patients older than 18 years of age undergoing SAVR between 1987 and 2016 at the Erasmus Medical Centre, Rotterdam, were included. In this SAVR population (total n=4404), 16% of the patients who have undergone SAVR had purely BAV (n=711) and only 7% of these purely BAV patients underwent concomitant aortic surgery (n=48, as shown in Figure 1). Patients without pure BAV were excluded (Sievers 0).[3] Likewise, patients without concomitant aortic surgery were excluded. Patients who did not receive biological or mechanical aorta valve prosthesis were also excluded. The valvular morphology was classified during the operation and defined by the attending surgeon. Electronical medical records were used to obtain patient and procedural characteristics. For inclusion in this study, bicuspid aortic valve was classified as purely bicuspid aortic valve according to Sievers classification (Sievers 0) . All the authors vouch for the validity of the data and adherence to the protocol.

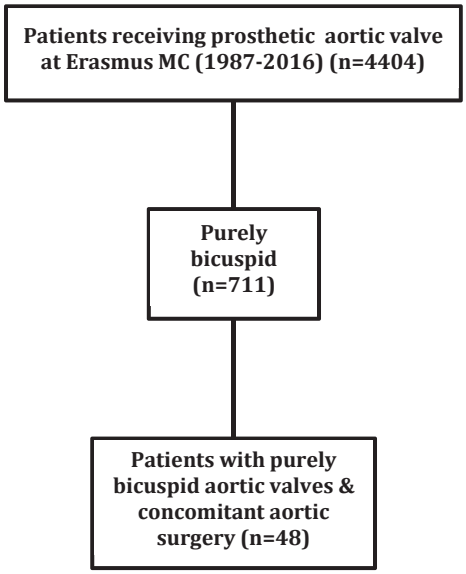


**Figure 1. Flow-chart of the patients included.**
A total of 4404 patients underwent surgical aortic valve replacement (SAVR) with a prosthetic valve, 711 patient had purely bicuspid aortic valve (BAV) of who 48 had purely BAV with concomitant aortic surgery.

## Goals and definitions

The primary aim was to assess the characteristics of patients with purely BAV requiring surgery. A further aim was to assess the survival after surgery of patients with purely BAV. The primary indication for operation (AS, aortic regurgitation (AR) or combined AS and AR) was determined based on the initial echocardiogram and according to the clinical guidelines in use at the time of the surgery.

## Statistical analysis

Discrete variables are presented as numbers, percentages or proportions, and compared with either the Chi Square test or the Fisher Exact test, where appropriate. Continuous variables are presented as means ± standard deviation or median with the interquartile range (IQR) if there was evidence of skewed data according to the Kolmogorov-Smirnov test, and compared with either the two-sample t-test or Wilcoxon rank-sum test, where appropriate.

The relative survival can be used as an estimate of cause-specific mortality. It is defined as the ratio between the observed survival rates and the expected survival rates in the general population.[6] The Human Mortality Database was used to obtain the age, sex and calendar year matched expected survival data of the general population in The Netherlands.[7] The Human Mortality Database is continuously updated and includes mortality data from The Netherlands up until 2016. Relative survival was estimated through the

Ederer II method.[8,9] Predictors of mortality were identified in a Cox proportional hazards model. Significant variables on univariable analyses were included in a multivariable Cox proportional hazards model. Sensitivity analysis was performed for isolated SAVR. Two-sided p-values <0.05 were considered to be statistically significant. Data analyses were done using SPSS 25.0 (SPSS Inc, Chicago, Illinois) and R software, version 3.5 (R Foundation, Vienna, Austria). Figures were generated using Microsoft Excel (Microsoft, Redmond, WA, USA) and R software, version 3.5 (R Foundation, Vienna, Austria).

## RESULTS

### Characteristics of patients with purely bicuspid aortic valves

A total of 48 purely BAV patients underwent SAVR with concomitant aortic surgery (Figure 2). The mean age of operated patients was 58.7 ± 13.2, with 9 patients younger than 50, and 10 patients being 70 or older. The prevalences of comorbidities such as hypertension (32%), hypercholesterolemia (10%), and diabetes mellitus (4%) are shown in Table 1.

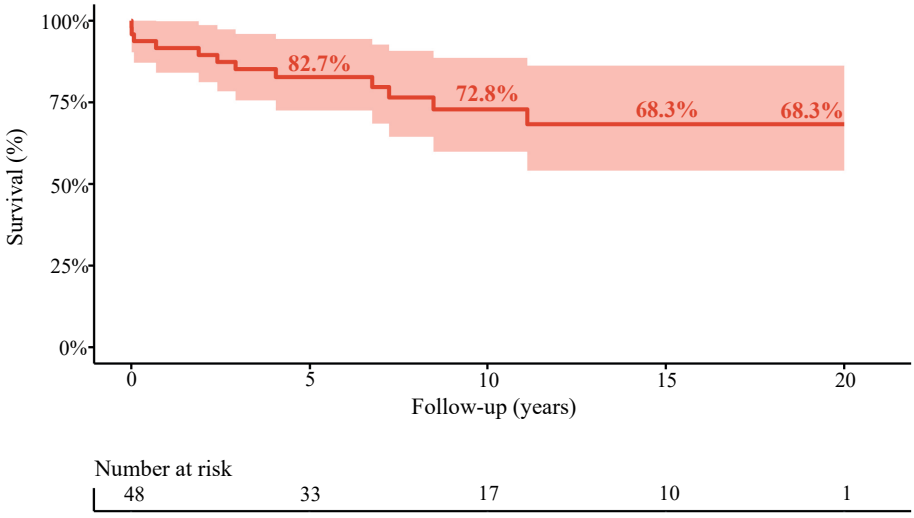


**Figure 2. Long-term survival after SAVR with aortic surgery.**
Survival in overall cohort. *Shaded area represents the 95% confidence interval.*

### Procedural characteristics

The indication for surgery was mainly AS (62%), followed by AR (19%) or combined AS and AR (19%). Type of aortic surgery was aortic root replacement in 21% of the patients and supracoronary ascendens replacement in 79% of the patients. Additionally, in 13

patients (27%), on top of the root- and/or ascending aorta, concomitant (hemi-)arch replacement was performed. Further concomitant surgery included CABG in 17% of the patients. The diameter of the implanted valve prosthesis was 24.8 ± 2.3. Further concomitant surgeries and characteristics are shown in Table 1.

**Table 1. Baseline and procedural characteristics in the overall cohort**

| | **Overall cohort (n=48)** |
|---|---|
| **Age at operation** | 58.7 ± 13.2 |
| **Gender (female)** | 16 (33%) |
| **Indication** | |
| - **AS** | 30 (62%) |
| - **AR** | 9 (19%) |
| - **Combined** | 9 (19%) |
| **Previous cardiac operation** | 6 (13%) |
| - **Previous aortic valve operation** | 0 |
| **Creatinine** | 0.93 (0.86-1.07) |
| - **≥2mg/dL** | 0 |
| **Atrial fibrillation** | 5 (10%) |
| **Diabetes mellitus** | 2 (4%) |
| **Decompensation cordis** | 4 (8%) |
| **Hypertension** | 15 (32%) |
| **Hypercholesterolemia** | 5 (10%) |
| **Previous myocardial infarction** | 3 (6%) |
| **Previous PCI** | 1 (2%) |
| **COPD** | 1 (2%) |
| **Endocarditis** | 2 (4%) |
| **History of cancer** | 3 (6%) |
| **Stroke/TIA** | 2 (4%) |
| - **Stroke** | 1 (2%) |
| - **TIA** | 2 (4%) |
| **Arterial disease** | 3 (6%) |
| - **Carotid** | 1 (2%) |
| - **Peripheral** | 2 (4%) |
| **Concomitant CABG** | 8 (17%) |
| **Aortic surgery** | |
| - **Aortic root replacement** | 10 (21%) |
| - **Supracoronay ascendens replacement** | 38 (79%) |
| - **Ascendens + Hemi(arch)** | 13 (27%) |
| **Valve size** | 24.8 ± 2.3 |
| **Urgency** | |
| **Emergent** | 3 (7%) |
| **Not emergent** | 42 (93%) |
| **LVEF** | |
| - **Preserved** | 35 (76%) |
| - **Mildy reduced** | 3 (7%) |
| - **Moderately reduced** | 6 (13%) |
| - **Severely reduced** | 2 (4%) |
| **Prosthetic valve (mechanical)** | 29 (60%) |
| **Prosthetic valve (biological)** | 19 (40%) |

### Long- term outcomes after surgery

A total of 12 patients died during follow-up. Survival was 92%, 90%, 83%, 73% and 68% at 1- , 2-, 5-, 10- and 20-years of follow-up in the overall cohort for patients with purely BAV (Figure 1). In age-, sex- and year- matched Dutch control the relative survival in patients with purely BAV was 99%, 96% 86%, 79%, and 77%, at 1-, 2-, 5-, 10-, 15-years of follow-up, respectively (Figure 3).

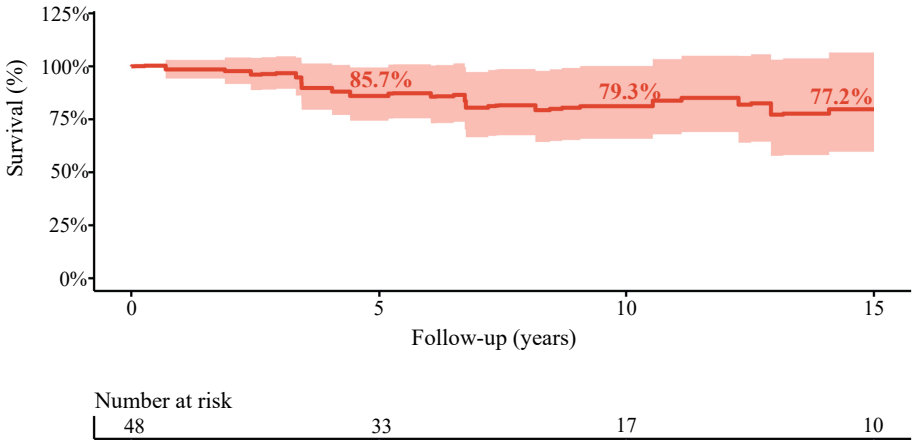


**Figure 3. Long-term relative survival after SAVR with aortic surgery compared to the Dutch population.**

Relative survival compared to the age-, gender-, and year-matched population in the overall cohort. *Shaded area represents the 95% confidence interval.*

### Factors associated with survival during follow-up in the age-matched population.

In univariable analyses, the presence of COPD was a predictor of survival (p=0.02). However, cardiovascular risk factors such as increasing age (p=0.20), atrial fibrillation (p=0.80), and concomitant CABG (p=0.64) were not predictors of survival (Table 2).

**Table 2. predictors of survival after SAVR with concomitant aortic surgery**

| Characteristics | Univariable HR (95% CI); p-value |
|---|---|
| **Age** | 1.04 (1.00-1.10); p=0.20 |
| **Sex (female)** | 1.7 (0.5-5.4); p=0.37 |
| **AS** | 1.7 (0.4-6.1); p=0.44 |
| **AR** | 0.2 (0.01-3.3); p=0.25 |
| **Hypertension** | 1.1 (0.3-3.7); p=0.86 |
| **Hypercholesterolemia** | 1.0 (0.8-1.1); p=0.29 |
| **Diabetes mellitus** | 1.4 (0.9-2.1); p=0.14 |
| **Arterial disease** | 2.3 (0.3-18.4); p=0.44 |
| **Renal failure** | 1.3 (0.6-3.0); p=0.49 |
| **Previous MI** | 3.1 (0.7-14.3); p=0.14 |
| **Previous PCI** | 1.1 (0.6-2.1); p=0.74 |
| **Decompensated heart failure** | 0.8 (0.1-6.1); p=0.82 |
| **LVEF <50%** | 1.8 (0.5-6.2); p=0.35 |
| **Atrial fibrillation** | 0.7 (0.1-6.0); p=0.80 |
| **Previous stroke or TIA** | 2.0 (0.2-15.3); p=0.52 |
| **COPD** | 1.9 (1.3-2.8); p=0.002 |
| **Concomitant CABG** | 1.4 (0.4-5.1); p=0.64 |
| **Emergent SAVR versus non-emergent** | 1.7 (0.2-13.5); p=0.62 |
| **Mechanical prosthesis** | 1.0 (0.2-4.3); p=0.97 |

## DISCUSSION

This study describes the characteristics and outcomes clinical characteristics of of patients with purely bicuspid aortic valves that underwent aortic root-, ascendens and arch replacement as concomitant surgery to SAVR as well as the long-term survival and predictors of survival in this population. We found that the purely BAV population requiring SAVR and concomitant aortic surgery (i) mostly consists of young patients, ii) has few cardiovascular risk factors, that were not found predictive for their survival , and (iii) has excellent long-term survival.

The mechanisms leading to development of BAV and the associated aortopathies is a matter of ongoing discussion. Adriana C. Gittenberger-de Groot and her team have performed an extensive amount of indispensable studies on the spectrum of BAV disease and associated aortic anomalies over the past three decades. This contribution includes several developmental, histopathological and anatomical studies on animal as well as human tissue such as meticulous explanation of cardiac development in congenital malformations[10], anatomical description of BAV and the aortic root[11], contribution of several cell lineages to the development of BAV and the associated aortic root anomalies.[12-14]

In addition, other groups described that patient specific factors such as aortic valve stenosis (AS) in combination with specific leaflet morphology (the type of BAV) and the resulted shear stress were associated with dilatation of the aorta.[15,16]

Our cohort consisted of relatively young patients with purely BAV; a minority of the BAV population.[3,17] Our patients often presented with aortic stenosis, yet the incidence of aortic regurgitation was close to 40%. This prevalence of aortic regurgitation was higher than the standard surgical aortic valve replacement population, which could be partly due to aortic root or proximal aorta dilatation.[4] Bicuspid aortic valve indicates abnormal leaflet modeling, subsequently leading to turbulence downstream and upstream of the aortic valve.[18] This turbulence increases the aortic wall shear stress and abnormal helical flow in the ascending aorta as shown with previous 4D magnetic resonance imaging.[19,20] In addition, increased matrix metalloproteinases activity in the aorta of BAV patients can affect the structural flexibility by altered elastin, collagen and smooth muscle composition of the elastic laminae (aortic media) and therefore lead to reduced compliance and increased aortic stiffness.[4,21] Therefore, BAV is associated with increased prevalence of aortic root dilatation and ascending aortic aneurysms[22], even in patients without yet developed valvular dysfunction.[23] Moreover, gender differences in aortic dimension of patient with BAV were associated with aortopathy. Male patients more often present with larger aortic annulus and sinotubular junction dimensions.[24] The majority of our patients, (two-third) described in this study, were male. This finding is similar to previous studies.[4] Patients with bicuspid valves also present with less cardiovascular risk factors compared to patients with tricuspid aortic morphology and at an earlier age. This is partly due to accelerated calcification.[25] Aside from aortopathy and subsequent aortic dissection, endocarditis was prevalent in 4% of our cohort, this rate is lower than the previously noted higher prevalence.[26]

In our cohort, the majority of the patients received mechanical valvular prosthesis. Mechanical prosthesis are undoubtedly superior regarding long-term durability and survival in the younger population[27], however, mechanical prosthesis might affect the quality of life of the patient due to anticoagulant medication and known bleeding risks, especially in an aging population.[28,29] Yet, the overall survival in our cohort was exceptionally high, with 68% of the population surviving at 20-years of follow-up. The relative survival of this population (79%) is close to that of the Dutch general population. This could be partly explained due to lower prevalence in cardiovascular risk profile of those patients.

**Limitations**

Given its retrospective and nonrandomized nature our study could be subject to shortcoming related to data capture and inherent confounders. Second, our study evaluated the patient characteristics and long-term mortality as outcomes. Other aspects of clinical

outcome and specific valve-related outcomes, including symptom improvement, quality of life, structural valve dysfunction at long-term follow-up were not assessed, and should be assessed in further studies. In our study we only included patients with purely BAV (Type 0) to create a homogenous BAV morphology, however, we are missing the other BAV types with associated raphe and the comparison with our population and TAV population in prevalence of aortopathy, clinical patient characteristics and survival.

## CONCLUSION

Patients with purely BAV undergoing SAVR with concomitant aortic surgery present with excellent survival rates. Additional studies are needed to examine the exact effect of intervention on other endpoints such as quality of life.

## REFERENCES


1. Nistri S, Basso C, Marzari C, Mormino P, Thiene G. Frequency of bicuspid aortic valve in young male conscripts by echocardiogram. Am J Cardiol. 2005;96(5):718-21.
2. Braverman AC, Guven H, Beardslee MA, Makan M, Kates AM, Moon MR. The bicuspid aortic valve. Curr Probl Cardiol. 2005;30(9):470-522.
3. Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. J Thorac Cardiovasc Surg. 2007;133(5):1226-33.
4. Fedak PW, Verma S, David TE, Leask RL, Weisel RD, Butany J. Clinical and pathophysiological implications of a bicuspid aortic valve. Circulation. 2002;106(8):900-4.
5. Mordi I, Tzemos N. Bicuspid aortic valve disease: a comprehensive review. Cardiol Res Pract. 2012;2012:196037.
6. Perme MP, Pavlic K. Nonparametric Relative Survival Analysis with the R Package relsurv. 2018. 2018;87(8):27.
7. Database HM. 2019 [Available from: https://www.mortality.org/.
8. Pohar M, Stare J. Relative survival analysis in R. Comput Methods Programs Biomed. 2006;81(3):272-8.
9. Pohar M, Stare J. Making relative survival analysis relatively easy. Comput Biol Med. 2007;37(12):1741-9.
10. Gittenberger-de Groot AC, Bartelings MM, Deruiter MC, Poelmann RE. Basics of cardiac development for the understanding of congenital heart malformations. Pediatr Res. 2005;57(2):169-76.
11. Bartelings MM, Bogers AJ, Galantowicz ME, Gittenberger-De Groot AC. Anatomy of the aortic and pulmonary roots. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu. 1998;1:157-64.
12. Peterson JC, Wisse LJ, Wirokromo V, van Herwaarden T, Smits AM, Gittenberger-de Groot AC, et al. Disturbed nitric oxide signalling gives rise to congenital bicuspid aortic valve and aortopathy. Dis Model Mech. 2020;13(9).
13. Bergwerff M, Verberne ME, DeRuiter MC, Poelmann RE, Gittenberger-de Groot AC. Neural crest cell contribution to the developing circulatory system: implications for vascular morphology? Circ Res. 1998;82(2):221-31.
14. Kappetein AP, Gittenberger-de Groot AC, Zwinderman AH, Rohmer J, Poelmann RE, Huysmans HA. The neural crest as a possible pathogenetic factor in coarctation of the aorta and bicuspid aortic valve. J Thorac Cardiovasc Surg. 1991;102(6):830-6.
15. Kimura N, Nakamura M, Komiya K, Nishi S, Yamaguchi A, Tanaka O, et al. Patient-specific assessment of hemodynamics by computational fluid dynamics in patients with bicuspid aortopathy. J Thorac Cardiovasc Surg. 2017;153(4):S52-S62 e3.
16. Youssefi P, Gomez A, He T, Anderson L, Bunce N, Sharma R, et al. Patient-specific computational fluid dynamics-assessment of aortic hemodynamics in a spectrum of aortic valve pathologies. J Thorac Cardiovasc Surg. 2017;153(1):8-20 e3.
17. Hayman S, Wright G, West C, Burstow D, Scalia GM. True Bicuspid Aortic Valves are Rare Compared with Functionally Bicuspid Aortic Valves. Heart, Lung and Circulation. 2008;17S:S63.
18. Robicsek F, Thubrikar MJ, Cook JW, Fowler B. The congenitally bicuspid aortic valve: how does it function? Why does it fail? Ann Thorac Surg. 2004;77(1):177-85.
19. Hope MD, Hope TA, Meadows AK, Ordovas KG, Urbania TH, Alley MT, et al. Bicuspid aortic valve: four-dimensional MR evaluation of ascending aortic systolic flow patterns. Radiology. 2010;255(1):53-61.

20. Barker AJ, Markl M, Burk J, Lorenz R, Bock J, Bauer S, et al. Bicuspid aortic valve is associated with altered wall shear stress in the ascending aorta. Circ Cardiovasc Imaging. 2012;5(4):457-66.
21. Verma S, Siu SC. Aortic dilatation in patients with bicuspid aortic valve. N Engl J Med. 2014;370(20):1920-9.
22. Tadros TM, Klein MD, Shapira OM. Ascending aortic dilatation associated with bicuspid aortic valve: pathophysiology, molecular biology, and clinical implications. Circulation. 2009;119(6):880-90.
23. Nkomo VT, Enriquez-Sarano M, Ammash NM, Melton LJ, 3rd, Bailey KR, Desjardins V, et al. Bicuspid aortic valve associated with aortic dilatation: a community-based study. Arterioscler Thromb Vasc Biol. 2003;23(2):351-6.
24. Kong WK, Regeer MV, Ng AC, McCormack L, Poh KK, Yeo TC, et al. Sex Differences in Phenotypes of Bicuspid Aortic Valve and Aortopathy: Insights From a Large Multicenter, International Registry. Circ Cardiovasc Imaging. 2017;10(3).
25. Wallby L, Janerot-Sjoberg B, Steffensen T, Broqvist M. T lymphocyte infiltration in non-rheumatic aortic stenosis: a comparative descriptive study between tricuspid and bicuspid aortic valves. Heart. 2002;88(4):348-51.
26. Ward C. Clinical significance of the bicuspid aortic valve. Heart. 2000;83(1):81-5.
27. Goldstone AB, Chiu P, Woo YJ. Prosthesis Type for Aortic- and Mitral-Valve Replacement. N Engl J Med. 2018;378(8):778-9.
28. Aicher D, Holz A, Feldner S, Kollner V, Schafers HJ. Quality of life after aortic valve surgery: replacement versus reconstruction. J Thorac Cardiovasc Surg. 2011;142(2):e19-24.
29. Panduranga P, Al-Mukhaini M, Al-Muslahi M, Haque MA, Shehab A. Management dilemmas in patients with mechanical heart valves and warfarin-induced major bleeding. World J Cardiol. 2012;4(3):54-9.

# 9 Coronary revascularization after surgical aortic valve replacement

Çelik M, Durko AP, Head SJ, Mahtab EAF, van Mieghem NM, Cummins PA, Kappetein AP, Bogers AJJC.

**Journal of Thoracic and CardioVascular Surgery Open. 2020.**

## ABSTRACT

**Objective:** It remains unclear how often coronary revascularization is necessary after aortic valve interventions, either by SAVR or transcatheter aortic valve replacement (TAVR). However, these data are relevant for treatment and prosthesis choice. The authors sought to analyze the incidence and characteristics of coronary revascularization after surgical aortic valve replacement (SAVR) during follow-up.

**Methods:** Of 2256 patients undergoing isolated SAVR between 1987 and 2015, 420 patients (mean age 56.9±15.5 years, 66.9% male) were followed at the Erasmus Medical Center. Incidence, predictors and characteristics of coronary revascularization were analyzed. Cumulative incidence of revascularization was assessed using a competing risk approach.

**Results:** Mean follow-up after SAVR was 17.2 years (total of 4,541 patient-years). A total of 24 patients underwent 28 procedures of revascularization. The cumulative incidence of revascularization after SAVR was 0.5%, 2.2%, 4.1%, and 6.9% at 1, 5, 10, and 20 years, respectively. The linearized rate of revascularization was 6.2 per 1,000 patient-years. PCI was the most common revascularization method (64%; N=18/28). Revascularization before SAVR (N=36/420; of whom 27 PCI) was an independent predictor of revascularization during follow-up (Hazard Ratio: 6.6, 95% confidence interval: 2.6-17.1; P<0.001).

**Conclusions:** After SAVR, the rate of coronary revascularization was 6.9% (N=24/420) at 20-year follow-up. Patients were at particular risk if they had undergone previous revascularization prior to SAVR. These data may furthermore be relevant to the TAVR population.


## CENTRAL MESSAGE

In a large SAVR cohort, the rate of coronary revascularization was 6.9% after 20-year follow-up. Previous revascularization was an independent predictor of revascularization after SAVR during follow-up.

## PERSPECTIVE STATEMENT

Coronary revascularization rates after SAVR can be used to predict the need for revascularization after TAVR, should TAVR further expand into younger, lower-risk populations. Dedicated studies are required to address the incidence, predictors, and feasibility of revascularization after TAVR.

## INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is now recommended for patients with severe aortic valve stenosis (AS) at intermediate and high surgical risk[1,2], adding more evidence to the already on-going increase in the number of performed TAVR procedures in North America and Europe.[3,4] Recent trials that included low-risk patients have reported non-inferiority or even superiority of TAVR versus surgical aortic valve replacement (SAVR).[5,6]

Reports have suggested that access to the coronary arteries may be difficult to establish after TAVR as a result of the positioning of the transcatheter valve.[7] When indication expand towards low-risk patients, who often are younger, the need for coronary revascularization after TAVR may increase. However, due to the advanced age and presence of multiple comorbidities of patients in current TAVR trials and the relatively short-term follow-up available the incidence of coronary revascularization has been difficult to determine. The probability of coronary revascularization after TAVR may increase in patients with longer life expectancies, with potential implications for procedure and prosthesis choices.

Surgical aortic valve replacement (SAVR) has been the standard of care for AS over the past 50 years. Therefore, long-term follow-up is available to determine the incidence of coronary revascularization after SAVR, in low-risk patients. Since the historical SAVR patient population overlaps with current and future TAVR patient populations, data of revascularization after SAVR can provide insights into determining which surgical or transcatheter prostheses may be more appropriate in specific patients. The aim of this study was to assess the incidence and risk factors of coronary revascularization during long-term follow-up after SAVR.



## METHODS

### Study design

This observational, retrospective study consisted of adult (≥18 years) patients who underwent isolated SAVR with a mechanical or bioprosthetic valve between 1987 and 2015 at the Erasmus Medical Center (Erasmus MC), Rotterdam, The Netherlands. To ensure that all coronary revascularization procedures during follow-up were captured, only patients followed up at the outpatient clinic of the Erasmus MC were included in this study (**Figure 1**). Patients undergoing concomitant procedures or with active endocarditis were excluded. Coronary artery disease (CAD) was routinely assessed before SAVR by coronary angiography, and patients with CAD underwent concomitant coronary artery bypass grafting (CABG) according to the recommendations of clinical guidelines in use at the time of surgery, and were excluded.

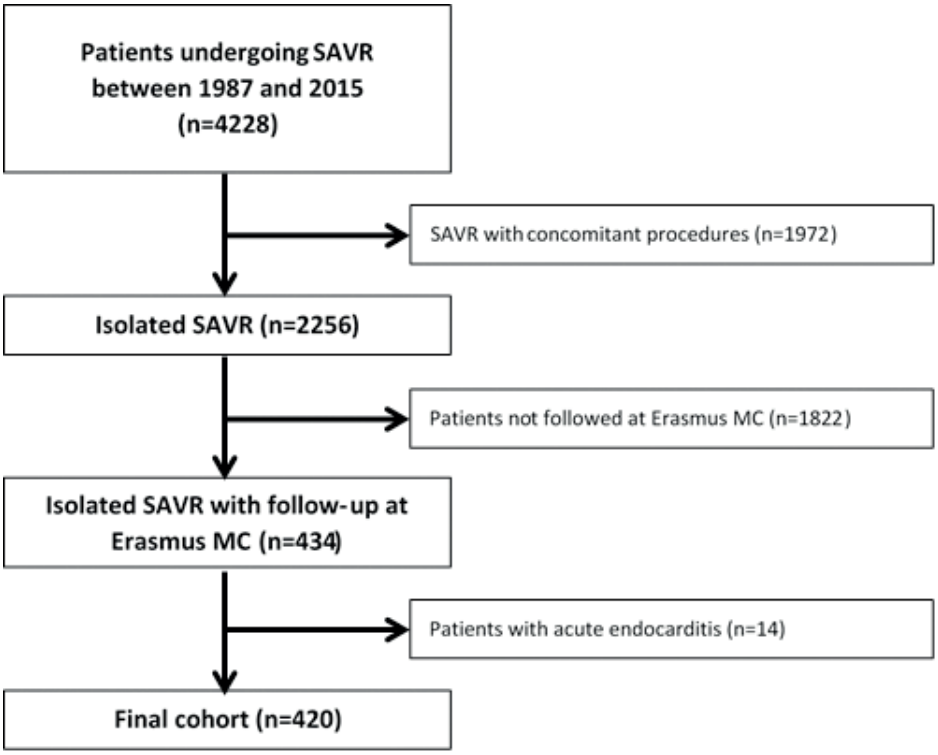


**Figure 1. Flowchart of patient inclusion**
A total of 4,228 patients underwent SAVR at the Erasmus MC between 1987 and 2015 of whom a total of 420 patients were eligible for the study. SAVR = surgical aortic valve replacement.

The study was approved by the local institutional review board and patient informed consent was waived. All the authors assured for the validity of the data and adherence to the protocol.

## Data collection and follow-up

Baseline patient and procedural characteristics were collected from electronic medical records. Survival status was obtained through the National Death Registry.

After SAVR, patients returned to their referring cardiologist at Erasmus MC for routine, regular outpatient clinic visits at 3 and 6 months postoperatively and (bi-)annually thereafter. If CAD was diagnosed and revascularization was deemed necessary, patients underwent either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) at the Erasmus MC.

## Endpoints and definitions

The primary endpoint was coronary revascularization either by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). SAVR within 24 hours of

establishing the indication was classified as urgent, between 24 hours and 3 days as semi-elective, and after 3 days as elective. Left ventricular function was classified as normal if the left ventricular ejection fraction (LVEF) was >50%, as mildly reduced if the LVEF was 40-50%, as moderately reduced if the LVEF was 30-40% and as severely reduced if the LVEF was less than 30%, as measured or estimated by a trained echocardiographer.

### Statistical analyses

Discrete variables are presented as numbers, percentages or proportions, and compared with either the Chi Square test or the Fisher Exact test, where appropriate. Continuous variables are presented as means ± standard deviation or median with the interquartile range (IQR) if there was evidence of skewed data according to the Kolmogorov-Smirnov test, and compared with either the two-sample t-test or Wilcoxon rank-sum test, where appropriate.

Probabilities of the occurrence of revascularization and mortality were visualized using cumulative incidence curves with their according 95% confidence intervals. The cumulative incidence based on Kaplan-Meier estimates do not reflect the competing risk of death and the occurrence of revascularization, and therefore overestimate the remaining lifetime risk of revascularization when the competing risk is high.[8] To account for this overestimation, competing risk survival analysis was performed by means of nonparametric methods using the cumulative incidence competing risk method.[9,10] Post-hoc subgroup analyses were performed according to whether revascularization had taken place prior to the SAVR procedure, age at time of SAVR (aged <65 or ≥65 years), history of hypercholesterolemia, history of diabetes mellitus, indication of SAVR (AS, AR, or combined disease), and type of implanted valve (mechanical or bioprosthetic). Competing risk survival analyses in subgroups were compared with the Fine and Gray test.[11] Furthermore, the linearized rate of revascularization was calculated per 1,000 patient-years of follow-up.

Predictors of revascularization after SAVR were identified in a Cox proportional hazards model. Significant variables on univariable analyses were included in a multivariable Cox proportional hazards model. Two-sided p-values <0.05 were considered to be statistically significant. Data analyses were performed using SPSS 24.0 (SPSS Inc, Chicago, Illinois) and R software, version 3.4 (R Foundation, Vienna, Austria).

## RESULTS

### Baseline and procedural characteristics

From 4228 patients who underwent SAVR between 1987 and 2015, 420 patients underwent isolated SAVR and were followed up at the Erasmus MC and were included in

this study (Figure 1). The mean age of the patients at the time of SAVR was 56.9 ± 15.5 years and 66.9% (281/420) were male. The primary indication for SAVR was pure AS in 52.1% (219/420). A total of 8.6% (36/420) had previous revascularization. Mechanical valve prostheses were used in 66.7% (280/420). The rates of survival were 98.3%, 96.4%, 87.4%, 71.8%, 58.6%, and 47.4%; at 30-days, and 1, 5, 10, 15, and 20 years of follow-up, respectively (Figure 2). Detailed baseline and procedural characteristics are provided in Table 1. Patients excluded from our study were older (66.1 ± 11.1 versus 56.9 ± 15.5 years, p<0.001), had undergone more redo SAVR procedures (16.7% versus 4.3%, p<0.001), more often underwent SAVR with an urgent indication (4.0% versus 0.4%, p<0.001) and had less frequent implantation of mechanical valve prosthesis (66.7% versus 48.0% p<0.001) compared to the included patients. Further detailed characteristics of patients excluded from our study are provided in Table 2.

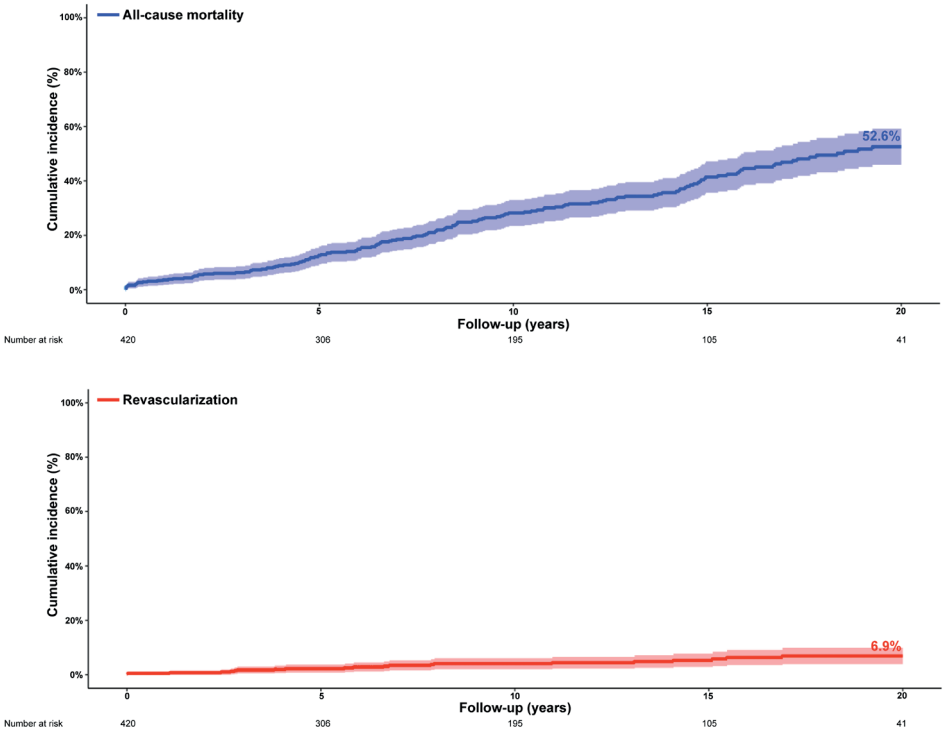


**Figure 2. Mortality and coronary revascularization after SAVR**

Competing risk cumulative incidences of mortality and coronary revascularization during 20-year follow-up according to: Blue line presents the cumulative incidence of all-cause mortality competing with the risk of revascularization in our cohort. Red line presents the cumulative incidence of revascularization with either PCI or CABG competing with the risk of revascularization in our cohort.

**Table 1. Baseline and procedural characteristics**

| | All patients (n=420) | No revascularization (n=396) | Revascularization (n=24) | P-value |
|---|---|---|---|---|
| **Age** | 56.9 ± 15.5 (420) | 56.8 ± 15.7 (396) | 58.5± 11.6 (24) | 0.592 |
| **Male sex** | 66.9 (281/420) | 67.2 (266/396) | 62.5 (15/24) | 0.637 |
| **Primary indication** | | | | 0.950 |
| - **AS** | 52.1 (219/420) | 52.3 (207/396) | 50.0 (12/24) | |
| - **AR** | 25.5 (107/420) | 25.5 (101/396) | 25.0 (6/24) | |
| - **Combined AS+AR** | 22.4 (94/420) | 22.2 (88/396) | 25.0 (6/24) | |
| **Bicuspid aortic valve** | 24.0 (101/420) | 24.0 (95/396) | 25.0 (6/24) | 0.910 |
| **Previous cardiac operation** | 28.6 (120/420) | 28.8 (114/396) | 25.0 (6/24) | 0.690 |
| - **SAVR** | 16.7 (70/420) | 16.7 (66/396) | 16.7 (4/24) | >0.999 |
| - **CABG** | 2.6 (11/420) | 2.3 (9/396) | 8.3 (2/24) | 0.071 |
| - **Other** | 9.3 (39/420) | 9.3 (39/396) | 0 | 0.107 |
| **Hypertension** | 29.8 (125/420) | 29.8 (118/396) | 29.2 (7/24) | 0.948 |
| **Hypercholesterolemia** | 12.4 (52/420) | 11.1 (44/396) | 33.3 (8/24) | 0.001 |
| **Diabetes mellitus** | 9.3 (39/420) | 8.8 (35/396) | 16.7 (4/24) | 0.199 |
| **Arterial disease** | 3.6 (15/420) | 3.3 (13/396) | 8.3 (2/24) | 0.195 |
| - **Peripheral** | 3.6 (15/420) | 3.3 (13/396) | 8.3 (2/24) | 0.195 |
| - **Carotid** | 0.5 (2/420) | 0.5 (2/396) | 0 | 0.727 |
| **Renal failure** | 2.6 (11/420) | 2.5 (10/420) | 4.2 (1/24) | 0.625 |
| **Previous myocardial infarction** | 4.3 (18/420) | 4.0 (16/396) | 8.3 (2/24) | 0.313 |
| **Previous revascularization** | 8.6 (36/420) | 7.3 (29/396) | 29.2 (7/24) | <0.001 |
| - **Previous PCI** | 6.4 (27/420) | 5.6 (22/396) | 20.8 (5/24) | 0.003 |
| - **Previous CABG** | 2.6 (11/420) | 2.3 (9/396) | 8.3 (2/24) | 0.071 |
| **Previous decompensated heart failure** | 16.9 (71/420) | 16.4 (65/396) | 25.0 (6/24) | 0.276 |
| **Left ventricular function** | | | | 0.460 |
| - **Preserved** | 77.6 (287/370) | 77.6 (273/370) | 77.8 (14/18) | |
| - **Mildly reduced** | 7.6 (28/370) | 8.0 (28/370) | 0 | |
| - **Moderately reduced** | 9.2 (34/370) | 8.8 (31/370) | 16.7 (3/18) | |
| - **Severely reduced** | 5.7 (21/370) | 5.7 (20/370) | 5.6 (1/18) | |
| **Atrial fibrillation** | 13.3 (56/420) | 13.4 (53/396) | 12.5 (3/24) | 0.902 |
| **Previous neurological event** | 10.5 (44/420) | 11.1 (44/396) | 0 | 0.084 |
| - **CVA** | 4.8 (20/420) | 5.1 (20/396) | 0 | 0.259 |
| - **TIA** | 7.1 (30/420) | 7.6 (30/396) | 0 | 0.162 |
| **COPD** | 8.3 (35/420) | 8.3 (33/396) | 8.3 (2/24) | >0.999 |
| **Liver disease** | 1.4 (6/420) | 1.5 (6/396) | 0 | 0.544 |
| **History of malignancy** | 8.1 (34/420) | 8.1 (32/396) | 8.3 (2/24) | 0.965 |
| **Urgency** | | | | 0.610 |
| - **Elective** | 49.3 (173/351) | 49.4 (165/334) | 47.1 (8/17) | |
| - **Semi-elective** | 46.7 (164/351) | 46.7 (156/334) | 47.1 (8/17) | |
| - **Urgent** | 4.0 (14/351) | 3.9 (13/334) | 5.9 (1/17) | |
| **Logistic EuroSCORE** | 5.7 ± 6.2 (204) | 5.5 ± 6.1 (193) | 8.8 ±7.3 (11) | 0.085 |
| **Mechanical prosthesis** | 66.7 (280/420) | 66.7 (264/396) | 66.7 (16/24) | >0.999 |

**Table 1. Baseline and procedural characteristics** (*continued*)

| | All patients (n=420) | No revascularization (n=396) | Revascularization (n=24) | P-value |
|---|---|---|---|---|
| **Year of operation** | | | | 0.383 |
| - **1987-1994** | 24.5 (103/420) | 23.7 (94/396) | 37.5 (9/24) | |
| - **1995-2001** | 23.3 (98/420) | 24.0 (95/396) | 12.5 (3/24) | |
| - **2002-2008** | 26.7 (112/420) | 26.8 (106/396) | 25.0 (6/24) | |
| - **2009-2015** | 25.5 (107/420) | 25.5 (101/396) | 25.0 (6/24) | |

Data is presented as % (n/N) and mean ± SD or median (IQR). AR = aortic regurgitation, AS = aortic stenosis, AVR = surgical aortic valve replacement, CABG = coronary artery bypass grafting, CVA = cerebrovascular accident, COPD = chronic obstructive pulmonary disease, TIA= transient ischemic attack, PCI = percutaneous coronary intervention.

**Table 2. Baseline and procedural characteristics**

| | Pt followed-up in Erasmus MC | Pt not followed-up in Erasmus MC | P-value |
|---|---|---|---|
| **Age** | 56.9 ± 15.5 (420) | 66.1 ± 11.1 (1782) | <0.001 |
| **Male sex** | 66.9 (281/420) | 57.4 (1023/1782) | <0.001 |
| **Primary indication** | | | |
| - **AS** | 52.1 (219/420) | 69.8 (1243/1782) | <0.001 |
| - **AR** | 25.5 (107/420) | 12.7 (226/1782) | <0.001 |
| - **Combined AS+AR** | 22.4 (94/420) | 17.3 (308/1782) | 0.015 |
| **Bicuspid aortic valve** | 24.0 (101/420) | 19.2 (343/1782) | 0.027 |
| **Previous cardiac operation** | 28.6 (120/420) | 8.6 (154/1782) | <0.001 |
| - **SAVR** | 16.7 (70/420) | 4.3 (76/1782) | <0.001 |
| - **CABG** | 2.6 (11/420) | 3.7 (66/1782) | 0.276 |
| - **Other** | 9.3 (39/420) | 2.4 (43/1782) | <0.001 |
| **Hypertension** | 29.8 (125/420) | 34.3 (612/1782) | 0.073 |
| **Hypercholesterolemia** | 12.4 (52/420) | 14.8 (264/1782) | 0.201 |
| **Diabetes mellitus** | 9.3 (39/420) | 12.2 (218/1782) | 0.091 |
| **Arterial disease** | 3.6 (15/420) | 2.6 (47/1782) | 0.298 |
| - **Peripheral** | 3.6 (15/420) | 2.4 (42/1782) | 0.159 |
| - **Carotid** | 0.5 (2/420) | 0.3 (5/1782) | 0.522 |
| **Renal failure** | 2.6 (11/420) | 2.3 (33/1782) | 0.312 |
| **Previous myocardial infarction** | 4.3 (18/420) | 5.6 (99/1782) | 0.297 |
| **Previous revascularization** | 8.6 (36/420) | 7.8 (139/1782) | 0.599 |
| - **Previous PCI** | 6.4 (27/420) | 5.1 (90/1782) | 0.257 |
| - **Previous CABG** | 2.6 (11/420) | 3.7 (66/1782) | 0.276 |
| **Previous decompensated heart failure** | 16.9 (71/420) | 13.7 (245/1782) | 0.097 |
| **Left ventricular function** | | | |
| - **Preserved** | 77.6 (287/370) | 82.5 (1348/1633) | 0.026 |
| - **Mildly reduced** | 7.6 (28/370) | 6.3 (103/1633) | 0.376 |
| - **Moderately reduced** | 9.2 (34/370) | 8.3 (136/1633) | 0.592 |
| - **Severely reduced** | 5.7 (21/370) | 2.8 (46/1633) | 0.006 |
| **Atrial fibrillation** | 13.3 (56/420) | 13.5 (241/1782) | 0.918 |
| **Previous neurological event** | 10.5 (44/420) | 8.0 (142/1782) | 0.096 |
| - **CVA** | 4.8 (20/420) | 3.5 (62/1782) | 0.212 |
| - **TIA** | 7.1 (30/420) | 5.1 (91/1782) | 0.099 |

**Table 2. Baseline and procedural characteristics** *(continued)*

| | Pt followed-up in Erasmus MC | Pt not followed-up in Erasmus MC | P-value |
|---|---|---|---|
| **COPD** | 8.3 (35/420) | 11.5 (205/1782) | 0.061 |
| **Liver disease** | 1.4 (6/420) | 0.2 (4/1782) | 0.001 |
| **History of malignancy** | 8.1 (34/420) | 6.1 (109/1782) | 0.139 |
| **Urgency** | | | |
| - **Elective** | 49.3 (173/351) | 62.0 (975/1573) | <0.001 |
| - **Semi-elective** | 46.7 (164/351) | 37.6 (591/1573) | 0.001 |
| - **Urgent** | 4.0 (14/351) | 0.4 (7/1573) | <0.001 |
| **Logistic EuroSCORE** | 5.7 ± 6.2 (204) | 5.8 ± 5.8 (970) | 0.740 |
| **Mechanical prosthesis** | 66.7 (280/420) | 48.0 (855/1782) | <0.001 |
| **Year of operation** | | | |
| - **1987-1994** | 24.5 (103/420) | 16.3 (290/1782) | <0.001 |
| - **1995-2001** | 23.3 (98/420) | 25.4 (452/1782) | 0.387 |
| - **2002-2008** | 26.7 (112/420) | 28.2 (502/1782) | 0.536 |
| - **2009-2015** | 25.5 (107/420) | 30.2 (538/1782) | 0.056 |

Data is presented as % (n/N) and mean ± SD or median (IQR). AR = aortic regurgitation, AS = aortic stenosis, AVR = surgical aortic valve replacement, CABG = coronary artery bypass grafting, CVA = cerebrovascular accident, COPD = chronic obstructive pulmonary disease, TIA= transient ischemic attack, PCI = percutaneous coronary intervention.

## Revascularization after SAVR

The mean follow-up after SAVR was 17.2 years, with a total follow-up accumulating to 4541 patient-years. During follow-up, 24 patients underwent coronary revascularization, with three patients requiring a second and one patient requiring a third revascularization procedure. In the time-to-first event competing risk analysis with mortality, the rates of revascularization were 0.5%, 0.5%, 2.2%, 4.1%, 5.3%, and 6.9%; at 30-days and, 1, 5, 10, 15, and 20 years of follow-up, respectively (Figure 2). The mean time to the first revascularization was 8.9 ± 7.4 (range 0 to 26.9 years). The linearized rate of revascularization was 6.2 per 1000 patient-years.

## Characteristics of revascularization

More patients underwent PCI than CABG, accounting for 64.2% of revascularization procedures (n=18/28). Three patients (12.5%) needed urgent revascularization due to acute myocardial infarction (treated with PCI in all cases). Single-vessel disease was present in 16 patients (67%) and multivessel disease was present in 8 patients (33%). Four patients had lesions in both the left and right coronary artery. Characteristics of revascularization are displayed in Table 3.

**Table 3. Characteristics of revascularization after SAVR**

| Patient | Date of SAVR | Revascularization after SAVR | | | | | Previous revascularization before SAVR | | Subsequent revascularization(s) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Date | Urgency | Lesion | Modality | Details | Date | Modality | Date | Modality |
| **#1** | 25-Jun-1987 | 01-Jun-1995 | Elective | OM, IM | PCI | | | | 11-Sep-1995 | PCI |
| **#2** | 12-Aug-1987 | 20-Dec-2007 | Elective | OM, PD | CABG | SVG-OM-PD | | | | |
| **#3** | 18-May-1988 | 24-Jun-2003 | Elective | LAD | CABG | SVG-LAD | | | | |
| **#4** | 03-Jun-1988 | 21-Nov-2003 | Elective | RCA | PCI | | | | | |
| **#5** | 01-Sep-1988 | 04-Aug-2015 | Elective | LAD, LCx | PCI | | | | | |
| **#6** | 21-Mar-1989 | 04-Nov-1994 | Elective | RCA | PCI | | | | 29-Jan-2001 & 12-Sep-2001 | CABG & CABG |
| **#7** | 25-Jul-1990 | 29-Mar-1993 | Elective | LAD | CABG | LIMA-LAD | | | | |
| **#8** | 07-Oct-1993 | 27-Sep-2004 | Elective | LAD | PCI | | | | 27-Aug-2012 | PCI |
| **#9** | 09-Nov-1993 | 10-Mar-2015 | Elective | LAD, RCA | PCI | | | | | |
| **#10** | 01-Jul-1998 | 03-Aug-2012 | Elective | | CABG | SVG-RCA | | | | |
| **#11** | 07-Aug-1998 | 30-Jun-2015 | Urgent | LAD, RCA | PCI | | | | | |
| **#12** | 02-Jun-2001 | 04-Jul-2014 | Elective | LAD | CABG | LIMA-LAD | | | | |
| **#13** | 28-Nov-2002 | 03-Sep-2009 | Elective | LAD, IM, OM | CABG | LIMA-LAD SVG-IM-OM | | | | |
| **#14** | 31-Jan-2003 | 06-Dec-2005 | Elective | RCA | PCI | | 30-10-2002 | PCI | | |
| **#15** | 20-Dec-2004 | 26-Oct-2010 | Elective | OM | PCI | | | | | |
| **#16** | 28-Jun-2006 | 02-May-2014 | Urgent | SVG | PCI | | 02-05-2000 | CABG | | |
| **#17** | 31-Oct-2008 | 07-Dec-2012 | Elective | RCA | PCI | | 19-01-2004 | PCI | | |
| **#18** | 04-Nov-2008 | 27-Aug-2012 | Elective | RCA | PCI | | 27-09-2004 | PCI | | |
| **#19** | 13-May-2009 | 31-Dec-2015 | Elective | LAD, LCx | PCI | | 20-05-2003 | PCI | | |
| **#20** | 02-Dec-2011 | 09-Jan-2013 | Elective | OM | PCI | | 04-11-2011 | PCI | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **#21** | 27-Apr-2012 | 05-Feb-2015 | Urgent | LAD | PCI | | 17-07-1997 | CABG |
| **#22** | 05-Oct-2012 | 11-Mar-2015 | Elective | LAD | CABG | LIMA-LAD | | |
| **#23** | 02-May-2013 | 02-May-2013 | Elective | PD | CABG | SVG-PD | | |
| **#24** | 18-Oct-2013 | 24-Oct-2013 | Elective | LCx | PCI | | | |

CABG, coronary artery bypass grafting; IM, intermediate artery; LAD, left anterior descending artery; LCx, left circumflex artery; LIMA, left internal mammary artery; OM, obtuse marginal artery; PD, posterior descending artery; PCI , percutaneous coronary intervention; RCA , right coronary artery; SVG, saphenous vein graft

## Subgroup analysis and predictors of revascularization after SAVR

The incidence of revascularization at 15-years of follow-up was significantly higher in patients with previous revascularization, than in patients without previous revascularization (22.1% versus 3.7%, P<0.001), respectively. Further, the incidence of revascularization was higher in patients with hypercholesterolemia compared to patients without hypercholesterolemia (14.2% versus 4.1%, P=0.002), respectively. There were no differences in revascularization rates during follow-up in subgroups according to age (4.9% for patients aged <65 versus 5.9% for patients aged ≥65, P=0.42), diabetes mellitus (8.8% for patients with a history of diabetes mellitus versus 5.0% for no diabetes mellitus, P=0.24) primary indication for SAVR (5.6% for AS versus 7.9% for AR versus 2.2% for combined disease, P=0.36), or type of valve used (6.8% for biological versus 4.4% for mechanical, P=0.16) (Figures 3 and 4).

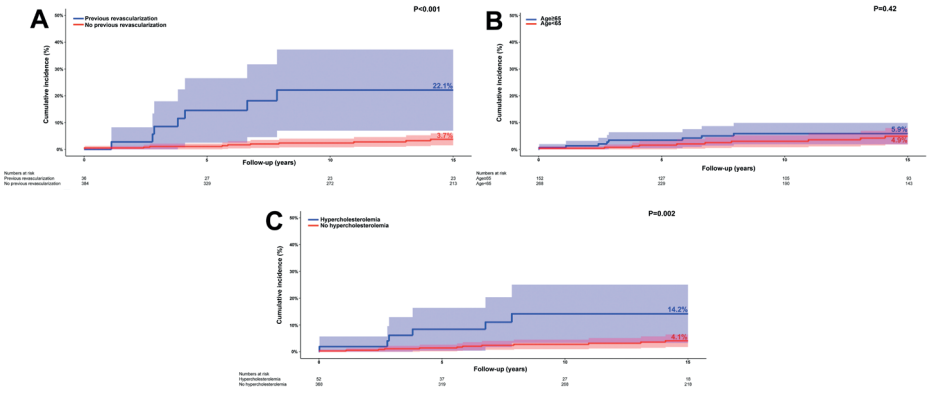


**Figure 3. Revascularization after SAVR in various patient subgroups**

Competing risk cumulative incidences of revascularization after SAVR in subgroups according to:
A) With and without previous revascularization, B) Age at SAVR below or above 65 years., C) With and without a history of hypercholesterolemia.

## Factors associated with coronary revascularization during follow-up

Patients that underwent coronary revascularization during follow-up more often had hypercholesterolemia at baseline (8/24 versus 44/396, P=0.001) and undergone revascularization before the index procedure (7/24 versus 29/396, P<0.001) than patients that did not undergo revascularization during follow-up (Table 1). In multivariable analyses, the presence of revascularization, hypercholesterolemia and diabetes mellitus before the index procedure were the only independent predictor of revascularization during follow-up (Table 4).

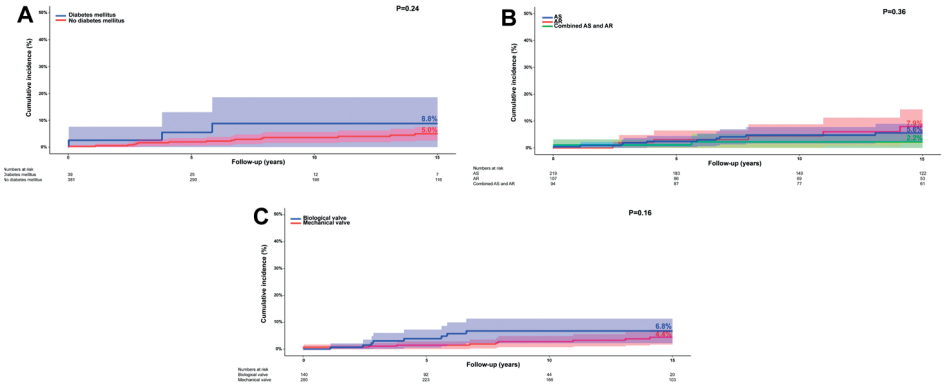


**Figure 4. Revascularization after SAVR in various patient subgroups**

Competing risk cumulative incidences of revascularization after SAVR in subgroups according to:
**A)** With and without a history of diabetes mellitus, B) Primary indication for SAVR, C) Mechanical or biological prosthesis received. Blue line shows the use of a biological valve

**Table 4. Predictors of revascularization after SAVR**

| Characteristics | Univariable HR (95% CI); P-value | Multivariable HR (95% CI); P-value |
|---|---|---|
| **Age** | 1.0 (1.0-1.1); P=0.16 | |
| **Sex (female)** | 1.5 (0.6-3.4); P=0.35 | |
| **Indication AS** | 1.1 (0.5-2.5); P=0.79 | |
| **Indication AR** | 1.1 (0.4-2.7); P=0.90 | |
| **Indication AS+AR** | 0.8 (0.3-2.1); P=0.68 | |
| **Hypertension** | 1.2 (0.5-2.9); P=0.68 | |
| **Hypercholesterolemia** | 5.0 (2.1-11.7); P<0.001 | 3.4 (1.3-8.6); P=0.010 |
| **Diabetes mellitus** | 3.2 (1.1-9.7); P=0.037 | 2.1 (0.7-6.5); P=0.214 |
| **Arterial disease** | 3.7 (0.9-15.9); P=0.08 | |
| **Renal failure** | 3.9 (0.5-29.1); P=0.19 | |
| **Previous MI** | 2.7 (0.6-11.7); P=0.17 | |
| **Previous revascularization** | 8.2 (3.3-20.2); P<0.001 | 6.6 (2.6-17.1); P<0.001 |
| **Decompensated heart failure** | 1.8 (0.7-4.6); P=0.20 | |
| **LVEF <50%** | 1.2 (0.4-3.6); P=0.76 | |
| **Atrial fibrillation** | 1.0 (0.3-3.4); P=0.97 | |
| **Previous stroke or TIA** | 0.0 (0.0-18.5); P=0.31 | |
| **COPD** | 1.7 (0.4-7.3); P=0.49 | |
| **Urgent SAVR versus non-urgent** | 1.6 (0.2-12.2); P=0.64 | |
| **Log EuroSCORE** | 1.1 (1.0-1.1); P=0.078 | |
| **Mechanical prosthesis** | 0.5 (0.2-1.3); P=0.18 | |

AS, aortic stenosis; AR, aortic regurgitation, CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio, MI, myocardial infarction; TIA, transient ischemic attack; LVEF, left ventricular ejection fraction; SAVR, surgical aortic valve replacement

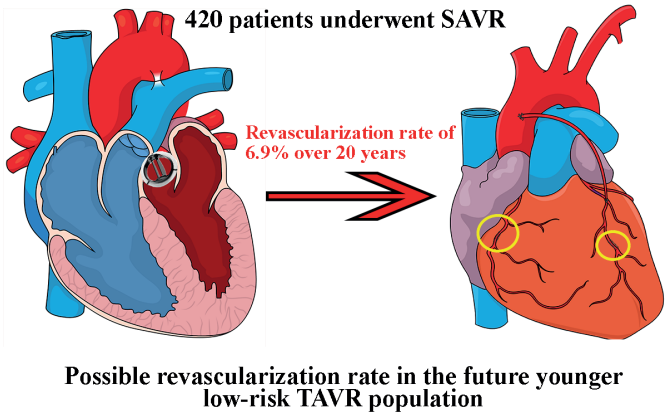


**Figure 5. Cumulative competing risk incidence of revascularization presented as a graphical abstract**
Competing risk cumulative incidence of coronary revascularization during 20-year after surgical aortic valve replacement. Coronary revascularization either done with coronary artery bypass grafting or percutaneous coronary intervention. Percutaneous coronary intervention is encircled

## DISCUSSION

In this cohort of 420 patients who underwent isolated SAVR, 24 (5.7%) patients underwent a total of 28 revascularization procedures. The cumulative incidence of revascularization was 6.9% at 20-year follow-up, with a linearized rate of 6.2 per 1000 patient-years. In the current study, concomitant CABG was generally performed in patients with significant coronary stenosis. The risk of requiring coronary intervention during follow-up after SAVR in patients with no significant coronary stenosis at the time of intervention appears to be low as 6.9% at 20-year follow-up (Figure 5).

The incidence of revascularization was higher than that of the general population. Subgroup analyses showed that patients who had undergone previous revascularization before SAVR and patients with a history of hypercholesterolemia had significantly higher rates of revascularization during follow-up. Clearly patients with already established CAD, but non-significant at the time of SAVR, carry a risk of progression of CAD to a severity requiring intervention. Other risk factors of CAD, like hypertension and diabetes, were not associated with revascularization in our multivariable analysis, although this may be the result of a relatively low sample size in our study.

Of the patients that underwent revascularization 16 patients had single-vessel disease and 8 patients two-vessel disease. There were no patients with left main or three-vessel disease. Considering the current guidelines for revascularization, the majority of patients would be referred for PCI on the basis of the complexity of coronary disease.[12] Eight patients with more complex coronary disease underwent CABG during follow-up.

These data are important in the era of expanding indications for TAVR. Recently, two randomized controlled trials showed significant benefit of TAVR compared with SAVR in the low-risk population.[5,6] Revascularization with PCI after TAVR can be associated with multiple technical challenges related to transcatheter heart valve platform, coronary access, with potential consequences of 1) damaging the prosthetic heart valve, 2) dissecting the coronary artery, 3) acute kidney injury related to increased contrast usage, and 4) an unsuccessful procedure.[13] Because CAD is present in 40-75% of patients undergoing TAVR[14], algorithms on obtaining coronary access have already been developed from experiences during concomitant or staged TAVR and PCI procedures.[7] The presence of CAD in the younger population undergoing TAVR is not well known as studies mostly consists of elderly patients. Therefore, this study is the first to systematically assess the long-term rate of revascularization after aortic valve intervention in low risk patients without CAD. Although our population consists exclusively of isolated SAVR procedures, it provides evidence on rates of revascularization that may be extrapolated to an overall TAVR population of low- to high-risk patients. Yet, literature also suggests that a proportion of patients might benefit from revascularization in the setting of acute coronary syndrome post-TAVR, and therefore higher incidences of revascularization could be expected in patients which initially would have been treated with medical therapy, when TAVR will expand towards the younger population.[15]

Of note, the mean age of our population was 57 years old as opposed to the current TAVR population with an advanced age, but a subgroup analysis according to age showed that the long-term rate of revascularization was comparable in patients younger or older or equal to 65 years. Expanding indication to lower risk patients may have consequences for valve choice, given the younger age, and considering that coronary access is more challenging with a supra-annular TAVR than an intra-annular TAVR.[7]



**Limitations**

This is a retrospective study that has inherent shortcomings related to data collection, changes in definitions of comorbidities, and patients being lost to follow-up. However, we included only patients who were followed after SAVR at our own outpatient clinic to minimize this risk. The multivariable analyses to identify predictors of revascularization may have been underpowered due to the small number of patients that needed a revascularization procedure and the unavailability of all known risk factors for coronary artery disease. Furthermore, although the decision was made not to include patients undergoing SAVR with concomitant CABG in this cohort, we did not have any information on the presence and degree of non-significant CAD that may increase the risk of coronary revascularization during follow-up as a result of progression of disease.

## CONCLUSION

In this retrospective analysis of patients that underwent isolated SAVR, the rate of requiring coronary revascularization at 20-year follow-up was relatively low. However, the rate was higher in patients who had undergone previous revascularization at the time of SAVR. These data provide some insights into requirements for coronary revascularization that may be relevant for the TAVR population. Future, larger studies are required on surgical and transcatheter cohorts to provide more insights into which patients are at particular risk of requiring coronary revascularization after aortic valve intervention.

## REFERENCES


1. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739-91.
2. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Fleisher LA, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017;70(2):252-89.
3. Rogers T, Thourani VH, Waksman R. Transcatheter Aortic Valve Replacement in Intermediate- and Low-Risk Patients. J Am Heart Assoc. 2018;7(10).
4. Walther T, Hamm CW, Schuler G, Berkowitsch A, Kotting J, Mangner N, et al. Perioperative Results and Complications in 15,964 Transcatheter Aortic Valve Replacements: Prospective Data From the GARY Registry. J Am Coll Cardiol. 2015;65(20):2173-80.
5. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. N Engl J Med. 2019.
6. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. N Engl J Med. 2019.
7. Yudi MB, Sharma SK, Tang GHL, Kini A. Coronary Angiography and Percutaneous Coronary Intervention After Transcatheter Aortic Valve Replacement. J Am Coll Cardiol. 2018;71(12):1360-78.
8. Abdel-Qadir H, Fang J, Lee DS, Tu JV, Amir E, Austin PC, et al. Importance of Considering Competing Risks in Time-to-Event Analyses: Application to Stroke Risk in a Retrospective Cohort Study of Elderly Patients With Atrial Fibrillation. Circ Cardiovasc Qual Outcomes. 2018;11(7):e004580.
9. Satagopan JM, Ben-Porat L, Berwick M, Robson M, Kutler D, Auerbach AD. A note on competing risks in survival data analysis. Br J Cancer. 2004;91(7):1229-35.
10. Scrucca L, Santucci A, Aversa F. Competing risk analysis using R: an easy guide for clinicians. Bone Marrow Transplant. 2007;40(4):381-7.
11. Scrucca L, Santucci A, Aversa F. Regression modeling of competing risk using R: an in depth guide for clinicians. Bone Marrow Transplant. 2010;45(9):1388-95.
12. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2018.
13. Alqahtani F, Ziada K, Rihal CS, Alkhouli M. Incidence and outcomes of early percutaneous coronary intervention after isolated valve surgery. Catheter Cardiovasc Interv. 2018:e27874.
14. Goel SS, Ige M, Tuzcu EM, Ellis SG, Stewart WJ, Svensson LG, et al. Severe aortic stenosis and coronary artery disease--implications for management in the transcatheter aortic valve replacement era: a comprehensive review. J Am Coll Cardiol. 2013;62(1):1-10.
15. Mentias A, Desai MY, Saad M, Horwitz PA, Rossen JD, Panaich S, et al. Incidence and Outcomes of Acute Coronary Syndrome After Transcatheter Aortic Valve Replacement. JACC Cardiovasc Interv. 2020.

# 10 Comparative study of male and female patients undergoing surgical aortic valve replacement

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**Submitted.**

## ABSTRACT

**Background:** Gender does have an effect on disease perception and outcomes after cardiac surgery.

**Objectives:** Quantify the differences in cardiovascular risk profiles within an age-matched cohort and assess the long-term survival differences in males and females who underwent surgical aortic valve replacement (SAVR) with or without concomitant coronary artery bypass surgery (CABG).

**Methods:** All-comers patients who underwent SAVR with or without CABG for aortic stenosis (AS) were included. Characteristics, clinical features, and survival up to 20 years were compared between female and male patients. Propensity matching using propensity scores were used to find matched patients from a comparison group.

**Results:** During the total study period between 1987 and 2017, there were 3462 patients (mean age 66.8 ± 11.1 years, 37.1% female) who underwent SAVR with or without CABG at our institution. In general, female patients were older than male patients (69.1 ± 10.3 versus 65.5 ± 11.3, respectively). In the age-matched cohort, female patients were less likely to have multiple comorbidities and undergo concomitant CABG. Twenty-year survival following the index procedure was higher in age-matched female patients (27.1%) compared to male patients (24.4%) in the overall cohort), p=0.018.

**Conclusions:** Substantial sex differences in cardiovascular risk profile exist. However, when SAVR with or without CABG is performed, extended long-term mortality is comparable between males and females. More research regarding sex-dimorphic mechanisms of aortic stenosis and coronary atherosclerosis would promote more awareness in terms of sex- and gender-specific risk factors after cardiac surgery and contribute to more guided personalized surgery in the future.

## INTRODUCTION

Aortic valve disease is an emerging health care problem worldwide due to the dramatic increase in life expectancy and subsequently exponentially increasing prevalence.[1] The 85 plus population is projected to increase 351% between 2010 and 2050. Fortunately, there have been significant advances in both surgical and percutaneous treatments of moderate-to-severe forms of aortic stenosis (AS) over the last decade.[2-5] Still, despite massive improvements in catheter-based techniques, surgical AVR remains the gold standard for the vast majority of patients with AS or aortic regurgitation (AR).[6]

Recent interest has focused on gender differences in preoperative and postoperative outcomes of patients undergoing coronary artery bypass grafting (CABG).[7-9] Female patients undergoing CABG have higher risk profiles and subsequently, being female is an independent predictor for worse outcomes. Besides, female patients are less likely and at a later stage to undergo CABG.[10] This underdiagnosis and undertreatment is also noted in valvular surgery.[11] Although women and men share similar incidence of severe AS, there are important gender-related differences regarding risk profiles referred for surgical aortic valve replacement. Females present with a distinct risk profile such as the smaller body size and older age, which poses unique challenges for the surgical team.[12]

Most studies on gender differences regarding cardiac surgery were performed with short-term outcomes.[13] Nevertheless, male-female differences in characteristics and long-term outcomes after SAVR remain scarce. In an era where TAVI indications are expanding toward younger patients preoperative gender-related differences have shown an association with short-term outcomes in patients undergoing TAVI.[14] Therefore, the characteristics of patients undergoing SAVR with or without coronary revascularization and the associated differences due to gender have become a focus in AVR studies. The purpose of this study is to (i) describe the differences in male and female patients undergoing SAVR with or without CABG, (ii) describe the differences in baseline after adjusting for age, and (iii) compare the long-term survival and predictors of survival in males and females.



## METHODS

### Study design

Patients who underwent SAVR between 1987 and 2016 at the Erasmus University Medical Centre in the Netherlands are included. Patients who did not undergo bioprosthetic or mechanical aortic valve prosthesis were excluded. Electronic medical records were used to retrieve patient and procedural characteristics. Survival status was obtained through the Death Registry, which is held nationally. This study was conducted according to the

privacy policy of the Erasmus Medical Centre and to the Erasmus Medical Centre regulations for the appropriate use of data in patient-oriented research (MEC-2019-0721).

### Endpoints and definitions

The primary endpoint is to assess the prevalence of female patients and the difference of patient characteristics regarding gender in the SAVR population. Further endpoints were noted as difference in survival between female and male patients. The primary indication for operation (AS, AR or combined AS and AR) was determined based on the initial echocardiogram and according to the clinical guidelines in use at the time of the surgery, corresponding to the current European and American valvular guidelines.[6,15]

### Statistical analysis

Continuous variables are presented as means ± standard deviation or median with the interquartile range (IQR, and compared with either the two-sample t-test or Wilcoxon rank-sum test. Discrete variables are presented as numbers, percentages or proportions, and compared with either the Chi Square test or the Fisher Exact test Trend analysis is performed with the $\chi^2$ test for trend (linear-by-linear association test).

Logistic regression was used to estimate each patient's probability of being female. Balance between treatment groups was assessed with the use of standardized mean differences. A standardized mean difference of 0.1 or less was deemed to be the ideal balance, and a standardized difference of 0.2 or less was deemed to be an acceptable balance.[16] The relative survival can be used as an estimate of cause-specific mortality. It is defined as the ratio between the observed survival rates and the expected survival rates in the general population.[17] The Human Mortality Database is used to obtain the age, sex and calendar year matched expected survival data of the general population in the Netherlands.[18] The Human Mortality Database is continuously updated and includes mortality data from the Netherlands up until 2016. Relative survival is estimated through the Ederer II method.[19,20] Two-sided p-values <0.05 were considered to be statistically significant. Data analyses were done using SPSS 25.0 (SPSS Inc, Chicago, Illinois) and R software, version 3.5 (R Foundation, Vienna, Austria).

## RESULTS

### Characteristics of female patients

A total of 3462 patients underwent SAVR with or without CABG. The incidence of female patients in the overall cohort according to the age was 26.3%, 28.8%, 26.1%, 31.5%, 43.9%, and 52.0% for patients aged <40, 40-49, 50-59, 60-69, 70-79, and 80≥, respectively (Figure 1), prevalence of female patients operated after 2000 or undergoing isolated

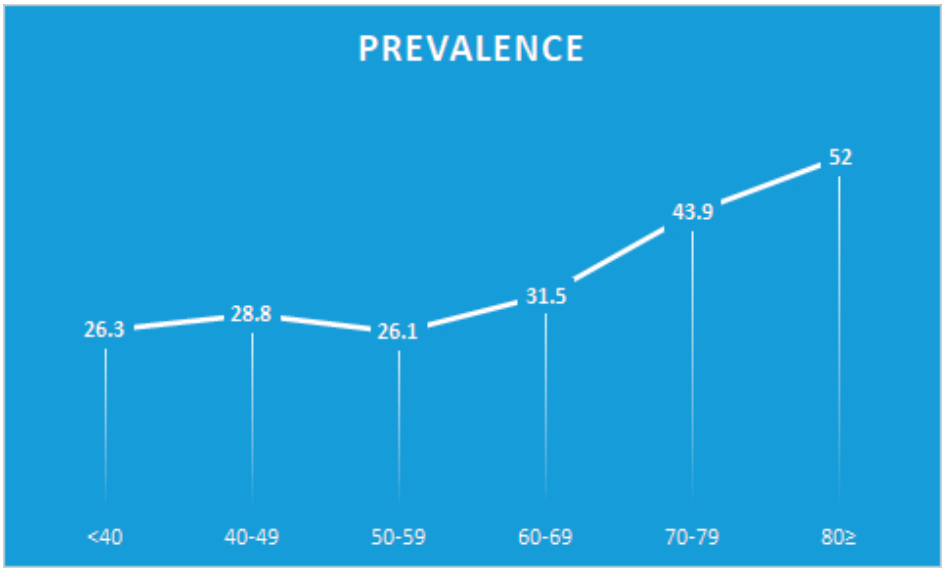


**Figure 1. Incidence of female patients**
Incidence of female patients according to different age categories in the overall cohort. Values given in percentages.

SAVR is presented in figures S1 and S2. Female patients were older than male patients at the time of surgery (mean age 61.1 ± 10.3 years vs. 65.5 ± 11.3 years, p< 0.001). The prevalence of hypertension (42.5% vs. 33.6%), diabetes mellitus (17.3% vs. 14.5%) and isolated AS (77.5% vs. 69.8%) were significantly higher in female patients compared to male patients (all p-values <0.05). Female patients had lower prevalence of myocardial infarction (7.6% vs. 15.3%) and previous PCI (5.0% vs. 8.8%), p<0.001. This difference persisted after accounting for age. Further the left ventricular ejection fraction at the time of surgery was better in female patients, with 86.3% of the patients having a LVEF of ≥50%, compared to 75.6% of the males (p<0.001). After adjustment for age, the differences in indication for surgery, hypertension, concomitant CABG, and preoperative left ventricular function remained. Detailed characteristics of the overall cohort, propensity-score matched cohort, and age-matched cohorts are shown in Table 1. Subanalyses on the characteristics of patients operated after 2000 and patients undergoing isolated SAVR are shown in Supplementary Table S1 and S2, respectively.

**Table 1.** Baseline characteristics, stratified according to the overall cohort, propensity score matched cohort, and age-matched cohort.

| | Female (1283) | Male (2179) | p-value | SMD | PSM-female (566) | PSM-male (566) | p-value | SMD | AM-female (1024) | AM-male (1024) | p-value | SMD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Age at operation** | 69.1 ± 10.3 | 65.5 ± 11.3 | <0.001 | 0.340 | 68.0 ± 10.7 | 67.8 ± 10.4 | 0.78 | 0.016 | 69.2 ± 10.1 | 69.2 ± 10.1 | >0.999 | <0.001 |
| **Indication** | | | <0.001 | 0.217 | | | 0.38 | 0.104 | | | 0.07 | 0.119 |
| - **AS** | 994 (77.5) | 1520 (69.8) | | | 445 (78.6) | 426 (75.3) | | | 811 (79.2) | 792 (77.3) | | |
| - **AR** | 100 (7.8) | 308 (14.1) | | | 48 (8.5) | 59 (10.4) | | | 78 (7.6) | 112 (10.9) | | |
| - **Combined** | 188 (14.7) | 347 (15.9) | | | 72 (12.7) | 81 (14.3) | | | 135 (13.2) | 120 (11.7) | | |
| **Bicuspid** | 195 (15.2) | 398 (18.3) | 0.023 | 0.082 | 87 (15.4) | 89 (15.7) | 0.87 | 0.010 | 148 (14.5) | 144 (14.1) | 0.85 | 0.011 |
| **Previous cardiac operation** | 76 (5.9) | 132 (6.1) | 0.931 | 0.006 | 31 (5.5) | 31 (5.5) | >0.999 | <0.001 | 53 (5.2) | 58 (5.7) | 0.70 | 0.022 |
| **Atrial fibrillation** | 171 (13.3) | 271 (12.4) | 0.480 | 0.027 | 72 (12.7) | 70 (12.4) | 0.93 | 0.011 | 128 (12.5) | 146 (12.5) | 0.27 | 0.052 |
| **Diabetes mellitus** | 222 (17.3) | 317 (14.5) | 0.035 | 0.075 | 112 (19.8) | 109 (19.3) | 0.88 | 0.013 | 193 (18.8) | 180 (17.6) | 0.49 | 0.033 |
| **Decompensation cordis** | 189 (14.7) | 320 (14.7) | >0.999 | 0.001 | 79 (14.0) | 74 (13.1) | 0.73 | 0.026 | 140 (13.7) | 124 (12.1) | 0.32 | 0.047 |
| **Hypertension** | 545 (42.5) | 733 (33.6) | <0.001 | 0.183 | 234 (41.3) | 228 (40.3) | 0.76 | 0.022 | 464 (45.3) | 389 (38.0) | 0.001 | 0.149 |
| **Hypercholesterolemia** | 241 (18.8) | 369 (16.9) | 0.182 | 0.048 | 114 (20.1) | 111 (19.6) | 0.88 | 0.013 | 212 (20.7) | 200 (19.5) | 0.544 | 0.029 |
| **Previous.myocardial infarction** | 97 (7.6) | 334 (15.3) | <0.001 | 0.246 | 51 (9.0) | 55 (9.7) | 0.76 | 0.024 | 75 (7.3) | 183 (17.9) | <0.001 | 0.32 |
| **Previous PCI** | 64 (5.0) | 191 (8.8) | <0.001 | 0.150 | 40 (7.1) | 36 (6.4) | 0.72 | 0.028 | 55 (5.4) | 102 (10.0) | <0.001 | 0.73 |
| **COPD** | 240 (11.0) | 240 (11.0) | 0.542 | 0.024 | 58 (10.2) | 71 (12.5) | 0.26 | 0.072 | 104 (10.2) | 118 (11.5) | 0.36 | 0.044 |
| **Endocarditis** | 31 (2.4) | 106 (4.9) | 0.001 | 0.131 | 17 (3.0) | 23 (4.1) | 0.42 | 0.057 | 24 (2.3) | 35 (3.4) | 0.19 | 0.064 |
| **History of cancer** | 94 (7.3) | 149 (6.8) | 0.635 | 0.019 | 47 (8.3) | 42 (7.4) | 0.66 | 0.033 | 78 (7.6) | 82 (8.0) | 0.81 | 0.015 |
| **Stroke/TIA** | 93 (7.2) | 208 (9.5) | 0.024 | 0.083 | 52 (9.2) | 54 (9.5) | 0.92 | 0.012 | 81 (7.9) | 98 (9.6) | 0.21 | 0.059 |
| - **Stroke** | 38 (3.0) | 97 (4.5) | 0.036 | 0.079 | 21 (3.7) | 28 (4.9) | 0.38 | 0.061 | 34 (3.3) | 43 (4.2) | 0.35 | 0.046 |
| - **TIA** | 62 (4.8) | 132 (6.1) | 0.151 | 0.054 | 35 (6.2) | 34 (6.0) | >0.999 | 0.007 | 53 (5.2) | 65 (6.3) | 0.30 | 0.050 |

**Table 1.** Baseline characteristics, stratified according to the overall cohort, propensity score matched cohort, and age-matched cohort. (*continued*)

| | Female (1283) | Male (2179) | p-value | SMD | PSM-female (566) | PSM-male (566) | p-value | SMD | AM-female (1024) | AM-male (1024) | p-value | SMD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Arterial disease** | 47 (3.4) | 125 (5.7) | 0.009 | 0.098 | 27 (4.8) | 25 (4.4) | 0.89 | 0.017 | 39 (3.8) | 56 (5.5) | 0.09 | 0.079 |
| - **Carotid** | 5 (0.4) | 24 (1.1) | 0.043 | 0.083 | 3 (0.5) | 5 (0.9) | 0.72 | 0.042 | 5 (0.5) | 13 (1.3) | 0.10 | 0.084 |
| - **Peripheral** | 42 (3.3) | 107 (4.9) | 0.027 | 0.083 | 24 (4.2) | 21 (3.7) | 0.76 | 0.027 | 34 (3.3) | 48 (4.7) | 0.14 | 0.070 |
| **CABG** | 380 (29.6) | 884 (40.6) | <0.001 | 0.231 | 184 (32.5) | 174 (30.7) | 0.57 | 0.038 | 300 (29.3) | 472 (46.1) | <0.001 | 0.32 |
| **Valve size** | 21.9 ± 1.8 | 24.6 ± 2.1 | <0.001 | 1.356 | 22.7 ± 1.8 | 22.9 ± 1.6 | 0.053 | 0.115 | 21.9 ± 1.7 | 24.4 ± 2.0 | <0.001 | 1.317 |
| **Urgency** | | | 0.137 | 0.100 | | | 0.07 | 0.177 | | | 0.21 | 0.108 |
| **Urgent** | 11 (1.0) | 29 (1.5) | | | 5 (0.9) | 6 (1.1) | | | 7 (0.7) | 9 (0.9) | | |
| **Semi (-elective)** | 1123 (99.0) | 1883 (98.5) | | | 561 (99.1) | 560 (98.9) | | | 1017 (99.3) | 1015 (99.1) | | |
| **LVEF** | | | <0.001 | 0.299 | 470 (83.0) | 474 (83.7)42 | 0.67 | 0.074 | | | <0.001 | 0.245 |
| - **Preserved** | 1013 (86.3) | 1524 (75.6) | | | 38 (6.7) | (7.4) | | | 882 (86.1) | 791 (77.2) | | |
| - **Mildy reduced** | 54 (4.6) | 166 (8.2) | | | 50 (8.8) | 40 (7.1) | | | 52 (5.1) | 89 (8.7) | | |
| - **Moderately reduced** | 91 (7.8) | 230 (11.4) | | | 8 (1.4) | 10 (1.8) | | | 79 (7.7) | 113 (11.0) | | |
| - **Severely reduced** | | 97 (4.8) | | | | | | | 11 (1.1) | 31 (3.0) | | |
| | 16 (1.4) | | | | | | | | | | | |
| **Valve (biological)** | 587 (42.8) | 1004 (46.1) | 0.002 | 0.104 | 208 (36.7) | 202 (35.7) | 0.76 | 0.022 | 385 (37.6) | 326 (31.8) | 0.007 | 0.121 |

AM, age-matched; AS, aortic stenosis; AI, aortic insufficiency, AR, aortic regurgitation, CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio, MI, myocardial infarction; TIA, transient ischemic attack; LVEF, left ventricular ejection fraction; PSM, propensity score matched; PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; SMD, standardized mean difference.

### Procedural characteristics of female patients

The indication for surgery was AS (77.5%), AR (7.8%). or combined AS and AR (14.7%). Concomitant CABG was performed less often compared to male patients (29.6% versus 40.6%, p<0.001), this difference remained after age-matching (p<0.001). The use of bioprosthetic valve was lower in female than in male patients (42.8% vs. 46.1%, p=0.002), after accounting for age, female patients were more likely to receive bioprosthetic valves (37.6% vs. 31.8%, p=0.007). The diameter of the implanted prosthesis was smaller in female patients compared to male patients in both unmatched (21.9 ± 1.8mm vs. 24.6 ± 2.1mm, p<0.001) and age-matched population (21.9 ± 1.8mm vs. 24.4 ± 2.0mm, p<0.001).

### Long- term outcomes after surgery

A total of 1941 patients died during follow-up (1185 male and 756 female patients, p=0.009). Survival according gender was 86.2% vs. 81.8% at 5-year, 61.1% vs. 59.7% at 10-year, 18.9% vs. 25.4% at 20-years of follow-up (p=0.09), in male and female patients respectively, (Figures 2A-C). The difference did not persist after propensity score matching (p=0.17) and reverted after age-matching. In age-, gender-, and year- matched Dutch control, the relative survival in female patients was 109.9%, 111.4%, 107.9%, and 96.9%, at 5-, 10-, 15-, 20-years of follow-up, respectively (Figure 3B). The relative survival in male patients was 96.8%, 89.0%, 76.5%, and 66.0% at 5-, 10-, 15-, and 20-year of follow-up, respectively (Figure 3A). Survival for patients operated after 2000 are shown in figures S3 and S4.

### Factors associated with survival during follow-up in the age-matched population.

In multivariable analyses, the presence of cardiovascular risk factors such as increasing age (p<0.001), diabetes mellitus (p<0.001), previous MI (p=0.013), and the presence of decompensation (p=0.002), fibrillation (p<0.001), previous stroke (p=0.016) and the need for concomitant CABG (p=0.001) were predictors of mortality in the age-matched female population (Table 2). In the age-matched male population, increasing age (p<0.001), diabetes (p=0.004), hypercholesterolemia (p=0.001), decompensation (p=0.011) and COPD (p=0.04) were independent predictors of mortality. Further predictors are shown in table 2 and in tables S3 and S4 for patients operated after 2000 and patients undergoing isolated SAVR, respectively.

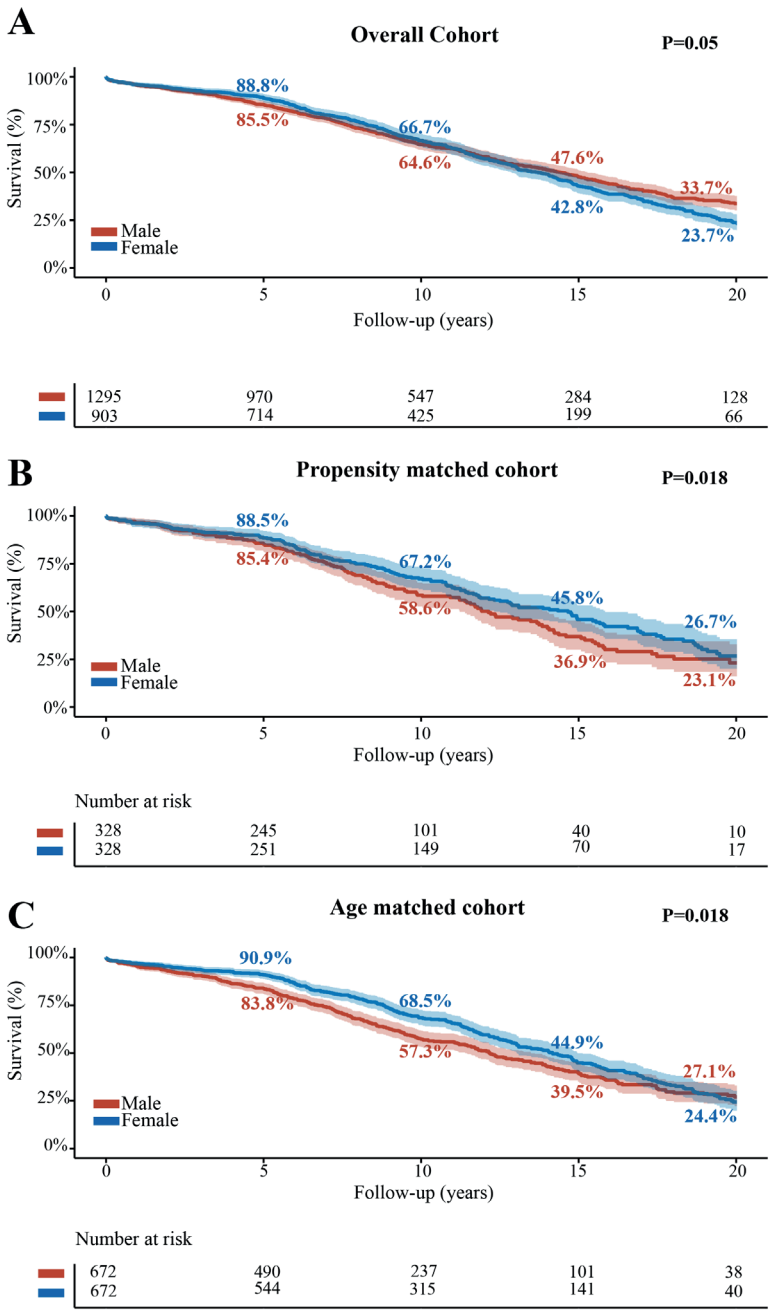


**Figure 2. Survival after SAVR ± CABG**

A) Survival in the overall cohort, B) Survival in the propensity matched cohort, C) Survival in the age matched cohort.

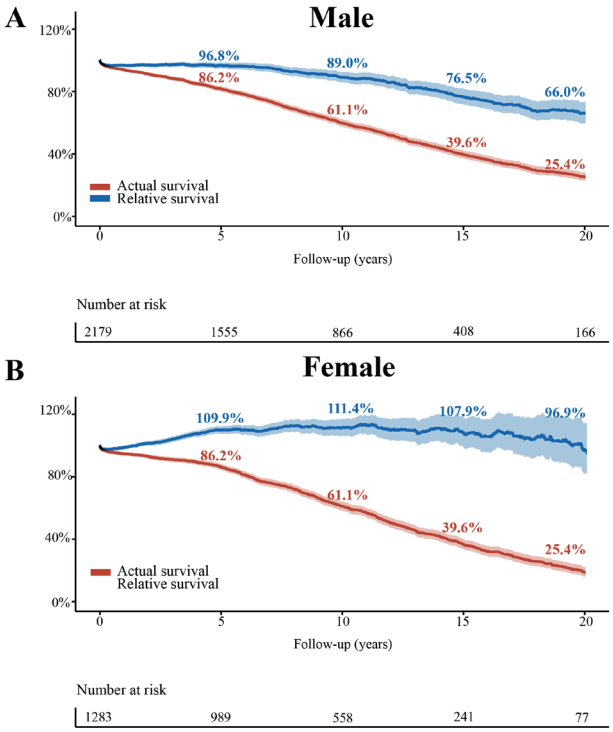


**Figure 3. Survival in male and female patients and the relative age, and calendar-year matched population in the overall cohort.**

**A)** Survival in the male cohort, B) Survival in the female cohort. *Red line represents actual survival in female patients.*

**Table 2. Predictors of survival after SAVR in age- matched female and male cohort.**

| | Age-matched female population | | Age-matched male population | |
|---|---|---|---|---|
| Characteristics | Univariable HR (95% CI); P-value | Multivariable HR (95% CI); P-value | Univariable HR (95% CI); P-value | Multivariable HR (95% CI); P-value |
| **Age** | 1.06 (1.05-1.08); P<0.001 | 1.06 (1.04-1.07); P<0.001 | 1.08 (1.07-1.09); P<0.001 | 1.07 (1.06-1.09); P<0.001 |
| **Indication AS** | 1.3 (1.1-1.6); P=0.005 | 1.0 (0.8-1.3); P=0.97 | 1.4 (1.2-1.8); P<0.001 | 0.8 (0.7-1.1); P=0.21 |
| **Indication AR** | 0.6 (0.4-0.8); P=0.002 | 0.9 (0.6-1.3); P=0.49 | 0.6 (0.4-0.8); P<0.001 | 0.8 (0.5-1.1); P=0.13 |
| **Indication AS+AR** | 0.9 (0.7-1.1); P=0.41 | | 0.9 (0.7-1.1); P=0.38 | |
| **Hypertension** | 1.1 (0.9-1.2); P=0.53 | | 1.2 (1.0-1.5); P=0.031 | 1.1 (0.9-1.3); P=0.37 |
| **Hypercholesterolemia** | 1.0 (0.8-1.2); P=0.70 | | 0.8 (0.7-1.0); P=0.10 | 0.7 (0.5-0.8); P=0.001 |
| **Diabetes mellitus** | 1.9 (1.5-2.3); P<0.001 | 1.5 (1.2-1.9); P<0.001 | 1.5 (1.2-1.9); P<0.001 | 1.4 (1.1-1.8); P=0.004 |
| **Arterial disease** | 1.6 (1.1-2.5); P=0.024 | 1.5 (1.0-2.4); P=0.054 | 1.7 (1.2-2.4); P=0.002 | 1.5 (1.1-2.1); P=0.023 |
| **Renal failure** | 5.7 (3.1-10.8); P<0.001 | 6.7 (3.5-12.8); P<0.001 | 1.9 (1.0-3.6); P=0.043 | 1.3 (0.7-2.5); P=0.43 |
| **Previous MI** | 1.8 (1.4-2.5); P<0.001 | 1.5 (1.1-2.0); P=0.013 | 1.5 (1.3-1.9); P<0.001 | 1.1 (0.9-1.4); P=0.35 |
| **Previous PCI** | 1.1 (0.8-1.6); P=0.60 | | 1.3 (0.9-1.7); P=0.13 | 1.2 (0.9-1.6); P=0.29 |
| **Decompensated heart failure** | 1.9 (1.5-2.3); P<0.001 | 1.5 (1.1-1.8); P=0.002 | 1.5 (1.2-1.9); P=0.001 | 1.4 (1.1-1.8); P=0.011 |
| **LVEF <50%** | 1.3 (1.0-1.6); P=0.038 | 1.0 (0.8-1.3); P=0.80 | 1.2 (1.0-1.5); P=0.09 | 1.3 (1.0-1.6); P=0.03 |
| **Atrial fibrillation** | 2.1 (1.7-2.6); P<0.001 | 1.6 (1.2-2.0); P<0.001 | 1.8 (1.5-2.3); P<0.001 | 1.3 (1.1-1.7); P=0.014 |
| **Previous stroke or TIA** | 1.4 (1.0-1.9); P=0.052 | 1.5 (1.1-2.0); P=0.016 | 1.2 (0.9-1.5); P=0.30 | |
| **COPD** | 1.3 (0.9-1.7); P=0.12 | 1.3 (1.0-1.7); P=0.09 | 1.8 (1.4-2.3); P<0.001 | 1.4 (1.1-1.8); P=0.04 |
| **Urgent SAVR versus non-urgent** | 0.5 (0.1-2.0); P=0.32 | | 1.0 (0.5-2.0); P=0.89 | |
| **Mechanical prosthesis** | 0.5 (0.4-0.6); P<0.001 | 0.9 (0.7-1.1); P=0.31 | 0.5 (0.4-0.5); P<0.001 | 1.0 (0.8-1.3); P=0.96 |
| **CABG** | 1.8 (1.5-2.2); P<0.001 | 1.3 (1.1-1.6); P=0.001 | 1.5 (1.3-1.8); P<0.001 | 1.1 (0.9-1.3); P=0.33 |

Abbreviations as in Table 1. CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.

## DISCUSSION

The observed male-female differences in presentation, procedural characteristics, and treatment outcomes in patients undergoing SAVR ± CABG highlight the importance of understanding the gender-related differences in patients undergoing SAVR. In this study we identified four major findings of interest (i) female patients had fewer cardiovascular risk factors at presentation, (ii) the difference in cardiovascular risk factors remained after age-matching, (iii) long-term survival rates are comparable between female and

male patients, and (iv) the long-term survival after SAVR is exceptionally higher in female patients than the age-, sex- and calendar matched Dutch population.

Males and females differ psychologically, based on, amongst others, biological endowments, effects of gender-related hormones, and physical activity.[21] Women tend to develop cardiovascular disease later on in life compared to men, which is explained by differences in the distribution of baseline risk factors and age-related changes of aforementioned; subsequently, the prevalence of comorbidities is higher in males than females.[22] Men are also more likely to have had a history of myocardial infarction or percutaneous coronary revascularization, which is in line with current evidence regarding patients undergoing CABG.[23] Female patients present at a later stadium of disease, as shown in a cohort from Toronto[24], and are more likely to present in urgent settings, with worse left ventricular function and more often do need concomitant CABG. Female patients also present with a higher transaortic valve gradients, lower effective aortic valve orifice areas, and a higher prevalence of cardiac decompensation at the time of referral.[25] While heart disease seems to be equally prevalent in men and women[1], late presentation subsequently leads to surgical undertreatment of cardiovascular patients.[26,27]

To account for the difference in age and the association of age with cardiovascular risk factors[28], we accounted for age as variable and exactly matched on age to perform analysis on an age-matched group. However, the perceived differences in less prevalent systemic cardiovascular risk factors remained in the age-matched cohort, highlighting the gender-related differences in male and female patients undergoing SAVR with or without CABG, despite being of the same age. Female patients aged 50 or above tend to have higher incidences of hypertension than male patients but have a lower incidence of coronary artery disease and subsequent interventions. Females also have a higher risk of stroke in general at a given age than males, and a cumulative higher incidence of stroke, most commonly due to their longer life expectancy.[29]

Postoperative short- and long-term survival seems to be in favour of men.[30] Generally, female patients do have a more prolonged overall survival general survival, general cardiac surgery as well as CAGB. The comparable survival in female patients was consistent throughout the 20-year study period. This is particularly surprising because female patients presented with a worse risk profile, including older age, and more advanced severity of AS, displayed by decompensation and urgency of surgery. This finding, however, may be explained by the demographic background of the general population in the Netherlands. Whereas the mean life expectancy of men currently is 80 years, it is 83 years for women. Female patients live longer in general and the patients' longevity might be better after alleviating the valvular problem. As seen in the initial period after operation, relative survival compared to the Dutch-matched population seems excellent.

In multivariable analyses, the presence of cardiovascular risk factors such as increasing age, diabetes, hypertension, hypercholesterolemia, arterial disease, and AF were predic-

tors of mortality in the age-matched female population.[31] Further, in our cohort, female patients received smaller prostheses. Prosthesis-patient mismatch is also a known predictor of mortality following SAVR.[32,33] Prosthesis-patient mismatch is also a well-known problem after TAVI. Kodali et al. reported that at 30 days after TAVI women higher aortic mean gradients after intervention (9.76 mmHg versus 8.91 mmHg; p<0.001) and aortic valve areas (1.57 $cm^2$ versus 1.83 $cm^2$; p<0.001) and, while this difference disappeared after indexing for body size (0.96 $cm^2$ versus 0.96 $cm^2$; p=0.80).[34] This might influence the cardiac index and the subsequent associated mortality with prosthesis-patient mismatch in male patients.

Current emerging data is demonstrating superior outcomes of TAVI in women compared to men.[35] A large report from the ACC/TVT registry examined sex differences among 11 808 patients who underwent TAVI and found no difference in in-hospital mortality in women versus men after TAVI but significantly better 1-year survival in female patients versus male patients (adjusted hazard ratio: 0.73; 95% CI, 0.63–0.85; P<0.001).[35] Similarly, in a patient-level meta-analysis including 11 310 patients, women had similar mortality compared with men at 30 days but had significantly better long-term survival (adjusted hazard ratio: 0.79; 95% CI, 0.73–0.86; P=0.001), despite higher rates of in-hospital complications[36], which is in line with earlier meta-analysis.[37] However, the earlier demonstrated survival benefit associated with female gender identified in previous studies might diminish, due to the recent availability of larger valves (e.g. the 29-mm size), and the lack of standardization for pre-procedural multidetector CT imaging both subsequently leading to paravalvular leakage and unsuitable valve sizes associated with increased mortality.[38]

### Limitations

Our study has multiple limitations. Our study is retrospective and single-center, which has its inherent shortcomings related to data capture, changes in definitions of co-morbidities, and patients being lost to follow-up, especially with a 30-year follow-up. Secondly, female patients tend to present later, we did not have data regarding initial presentation for the aortic valvular pathology and timing of AVR between female and males. Further, other aspects of clinical outcome and specific valve-related outcomes, including symptom improvement, quality of life, structural valve dysfunction was not uniformly assessed, and need to be investigated in prospective settings.

## CONCLUSION

Women undergo less surgical aortic valve replacement than men. Women also have a distinct risk profile, which poses unique challenges for surgical treatment of the diseased

valve. Nevertheless, despite our data shown that women tend to be older and have more comorbidities than men, women tend to have similar mortality rates and benefit from these procedures. Although posthoc analyses suggest the superiority of TAVI in female patients compared male patients, appropriateness criteria for the mode of intervention should be affected by gender, and female patients should be treated appropriately.

## REFERENCES


1. Benjamin EJ, Virani SS, Callaway CW, et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. *Circulation.* 2018;137(12):e67-e492.
2. Mack MJ, Leon MB, Smith CR, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet.* 2015;385(9986):2477-2484.
3. Bilkhu R, Borger MA, Briffa NP, Jahangiri M. Sutureless aortic valve prostheses. *Heart.* 2019;105(Suppl 2):s16-s20.
4. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. *N Engl J Med.* 2019;380(18):1695-1705.
5. Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. *N Engl J Med.* 2019;380(18):1706-1715.
6. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J.* 2017;38(36):2739-2791.
7. Blankstein R, Ward RP, Arnsdorf M, Jones B, Lou YB, Pine M. Female gender is an independent predictor of operative mortality after coronary artery bypass graft surgery: contemporary analysis of 31 Midwestern hospitals. *Circulation.* 2005;112(9 Suppl):I323-327.
8. Sawatzky JA, Naimark BJ. The coronary artery bypass graft surgery trajectory: Gender differences revisited. *Eur J Cardiovasc Nurs.* 2009;8(4):302-308.
9. Koch CG, Khandwala F, Nussmeier N, Blackstone EH. Gender profiling in coronary artery bypass grafting. *J Thorac Cardiovasc Surg.* 2003;126(6):2044-2051.
10. Koch CG, Khandwala F, Nussmeier N, Blackstone EH. Gender and outcomes after coronary artery bypass grafting: a propensity-matched comparison. *J Thorac Cardiovasc Surg.* 2003;126(6):2032-2043.
11. Iung B, Baron G, Butchart EG, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *Eur Heart J.* 2003;24(13):1231-1243.
12. Nitsche C, Koschutnik M, Kammerlander A, Hengstenberg C, Mascherbauer J. Gender-specific differences in valvular heart disease. *Wien Klin Wochenschr.* 2020;132(3-4):61-68.
13. Chaker Z, Badhwar V, Alqahtani F, et al. Sex Differences in the Utilization and Outcomes of Surgical Aortic Valve Replacement for Severe Aortic Stenosis. *J Am Heart Assoc.* 2017;6(9).
14. Vlastra W, Chandrasekhar J, Garcia Del Blanco B, et al. Sex Differences in Transfemoral Transcatheter Aortic Valve Replacement. *J Am Coll Cardiol.* 2019;74(22):2758-2767.
15. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2017;70(2):252-289.
16. Silber JH, Rosenbaum PR, Trudeau ME, et al. Multivariate matching and bias reduction in the surgical outcomes study. *Med Care.* 2001;39(10):1048-1064.
17. Perme MP, Pavlic K. Nonparametric Relative Survival Analysis with the R Package relsurv. *2018.* 2018;87(8):27.
18. Database HM. 2019; https://www.mortality.org/. Accessed October 5, 2019.
19. Pohar M, Stare J. Relative survival analysis in R. *Comput Methods Programs Biomed.* 2006;81(3):272-278.
20. Pohar M, Stare J. Making relative survival analysis relatively easy. *Comput Biol Med.* 2007;37(12):1741-1749.

21. Everett B, Zajacova A. Gender differences in hypertension and hypertension awareness among young adults. *Biodemography Soc Biol.* 2015;61(1):1-17.
22. Rankin JS, Hammill BG, Ferguson TB, Jr., et al. Determinants of operative mortality in valvular heart surgery. *J Thorac Cardiovasc Surg.* 2006;131(3):547-557.
23. Swaminathan RV, Feldman DN, Pashun RA, et al. Gender Differences in In-Hospital Outcomes After Coronary Artery Bypass Grafting. *Am J Cardiol.* 2016;118(3):362-368.
24. Ibrahim MF, Paparella D, Ivanov J, Buchanan MR, Brister SJ. Gender-related differences in morbidity and mortality during combined valve and coronary surgery. *J Thorac Cardiovasc Surg.* 2003;126(4):959-964.
25. Caballero-Borrego J, Gomez-Doblas JJ, Valencia-Serrano FM, et al. [Influence of sex on perioperative outcomes in patients undergoing valve replacement for severe aortic stenosis] Influencia del sexo en el pronostico perioperatorio de pacientes sometidos a sustitucion valvular por estenosis aortica severa. *Rev Esp Cardiol.* 2009;62(1):31-38.
26. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet.* 2006;368(9540):1005-1011.
27. Mosca L, Manson JE, Sutherland SE, Langer RD, Manolio T, Barrett-Connor E. Cardiovascular disease in women: a statement for healthcare professionals from the American Heart Association. Writing Group. *Circulation.* 1997;96(7):2468-2482.
28. Dhingra R, Vasan RS. Age as a risk factor. *Med Clin North Am.* 2012;96(1):87-91.
29. Reeves MJ, Bushnell CD, Howard G, et al. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. *Lancet Neurol.* 2008;7(10):915-926.
30. Pathak LA, Shirodkar S, Ruparelia R, Rajebahadur J. Coronary artery disease in women. *Indian Heart J.* 2017;69(4):532-538.
31. Tjang YS, van Hees Y, Korfer R, Grobbee DE, van der Heijden GJ. Predictors of mortality after aortic valve replacement. *Eur J Cardiothorac Surg.* 2007;32(3):469-474.
32. Astudillo LM, Santana O, Urbandt PA, et al. Clinical predictors of prosthesis-patient mismatch after aortic valve replacement for aortic stenosis. *Clinics (Sao Paulo).* 2012;67(1):55-60.
33. Head SJ, Mokhles MM, Osnabrugge RL, et al. The impact of prosthesis-patient mismatch on long-term survival after aortic valve replacement: a systematic review and meta-analysis of 34 observational studies comprising 27 186 patients with 133 141 patient-years. *Eur Heart J.* 2012;33(12):1518-1529.
34. Kodali S, Williams MR, Doshi D, et al. Sex-Specific Differences at Presentation and Outcomes Among Patients Undergoing Transcatheter Aortic Valve Replacement: A Cohort Study. *Ann Intern Med.* 2016;164(6):377-384.
35. Chandrasekhar J, Dangas G, Yu J, et al. Sex-Based Differences in Outcomes With Transcatheter Aortic Valve Therapy: TVT Registry From 2011 to 2014. *J Am Coll Cardiol.* 2016;68(25):2733-2744.
36. O'Connor SA, Morice MC, Gilard M, et al. Revisiting Sex Equality With Transcatheter Aortic Valve Replacement Outcomes: A Collaborative, Patient-Level Meta-Analysis of 11,310 Patients. *J Am Coll Cardiol.* 2015;66(3):221-228.
37. Zhao ZG, Liao YB, Peng Y, et al. Sex-related differences in outcomes after transcatheter aortic valve implantation: a systematic review and meta-analysis. *Circ Cardiovasc Interv.* 2013;6(5):543-551.
38. Szerlip M, Gualano S, Holper E, et al. Sex-Specific Outcomes of Transcatheter Aortic Valve Replacement With the SAPIEN 3 Valve: Insights From the PARTNER II S3 High-Risk and Intermediate-Risk Cohorts. *JACC Cardiovasc Interv.* 2018;11(1):13-20.

**Table S1.** Baseline characteristics, stratified according to the overall cohort, propensity score matched cohort, and age-matched cohort in patients operated after 2000.

| | Female (850) | Male (n=1483) | p-value | SMD | PSM-female (402) | PSM-male (402) | p-value | SMD | AM-female (748) | AM-male (748) | p-value | SMD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Age at operation** | 69.2 ± 10.8 | 66.0 ± 11.8 | <0.001 | 0.275 | 68.0 ± 11.1 | 67.9 11.2 | 0.96 | 0.004 | 69.2 ± 10.4 | 69.2 ± 10.4 | >0.999 | <0.001 |
| **Indication** | | | <0.001 | 0.227 | | | 0.78 | 0.074 | | | 0.12 | 0.125 |
| - **AS** | 690 (81.2) | 1097 (74.0) | | | 323 (80.3) | 320 (79.6) | | | 608 (81.3) | 581 (77.7) | | |
| - **AR** | 62 (7.3) | 210 (14.2) | | | 32 (8.0) | 32 (8.0) | | | 56 (7.5) | 83 (11.1) | | |
| - **Combined** | 97 (11.4) | 174 (11.7) | | | 47 (11.7) | 50 (12.4) | | | 84 (11.2) | 84 (11.2) | | |
| **Bicuspid** | 89 (11.6) | 192 (14.1) | 0.12 | 0.074 | 50 (12.4) | 44 (10.9) | 0.58 | 0.046 | 94 (12.6) | 87 (11.6) | 0.17 | 0.029 |
| **Previous cardiac operation** | 39 (4.6) | 88 (5.9) | 0.199 | 0.060 | 20 (5.0) | 20 (5.0) | >0.999 | <0.001 | 32 (4.3) | 38 (5.1) | 0.54 | 0.038 |
| **Creatinine** | | | 0.03 | 0.109 | | | 0.66 | 0.047 | | | 0.02 | 0.12 |
| - **≥2mg/dL** | 10 (1.3) | 39 (2.9) | | | 9 (2.2) | 12 (3.0) | | | 10 (1.3) | 24 (3.2) | | |
| **Atrial fibrillation** | 105 (12.4) | 183 (12.3) | >0.999 | <0.001 | 51 (12.7) | 50 (12.4) | >0.999 | 0.008 | 87 (11.6) | 106 (14.2) | 0.17 | 0.076 |
| **Diabetes mellitus** | 165 (19.4) | 273 (18.4) | 0.588 | 0.026 | 85 (21.1) | 92 (22.9) | 0.61 | 0.042 | 151 (20.2) | 138 (18.4) | 0.43 | 0.044 |
| **Decompensation cordis** | 111 (13.1) | 173 (11.7) | 0.355 | 0.042 | 56 (13.9) | 53 (13.2) | 0.84 | 0.022 | 97 (13.0) | 79 (10.6) | 0.17 | 0.075 |
| **Hypertension** | 410 (48.2) | 603 (40.7) | <0.001 | 0.153 | 190 (47.3) | 173 (43.0) | 0.26 | 0.085 | 377 (50.4) | 297 (39.7) | <0.001 | 0.216 |
| **Hypercholesterolemia** | 199 (23.4) | 328 (22.1) | 0.504 | 0.031 | 89 (22.1) | 101 (25.1) | 0.36 | 0.070 | 177 (23.7) | 174 (23.3) | 0.90 | 0.009 |
| **Previous myocardial infarction** | 70 (8.2) | 241 (16.3) | <0.001 | 0.246 | 40 (10.0) | 44 (10.9) | 0.73 | 0.033 | 62 (8.3) | 132 (17.6) | <0.001 | 0.281 |
| **Previous PCI** | 49 (5.8) | 170 (11.5) | <0.001 | 0.204 | 32 (8.0) | 30 (7.5) | 0.90 | 0.019 | 47 (6.3) | 99 (13.2) | <0.001 | 0.236 |
| **COPD** | 103 (12.1) | 181 (12.2) | >0.999 | 0.003 | 56 (13.9) | 53 (13.2) | 0.39 | 0.069 | 85 (11.4) | 98 (13.1) | 0.34 | 0.053 |
| **Endocarditis** | 17 (2.0) | 78 (5.3) | <0.001 | 0.175 | 12 (3.0) | 8 (2.0) | 0.50 | 0.064 | 15 (2.0) | 33 (4.4) | 0.013 | 0.137 |
| **History of cancer** | 80 (9.4) | 124 (8.4) | 0.431 | 0.037 | 41 (10.2) | 40 (10.0) | >0.999 | 0.008 | 68 (9.1) | 70 (9.4) | 0.93 | 0.009 |
| **Stroke/TIA** | 74 (8.7) | 167 (11.3) | 0.060 | 0.085 | 36 (9.0) | 36 (9.0) | >0.999 | <0.001 | 64 (8.6) | 82 (11.0) | 0.14 | 0.081 |
| - **Stroke** | 27 (3.2) | 76 (5.1) | 0.036 | 0.098 | 14 (3.5) | 6 (4.0)17 (4.2) | 0.85 | 0.026 | 24 (3.2) | 30 (4.0) | 0.49 | 0.043 |
| - **TIA** | 53 (6.2) | 109 (7.3) | 0.350 | 0.044 | 25 (6.2) | 24 (6.0) | >0.999 | 0.010 | 46 (6.1) | 62 (8.3) | 0.13 | 0.083 |

**Table S1.** Baseline characteristics, stratified according to the overall cohort, propensity score matched cohort, and age-matched cohort in patients operated after 2000. (*continued*)

| | Female (850) | Male (n=1483) | p-value | SMD | PSM-female (402) | PSM-male (402) | p-value | SMD | AM-female (748) | AM-male (748) | p-value | SMD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Arterial disease** | 35 (4.1) | 100 (6.7) | 0.012 | 0.116 | 21 (5.2) | 20 (5.0) | >0.999 | 0.011 | 30 (4.0) | 52 (7.0) | 0.02 | 0.129 |
| - **Carotid** | 5 (0.6) | 21 (1.4) | 0.104 | 0.083 | 4 (1.0) | 5 (1.2) | >0.999 | 0.024 | 5 (0.7) | 12 (1.6) | 0.14 | 0.088 |
| - **Peripheral** | 30 (0.5) | 84 (5.7) | 0.028 | 0.102 | 17 (4.2) | 16 (4.0) | >0.999 | 0.013 | 25 (3.3) | 43 (5.7) | 0.04 | 0.116 |
| **CABG** | 240 (28.2) | 606 (40.9) | <0.001 | 0.268 | 128 (31.8) | 134 (33.3) | 0.71 | 0.032 | 215 (28.7) | 345 (46.1) | <0.001 | 0.365 |
| **Valve size** | 21.7 ± 1.7 | 24.4 ± 2.1 | | 1.384 | 22.6 ± 1.7 | 22.6 ± 1.5 | 0.86 | 0.012 | 21.7 ± (1.7) | 24.2 ± (2.0) | <0.001 | 1.349 |
| **Urgency** | 9 (1.1) | 22 (1.6) | 0.227 | 0.105 | 4 (1.0) | 4 (0.9) | 0.50 | 0.129 | 7 (1.0) | 11 (1.4) | 0.31 | 0.113 |
| - **Emergent** | 808 (98.9) | 1405 (98.4) | | | 398 (99.0) | 398 (99.1) | | | 741 (99.0) | 737 (98.6) | | |
| - **Not emergent** | | | | | | | | | | | | |
| **LVEF** | | | <0.001 | 0.328 | | | 0.34 | 0.19 | 648 (86.6) | 573 (76.6) | <0.001 | 0.279 |
| - **Preserved** | 701 (87.1) | 1067 (75.2) | | | 336 (83.6) | 317 (78.9) | | | 42 (5.6) | 82 (11.0) | | |
| - **Mildy reduced** | 43 (5.3) | 147 (10.4) | | | 29 (7.2) | 36 (9.0) | | | 50 (7.0) | 73 (9.8) | | |
| - **Moderately reduced** | 54 (6.7) | 150 (10.6) | | | 32 (8.0) | 40 (10.0) | | | 6 (0.8) | 20 (2.7) | | |
| - **Severely reduced** | 7 (0.9) | 55 (3.9) | | | 5 (1.2) | 9 (2.2) | | | | | | |
| **Valve (mechanical)** | 237 (27.9) | 487 (32.8) | 0.015 | 0.108 | 119 (29.6) | 121 (30.1) | 0.94 | 0.011 | 206 (27.5) | 183 (24.5) | 0.20 | 0.070 |

AM, age-matched; AS, aortic stenosis; AI, aortic insufficiency, AR, aortic regurgitation, CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio, MI, myocardial infarction; TIA, transient ischemic attack; LVEF, left ventricular ejection fraction; PSM, propensity score matched; PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; SMD, standardized mean difference.

**Table S2.** Baseline characteristics of patients undergoing isolated SAVR, stratified according to the overall cohort, propensity score matched cohort, and age-matched cohort in patients.

| | Female (n=903) | Male (n=1295) | p-value | SMD | PSM-female (328) | PSM-male (328) | p-value | SMD | AM-female (672) | AM-male (672) | p-value | SMD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Age at operation** | 67.9 ± 11.1 | 63.0 ± 12.3 | <0.001 | 0.425 | 66.1 ± 11.9 | 66.3 ± 11.7 | 0.81 | 0.019 | 67.1 ± 10.9 | 67.2 ± 10.9 | >0.999 | <0.001 |
| **Indication** | | | <0.001 | 0.318 | 240 (73.2) | 240 (73.2) | 0.99 | 0.024 | 520 (77.3) | 472 (70.2) | 0.009 | 0.186 |
| - **AS** | 687 (76.1) | 816 (63.1) | | | 34 (10.4) | 36 (11.0) | | | 56 (8.3) | 88 (13.1) | | |
| - **AR** | 74 (8.2) | 223 (17.2) | | | 54 (16.5) | 52 (15.9) | | | 96 (14.3) | 112 (16.7) | | |
| - **Combined** | 142 (15.7) | 25 (19.7) | | | | | | | | | | |
| **Bicuspid** | 175 (19.4) | 285 (22.0) | 0.15 | 0.065 | 59 (18.0) | 58 (17.7) | >0.999 | 0.008 | 133 (19.8) | 120 (17.9) | 0.40 | 0.050 |
| **Previous cardiac operation** | 55 (6.1) | 84 (.5) | 0.78 | 0.016 | 20 (6.1) | 21 (6.4) | >0.999 | 0.013 | 40 (6.0) | 44 (6.5) | 0.74 | 0.025 |
| **Creatinine** | 8 (0.9) | 42 (3.2) | 0.001 | 0.166 | 6 (1.8) | 7 (2.1) | >0.999 | 0.022 | 7 (1.0) | 18 (2.7) | 0.04 | 0.121 |
| - **≥2mg/dL** | | | | | | | | | | | | |
| **Atrial fibrillation** | 118 (13.1) | 166 (12.8) | 0.92 | 0.007 | 35 (10.7) | 45 (13.7) | 0.28 | 0.093 | 80 (11.9) | 96 (14.3) | 0.23 | 0.07 |
| **Diabetes mellitus** | 132 (14.6) | 139 (10.7) | 0.01 | 0.117 | 53 (16.2) | 53 (16.2) | >0.999 | <0.001 | 100 (14.9) | 88 (13.1) | 0.39 | 0.051 |
| **Decompensation cordis** | 115 (12.7) | 197 (15.2) | 0.12 | 0.071 | 40 (12.2) | 40 (12.2) | >0.999 | <0.001 | 77 (11.5) | 89 (13.2) | 0.36 | 0.054 |
| **Hypertension** | 369 (40.9) | 388 (30.0) | <0.001 | 0.229 | 127 (38.7) | 126 (38.4) | >0.999 | 0.006 | 282 (42.0) | 228 (33.9) | 0.003 | 0.166 |
| **Hypercholesterolemia** | 152 (16.8) | 182 (14.1) | 0.09 | 0.077 | 64 (19.5) | 55 (16.8) | 0.42 | 0.071 | 121 (18.0) | 113 (16.8) | 0.62 | 0.031 |
| **Previous myocardial infarction** | 39 (4.3) | 83 (6.4) | 0.04 | 0.093 | 18 (5.5) | 13 (4.0) | 0.46 | 0.072 | 22 (3.3) | 53 (7.9) | <0.001 | 0.20 |
| **Previous PCI** | 35 (3.9) | 91 (7.0) | 0.002 | 0.139 | 20 (6.1) | 22 (6.7) | 0.87 | 0.025 | 32 (4.8) | 59 (8.8) | 0.005 | 0.160 |
| **COPD** | 99 (11.0) | 148 (11.4) | 0.79 | 0.015 | 40 (12.2) | 43 (13.1) | 0.81 | 0.028 | 76 (11.3) | 88 (13.1) | 0.36 | 0.055 |
| **Endocarditis** | 27 (3.0) | 91 (7.0) | <0.001 | 0.186 | 17 (5.2) | 19 (5.8) | 0.86 | 0.027 | 21 (3.1) | 42 (6.2) | 0.01 | 0.148 |
| **History of cancer** | 62 (6.9) | 86 (6.6) | 0.90 | 0.009 | 26 (7.9) | 24 (7.3) | 0.88 | 0.023 | 44 (6.5) | 58 (8.6) | 0.18 | 0.079 |
| **Stroke/TIA** | 60(6.6) | 124 (9.6) | 0.02 | 0.108 | 32 (9.8) | 31 (9.5) | >0.999 | 0.010 | 50 (7.4) | 75 (11.2) | 0.02 | 0.128 |
| - **Stroke** | 24 (2.7) | 56 (4.3) | 0.053 | 0.091 | 13 (4.0) | 15 (4.6) | 0.85 | 0.030 | 21 (3.1) | 30 (4.5) | 0.25 | 0.070 |
| - **TIA** | 41 (4.5) | 81 (6.3) | 0.10 | 0.076 | 20 (6.1) | 22 (6.7) | 0.87 | 0.025 | 32 (4.8) | 54 (8.0) | 0.02 | 0.134 |
| **Arterial disease** | 18 (2.0) | 48 (3.7) | 0.03 | 0.103 | 7 (2.1) | 7 (2.1) | >0.999 | <0.001 | 14 (2.1) | 27 (4.0) | 0.06 | 0.113 |
| - **Carotid** | 1 (0.1) | 9 (0.7) | 0.09 | 0.082 | 0 | 2 (0.6) | 0.48 | 0.111 | 1 (0.1) | 7 (1.0) | 0.08 | 0.16 |
| - **Peripheral** | 17 (1.9) | 41 (3.2) | 0.09 | 0.092 | 7 (2.1) | 5 (1.5) | 0.77 | 0.046 | 13 (1.9) | 22 (3.3) | 0.17 | 0.084 |

**Table S2.** Baseline characteristics of patients undergoing isolated SAVR, stratified according to the overall cohort, propensity score matched cohort, and age-matched cohort in patients. (*continued*)

| | Female (n=903) | Male (n=1295) | p-value | SMD | PSM-female (328) | PSM-male (328) | p-value | SMD | AM-female (672) | AM-male (672) | p-value | SMD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Valve size** | 22.1 ± 1.8 | 24.7 ± 2.2 | <0.001 | 1.347 | 22.9 ± 1.8 | 23.0 ± 1.7 | 0.49 | 0.055 | 22.1 ± 1.8 | 24.5 ± 2.1 | <0.001 | 1.270 |
| **Urgency** | | | 0.002 | 0.196 | | | 0.13 | 0.209 | | | 0.01 | 0.193 |
| - **Emergent** | 5 (0.6) | 20 (1.7) | | | 3 (0.9) | 3 (0.9) | | | 4 (0.6) | 10 (1.5) | | |
| - **Not emergent** | 803 (99.4) | 1114 (98.3) | | | 325 (99.1) | 325 (99.1) | | | 668 (99.4) | 662 (98.5) | | |
| **LVEF** | | | <0.001 | 0.344 | | | 0.35 | 0.142 | | | <0.001 | 0.277 |
| - **Preserved** | 726 (88.5) | 914 (77.1) | | | 273 (83.2) | 269 (82.0) | | | 588 (87.5) | 531 (79.0) | | |
| - **Mildy reduced** | 34 (4.1) | 92 (7.8) | | | 26 (7.9) | 21 (6.4) | | | 34 (5.1) | 57 (8.5) | | |
| - **Moderately reduced** | 53 (6.5) | 119 (10.0) | | | 25 (7.6) | 28 (8.5) | | | 45 (6.7) | 57 (8.5) | | |
| - **Severely reduced** | 7 (0.9) | 61 (5.1) | | | 4 (1.2) | 10 (3.0) | | | 5 (0.7) | 27 (4.0) | | |
| **Valve (mechanical)** | 386 (42.7) | 687 (53.1) | <0.001 | 0.207 | 130 (39.6) | 136 (41.5) | 0.69 | 0.037 | 274 (40.8) | 251 (37.4) | 0.22 | 0.070 |

Abbreviations as in Table S1.

**Table S3. Predictors of survival after SAVR in overall age- matched female and male cohort operated after 2000.**

| | Age-matched female population | | Age-matched male population | |
|---|---|---|---|---|
| **Characteristics** | **Univariable HR (95% CI); P-value** | **Multivariable HR (95% CI); P-value** | **Univariable HR (95% CI); P-value** | **Multivariable HR (95% CI); P-value** |
| **Age** | 1.00 (0.99-1.00); P=0.32 | | 1.01 (1.00-1.01); P=0.13 | 1.00 (0.99-1.01); P=0.81 |
| **Indication AS** | 1.2 (0.8-1.6); P=0.33 | | 0.8 (0.6-1.1); P=0.15 | 0.8 (0.6-1.1); P=0.14 |
| **Indication AR** | 0.8 (0.6-1.0); P=0.027 | 0.8 (0.6-1.2); P=0.33 | 1.1 (0.9-1.4); P=0.39 | |
| **Indication AS+AR** | 0.8 (0.6-1.0); P=0.08 | 0.9 (0.6-1.5); P=0.78 | 1.0 (0.7-1.3); P=0.82 | |
| **Hypertension** | 1.7 (1.4-2.1); P<0.001 | 1.6 (1.3-1.9); P<0.001 | 1.4 (1.2-1.7); P<0.001 | 1.4 (1.1-1.7); P=0.004 |
| **Hypercholesterolemia** | 1.6 (1.3-1.9); P<0.001 | 1.2 (0.9-1.5); P=0.13 | 1.5 (1.2-1.8); P<0.001 | 1.3 (1.0-1.6); P=0.028 |
| **Diabetes mellitus** | 1.7 (1.3-2.2); P<0.001 | 1.5 (1.1-2.0); P=0.003 | 1.1 (0.9-1.5); P=0.32 | |
| **Arterial disease** | 1.4 (0.8-2.2); P=0.21 | | 1.5 (1.0-2.3); P=0.052 | 1.4 (0.9-2.2); P=0.12 |
| **Renal failure** | 2.0 (0.7-6.4); P=0.22 | | 1.7 (0.8-3.3); P=0.16 | 1.4 (0.7-2.9); P=0.38 |
| **Previous MI** | 1.2 (0.8-1.8); P=0.34 | | 1.0 (0.8-1.4); P=0.76 | |
| **Previous PCI** | 1.3 (0.8-1.9); P=0.26 | | 1.3 (1.0-1.8); P=0.051 | 1.3 (1.0-1.8); P=0.08 |
| **Decompensated heart failure** | 1.2 (0.9-1.7); P=0.21 | | 1.1 (0.8-1.6); P=0.44 | |
| **LVEF <50%** | 1.1 (0.8-1.4); P=0.68 | | 1.4 (1.1-1.8); P=0.002 | 1.4 (1.1-1.8); P=0.004 |
| **Atrial fibrillation** | 0.7 (0.5-1.0); P=0.058 | 0.6 (0.4-0.8); P=0.0041 | 1.0 (0.7-1.4); P=0.96 | |
| **Previous stroke or TIA** | 1.4 (1.0-2.0); P=0.046 | 1.4 (1.0-2.0); P=0.048 | 1.1 (0.8-1.5); P=0.73 | |
| **COPD** | 1.4 (1.1-1.9); P=0.01 | 1.5 (1.1-2.0); P=0.010 | 0.7 (0.5-1.0); P=0.08 | 0.7 (0.5-1.0); P=0.03 |
| **Urgent SAVR versus non-urgent** | 2.0 (0.8-4.9); P=0.12 | | 0.9 (0.4-1.9); P=0.79 | |
| **Mechanical prosthesis** | 0.8 (0.7-1.0); P=0.08 | 0.9 (0.7-1.1); P=0.36 | 0.8 (0.6-0.9); P=0.011 | 0.7 (0.5-1.0); P=0.04 |
| **CABG** | 1.0 (0.8-1.3); P=0.76 | | 0.8 (0.7-1.0); P=0.048 | 0.8 (0.6-0.93); P=0.07 |

Abbreviations as in Table S1. CI, confidence interval; HR, hazard ratio

**Table S4. Predictors of survival after isolated SAVR in overall age- matched female and male cohort.**

| | Age-matched female population | | Age-matched male population | |
|---|---|---|---|---|
| **Characteristics** | **Univariable HR (95% CI); P-value** | **Multivariable HR (95% CI); P-value** | **Univariable HR (95% CI); P-value** | **Multivariable HR (95% CI); P-value** |
| **Age** | 1.0 (0.99-1.00); P=0.27 | | 1.01 (1.00-1.02); P=0.023 | 0.98 (0.97-1.00); P=0.019 |
| **Indication AS** | 1.1 (0.7-1.5); P=0.75 | | 1.0 (0.7-1.3); P=0.76 | |
| **Indication AR** | 0.8 (0.6-1.1); P=0.11 | 1.0 (0.7-1.4); P=0.99 | 0.8 (0.6-1.0); P=0.03 | 1.0 (0.7-1.4); P=0.93 |
| **Indication AS+AR** | 0.8 (0.6-1.1); P=0.13 | 0.9 (0.6-1.4); P=0.57 | 0.7 (0.5-0.9); P=0.06 | 0.7 (0.5-1.0); P=0.06 |
| **Hypertension** | 1.4 (1.1-1.7); P=0.003 | 1.1 (0.9-1.4); P=0.35 | 1.5 (1.2-1.8); P=0.001 | 1.3 (1.0-1.6); P=0.06 |
| **Hypercholesterolemia** | 1.7 (1.4-2.2); P<0.001 | 1.4 (1.1-1.9); P=0.01 | 1.9 (1.4-2.4); P<0.001 | 1.5 (1.1-2.0); P=0.005 |
| **Diabetes mellitus** | 1.6 (1.2-2.2); P=0.002 | 1.4 (1.0-1.9); P=0.03 | 1.7 (1.2-2.4); P=0.001 | 0.3 (0.9-1.8); P=0.14 |
| **Arterial disease** | 1.4 (0.7-3.0); P=0.38 | | 1.7 (1.0-3.0); P=0.054 | |
| **Renal failure** | 6.7 (2.1-21.2); P=0.001 | 5.4 (1.7-17.6); P=0.01 | 2.9 (1.4-5.8); P=0.003 | 2.3 (1.0-5.3); P=0.04 |
| **Previous MI** | 0.7 (0.3-1.5); P=0.70 | | 1.3 (0.9-2.0); P=0.15 | 1.0 (0.6-1.6); P=0.97 |
| **Previous PCI** | 0.9 (0.5-1.5); P=0.63 | | 1.5 (1.0-2.1); P=0.057 | 1.2 (0.8-1.9); P=0.36 |
| **Decompensated heart failure** | 1.1 (0.8-1.7); P=0.46 | | 1.0 (0.7-1.4); P=0.90 | |
| **LVEF <50%** | 0.9 (0.6-1.3); P=0.56 | | 1.1 (0.9-1.5); P=0.33 | |
| **Atrial fibrillation** | 0.9 (0.6-1.4); P=0.61 | | 1.0 (0.7-1.4); P=0.89 | |
| **Previous stroke or TIA** | 1.4 (0.9-2.1); P=0.11 | 1.4 (0.9-2.1); P=0.11 | 1.2 (0.8-1.6); P=0.35 | |
| **COPD** | 1.8 (1.3-2.5); P<0.001 | 1.7 (1.2-2.3); P=0.002 | 1.2 (0.9-1.8); P=0.27 | |
| **Urgent SAVR versus non-urgent** | 1.5 (0.5-3.9); P=0.46 | | 1.0 (0.4-2.8); P=0.94 | |
| **Mechanical prosthesis** | 0.8 (0.7-1.0); P=0.08 | 0.5 (0.4-0.7); P<0.001 | 0.5 (0.4-0.6); P<0.001 | 0.4 (0.3-0.6); P<0.001 |

Abbreviations as in Table 1. CI, confidence interval; HR, hazard ratio.

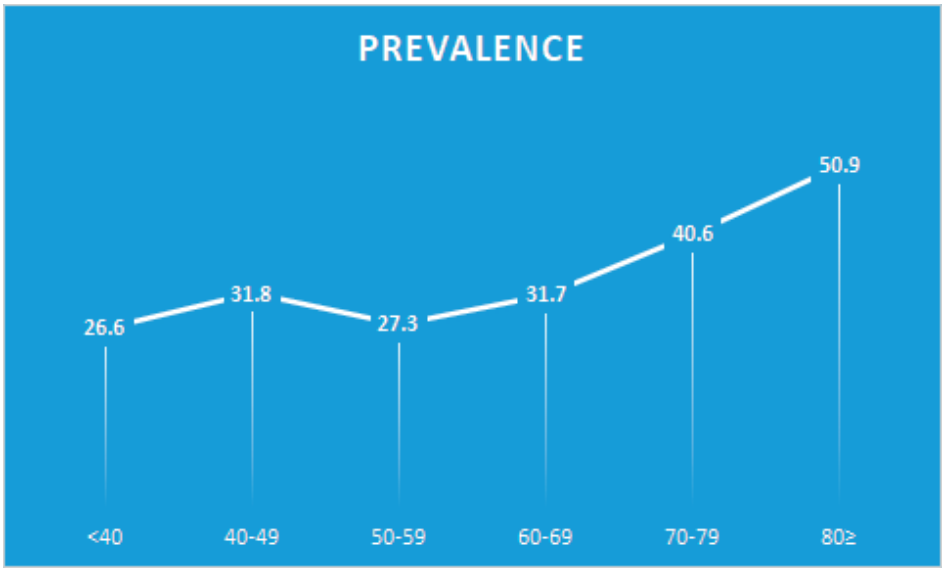


**Figure S1. Incidence of female patients undergoing the index procedure after 2000.**
Incidence of female patients according to different age categories for patients operated after 2000. Values given in percentages.

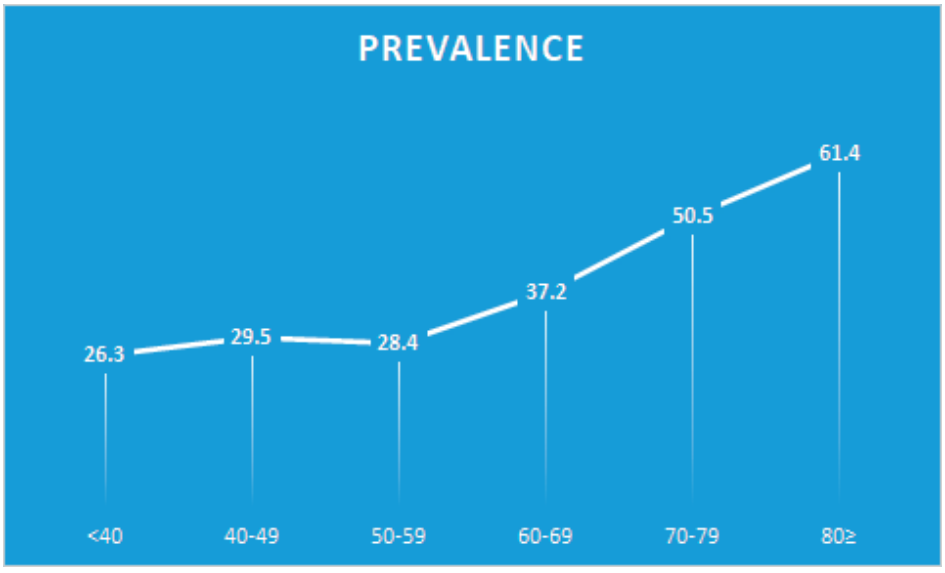


**Figure S2. Incidence of female patients undergoing isolated SAVR.**
Incidence of female patients according to different age categories for patients undergoing isolated SAVR. Values given in percentages.

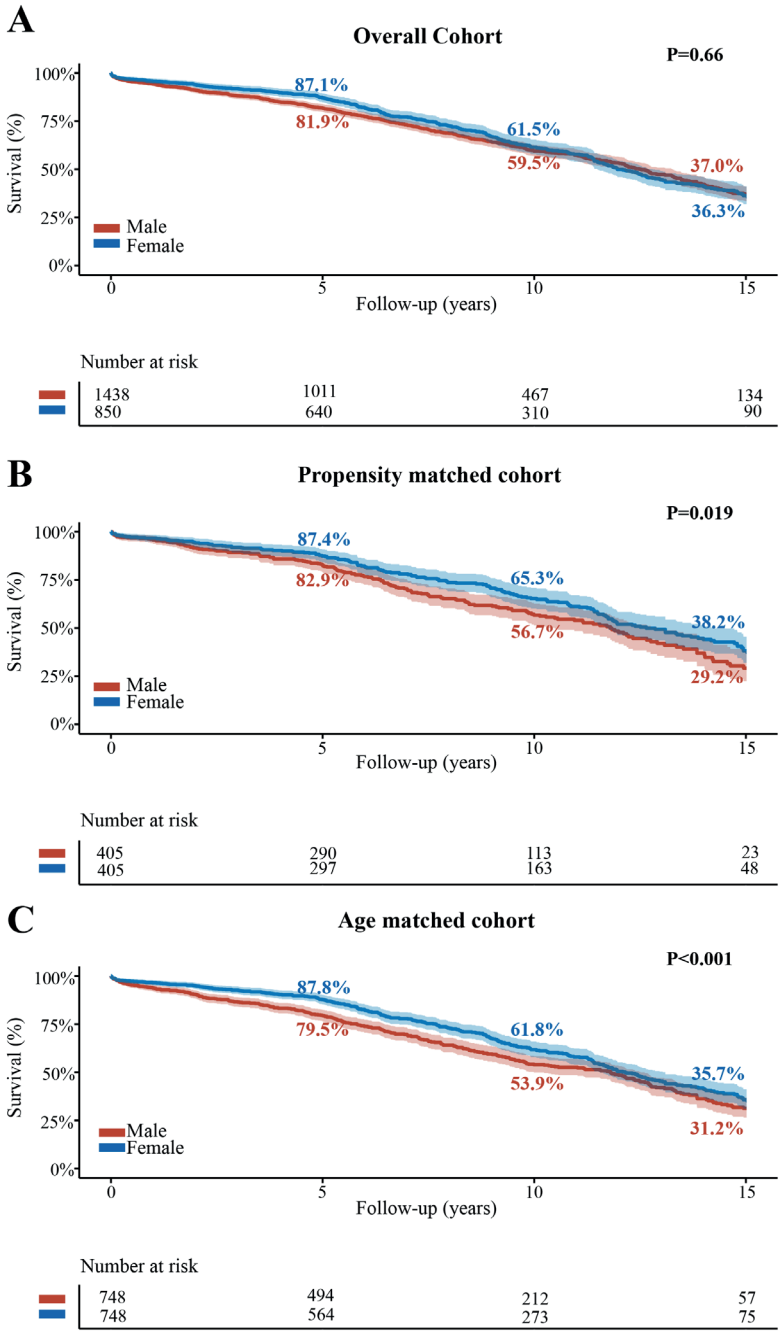


**Figure S3. Survival in patients undergoing the index procedure after 2000.**
A) Survival in the overall cohort, B) Survival in the propensity matched cohort, C) Survival in the age matched cohort.

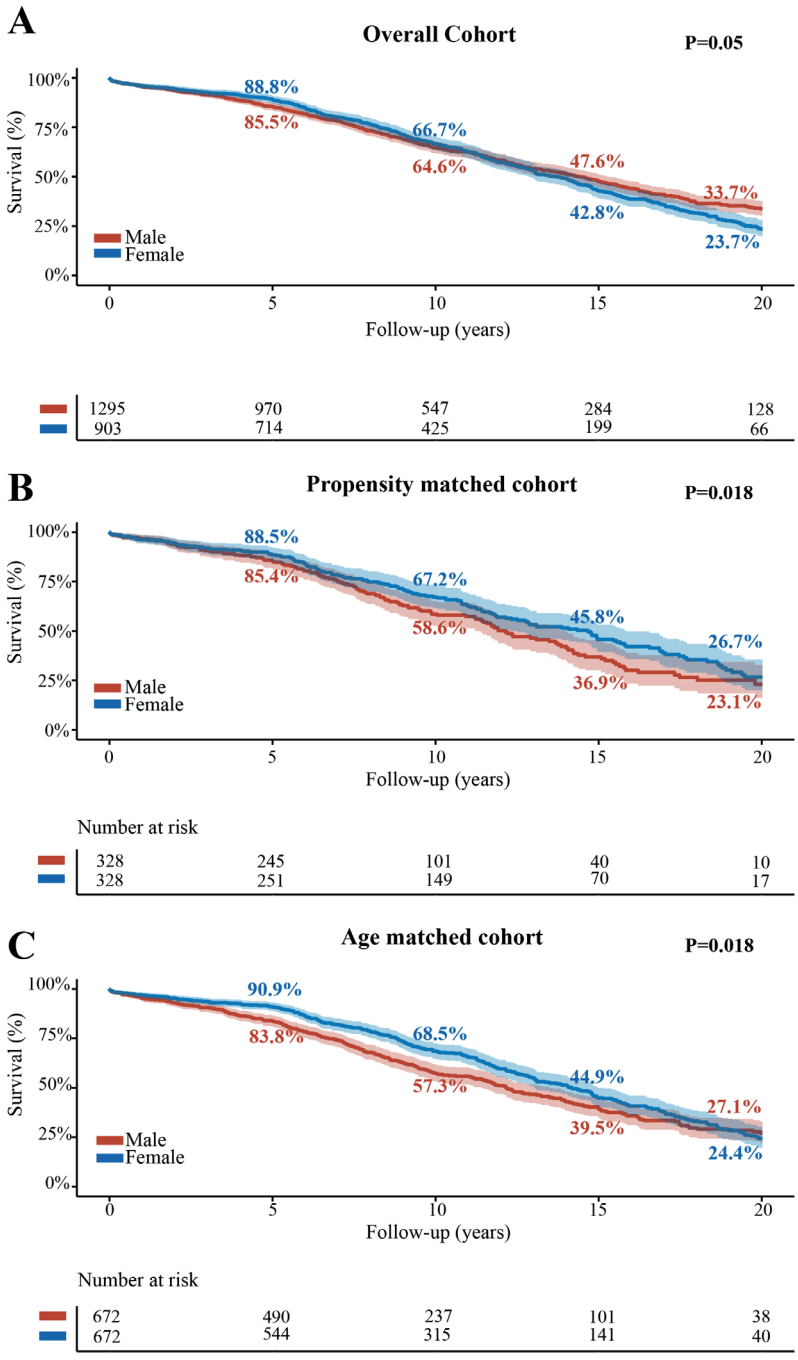


**Figure S4. Survival in male and female patients undergoing isolated SAVR.**
Survival in the overall cohort, B) Survival in the propensity matched cohort, C)Survival in the age matched cohort

# 11 Asymptomatic Patients with Severe Aortic Stenosis and the Impact of Intervention

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## ABSTRACT

**Objectives:** The exact timing of aortic valve replacement (AVR) in asymptomatic patients with severe aortic stenosis (AS) remains a matter of debate. Therefore, we describe the natural history of asymptomatic patients with severe AS and the effect of AVR on the long-term survival.

**Methods:** Asymptomatic patients who were found to have severe AS between June 2006 and May 2009 were included. Severe aortic stenosis was defined as peak aortic jet velocity Vmax ≥4.0 m/s or aortic valve area (AVA) ≤1cm$^2$. Development of symptoms, and the incidence of AVR, and all-cause mortality were assessed.

**Results:** A total of 59 asymptomatic patients with severe AS were followed with a mean follow-up of 8.9 ± 0.4 years. Total of 51 (86.4%) patients developed AS related symptoms, subsequently 46 patients underwent AVR. The mean 1-year, 2-year, 5-year and 10-year overall survival rates were higher in patients receiving AVR compared to those who did not undergo AVR during follow-up (100%, 93.5%, 89.1%, and 69.4% versus 92.3%, 84.6%, 65.8% and 28.2% respectively; p<0.001). Asymptomatic patients with severe AS receiving AVR during follow-up showed an incremental benefit of survival of up to 31.9 months compared to conservatively managed patients (p=0.002).

**Conclusions:** The majority of asymptomatic patients turn symptomatic during follow-up. AVR during follow-up is associated with better survival in asymptomatic severe AS patients.

## INTRODUCTION

Aortic stenosis (AS) is the most common valvular heart disease, with a prevalence of approximately 5% in adults above the age of 65 years.[1] The prevalence is expected to grow exponentially within the next decades due to an aging population in developed countries.[2] Patients with symptomatic severe AS currently hold class IB recommendation for surgical aortic valve replacement (SAVR) treatment due to the dismal prognosis once symptoms are present.[3,4] Yet, up to 50% of the patients with severe AS report no symptoms at initial diagnosis.[5]

Due to the low risk of sudden cardiac death, which is believed to be approximately 1%, conservative approach is currently the treatment of choice in the asymptomatic population. New evidence challenges this belief and the incidence of sudden death might be higher than previously expected.[6] In addition, majority of these patients develop AS related symptoms and require intervention within the first 2 years of follow-up.[7] In the present study, we aimed to study the natural history of a cohort of consecutive asymptomatic patients with severe AS and evaluating the implications of aortic valve intervention (AVR) on long-term survival.

## METHODS

### Patient population

This retrospectively analyzed, prospective multicenter study enrolled asymptomatic adult (≥18 years) patients diagnosed with severe AS at seven Cardiology clinics in the Rotterdam area between June 2006 and May 2009. Patients were deemed asymptomatic if they had no cardiac symptoms at baseline visit (angina, shortness of breath or syncope). In accordance with the European Society of Cardiology and American College of Cardiology/American Heart Association Guidelines for the Management of Patients With Valvular Heart Disease, severe AS was defined as aortic jet maximal velocity Vmax ≥4.0 m/s or aortic valve area (AVA) ≤1 $cm^2$.[8,9] Patients had a normal left ventricular ejection fraction (≥50%). After inclusion in the present cohort, asymptomatic patients were invited for exercise testing at baseline. A positive exercise test was defined according to the ACC/AHA guidelines.[10] The study was approved by the medical ethics committee of Erasmus University Medical Center and patient informed consent was waived. All the authors vouch for the validity of the data and adherence to the protocol.

### Endpoints and definitions

The primary endpoint was all-cause mortality. The secondary endpoints were the development of AS related symptoms and the need of AVR with either SAVR or TAVI. SAVR within 24 hours of establishing the indication was classified as urgent.

### Statistical analysis

Discrete variables are presented as numbers, percentages or proportions. Continuous variables are presented as means ± standard deviation, and presented as median with the interquartile range (IQR) if there was evidence of skewed data according to the Kolmogorov-Smirnov test. Discrete variables were compared with either the Chi Square test or the Fisher Exact test, where appropriate. Continuous variables were compared with either the two-sample t-test or Wilcoxon rank-sum test, where appropriate.

Cumulative incidence were assessed using Kaplan-Meier curves to estimate the probability of i) symptom development, ii) AVR, iii) all-cause mortality in the overall cohort, and iv) all-cause mortality in patients separated by whether they underwent AVR during follow-up. The incidence of AVR during follow-up was calculated and expressed as number of AVRs per 1,000 patient-years.

Predictors of i) all-cause mortality and ii) AVR were identified in a Cox proportional hazards model. Significant variables on univariable analyses were included in a multivariable Cox proportional hazards model. Further, the restricted mean survival time at 10-years of follow-up was calculated to substantiate the overall treatment effect. Two-sided p-values <0.05 were considered to be statistically significant. Data analyses were performed using SPSS 25.0 (SPSS Inc, Chicago, Illinois) and R software, version 3.4 (R Foundation, Vienna, Austria).

## RESULTS

### Baseline characteristics

The final study population consisted of 59 asymptomatic patients with severe AS (Figure S1). The mean age of the patients was 68.2 ± 10.7 years. Patients receiving AVR during follow-up were younger compared to patients with a conservative approach, 66.5 ± 10.6 versus 74.1 ± 8.9; p=0.022, respectively. Asymptomatic patients with AVR during follow-up had a trend toward being more female (30.4% versus 7.7%, p=0.096) and had less diabetes mellitus (13.0% versus 46.2%, p=0.009). No difference in baseline severity of AS was noted, based on AVA (0.85 ± 0.27 versus 0.80 ± 0.30, p=0.536) and Vmax (4.23 ± 0.68 versus 4.28 ± 0.70, p=0.823). Further baseline characteristics for the overall cohort and patients undergoing AVR and no AVR during follow-up are shown in Table 1.

**Table 1. Baseline characteristics of the asymptomatic population**

| | All (n=59) | Conservative treatment (n=13) | AVR (n=46) | P-value |
|---|---|---|---|---|
| **Age (years)** | 68.8 ± 10.6 | 74.1 ± 8.9 | 66.5 ± 10.6 | 0.345 |
| **Female** | 15 (25.4) | 1 (7.7) | 14 (30.4) | 0.096 |
| **BMI** | 27.1 ± 3.7 | 27.5 ± 3.9 | 26.9 ± 3.7 | 0.661 |
| **BSA** | 1.93 ± 0.20 | 2.00 ± 0.12 | 1.91 ± 0.21 | 0.226 |
| **Previous CABG** | 2 (3.4) | 0 | 2 (4.3) | 0.444 |
| **Smoking** | 42 (71.2) | 10 (76.9) | 32 (69.6) | 0.605 |
| **Atrial fibrillation** | 4 (7.0) | 2 (15.4) | 2 (4.5) | 0.179 |
| **Carotid disease** | 1 (1.7) | 1 (7.7) | 0 | 0.058 |
| **Coronary artery disease** | 4 (6.8) | 0 | 4 (8.7) | 0.271 |
| **COPD** | 6 (10.2) | 2 (15.4) | 4 (8.7) | 0.481 |
| **Diabetes** | 12 (20.3) | 6 (46.2) | 6 (13.0) | 0.009 |
| **Hyperlipidemia** | 29 (49.2) | 8 (61.5) | 21 (45.7) | 0.312 |
| **Hypertension** | 29 (49.2) | 5 (38.5) | 24 (52.2) | 0.383 |
| **Myocardial infarction** | 4 (6.8) | 0 | 4 (8.7) | 0.271 |
| **Peripheral arterial disease** | 5 (8.5) | 0 | 5 (10.9) | 0.214 |
| **Stroke** | 12 (20.3) | 3 (23.1) | 9 (19.6) | 0.781 |
| **NT-proBNP (pmol/l)** | 32.0 (18.0-97.0) | 33.0 (12.8-149.3) | 32.0 (18.0-89.0) | 0.976 |
| **Baseline positive stress test** | 15 (25.4) | 4 (30.8) | 11 (24.4) | 0.646 |
| **Logistic EuroSCORE** | 4.0 (2.1-6.9) | 4.7 (3.2-8.1) | 3.9 (2.1-5.5) | 0.485 |
| **STS score** | 3.8 (2.0-6.0) | 5.2 (2.2-8.6) | 3.6 (2.0-5.0) | 0.403 |
| **No medication** | 13 (22.0) | 2 (15.4) | 11 (23.9) | 0.512 |
| **Diuretics** | 11 (18.6) | 3 (23.1) | 8 (17.4) | 0.642 |
| **Ace Inhibitor** | 14 (23.7) | 4 (30.8) | 10 (21.7) | 0.499 |
| **A2 antagonist** | 11 (18.6) | 5 (38.5) | 6 (13.0) | 0.038 |
| **B blocker** | 15 (25.4) | 1 (7.7) | 14 (30.4) | 0.096 |
| **Calcium antagonist** | 8 (13.6) | 2 (15.4) | 6 (13.0) | 0.828 |
| **Digoxine** | 4 (6.8) | 0 | 4 (8.7) | 0.271 |
| **Echocardiographic parameters** | | | | |
| **Vmax (m/s)** | 4.24 ± 0.68 | 4.28 ± 0.70 | 4.23 ± 0.68 | 0.823 |
| **AVA ($cm^2$)** | 0.85 ± 0.28 | 0.80 ± 0.30 | 0.85 ± 0.27 | 0.536 |
| **iAVA ($cm^2/m^2$)** | 0.44 ± 0.15 | 0.41 ± 0.16 | 0.44 ± 0.14 | 0.423 |
| **MAG (mmHg)** | 42.8 ± 15.0 | 44.3 ± 17.4 | 42.3 ± 14.4 | 0.684 |
| **PAG (mmHg)** | 73.2 ± 23.6 | 75.3 ± 24.1 | 72.6 ± 23.7 | 0.720 |
| **AR grade I/II** | 29 (50.0) | 6 (46.2) | 23 (51.1) | 0.753 |
| **MR grade I/II** | 12 (20.7) | 4 (30.8) | 8 (17.8) | 0.308 |
| **LVEF** | 62.5 ± 5.9 | 61.1 ± 5.9 | 62.7 ± 5.7 | 0.374 |
| **LF/LG AS (%)** | 5 (8.5) | 0 | 5 (10.9) | 0.214 |
| **LVH (%)** | 14 (25.5) | 2 (16.7) | 12 (27.9) | 0.429 |

**Table 1. Baseline characteristics of the asymptomatic population** (*continued*)

| | All (n=59) | Conservative treatment (n=13) | AVR (n=46) | P-value |
|---|---|---|---|---|
| **TAPSE (mm)** | 25.1 ± 3.7 | 23.6 ± 2.8 | 25.5 ± 3.9 | 0.104 |
| **LVEDD (mm)** | 49.0 ± 6.0 | 49.6 ± 5.1 | 25.5 ± 3.9 | 0.687 |
| **LVESD (mm)** | 31.4 ± 6.2 | 30.3 ± 5.7 | 31.7 ± 6.4 | 0.466 |
| **LVFS (%)** | 36.1 ± 8.8 | 38.6 ± 11.0 | 35.4 ± 8.1 | 0.248 |
| **LA (mm)** | 41.3 ± 6.4 | 42.2 ± 6.8 | 41.0 ± 6.3 | 0.563 |
| **IVSd (mm)** | 12.6 ± 2.7 | 12.5 ± 2.0 | 12.6 ± 2.9 | 0.834 |
| **IVCd (mm)** | 17.4 ± 3.6 | 16.4 ± 2.7 | 17.7 ± 3.8 | 0.252 |
| **PWd (mm)** | 10.8 ± 2.0 | 11.5 ± 1.7 | 10.7 ± 2.1 | 0.161 |
| **E' (cm/s)** | 79.5 ± 23.6 | 69.1 ± 29.9 | 82.0 ± 21.4 | 0.103 |
| **A' (cm/s)** | 89.9 ± 37.2 | 104.2 ± 59.9 | 86.0 ± 27.9 | 0.134 |
| **E'A' ratio** | 1.0 ± 0.57 | 0.8 ± 0.5 | 1.1 ± 0.6 | 0.120 |
| **LVET (ms)** | 322.1 ± 32.2 | 312.6 ± 43.9 | 324.8 ± 28.4 | 0.296 |
| **DT (ms)** | 239.4 ± 63.3 | 217.5 ± 52.6 | 245.3 ± 65.2 | 0.198 |

values are presented as mean ± SD or n (%)

***A'**, peak velocity of diastolic mitral annular motion; **AR**, aortic regurgitation; **AVA**, aortic valve area; **BMI**, body mass index; **BSA**, body surface area; **COPD**, chronich obstructive pulmonary disease; **DT**, deceleration time; **iAVA** , indexed aortic valve area; **E'**, peak velocity of early diastolic mitral annular motion; **E'A' ratio**, ratio of E' to A'; **IVCd**, inferior vena cava dimension; **IVSd**, interventricular septum dimension; **LA**, left atrium; **LF/LG AS**, low-flow/low-grade AS; **LVEDD**, left ventricular end diastolic diameter; **LVEF**, left ventricular ejection fraction; **LVESD**, left ventricular end systolic diameter; **LVET**, left ventricular ejection time; **LVFS**, left ventricular fractional shortening; **LVH**, left ventricular hypertrophy; **MAG** , mean aortic gradient; **MR**, mitral regurgitation; **PAD**, peripheral arterial disease; **PAG**, peak aortic gradient; **PWd**, posterior wall dimension, **TAPSE**, tricuspid annular plane systolic excursion; **Vmax**, maximal velocity*

## Natural course of asymptomatic severe stenosis

Forty-seven out of the 59 patients underwent an exercise stress test at baseline. Of these 47 patients, 15 (32%) tested positive and 32 (68%) patients tested negative. The other twelve patients were unable to undergo an exercise stress test. Nearly half of the patients had their symptoms unmasked by baseline exercise test or eventually develop symptoms within the first year after initial diagnosis (n=26; 44%), but the vast majority of patients had symptoms (n=51/59, 86.4%) before AVR or death (Figure 1A). Mean time to symptom onset was 2.6 ± 0.4 years. During follow-up, 46 patients required AVR of whom 11 (24.4%) had a positive exercise test at baseline. Three patients underwent TAVI . Eight patients died before undergoing AVR. Cumulative incidence of AVR was 13.6% and 91.4% at 1-year and 10-years, respectively (Figure 1B). The linearized incidence rate of AVR was 95.5 per 1000 patient-years. Baseline characteristics of patients who did not undergo AVR according to survival status is shown in Table S1.

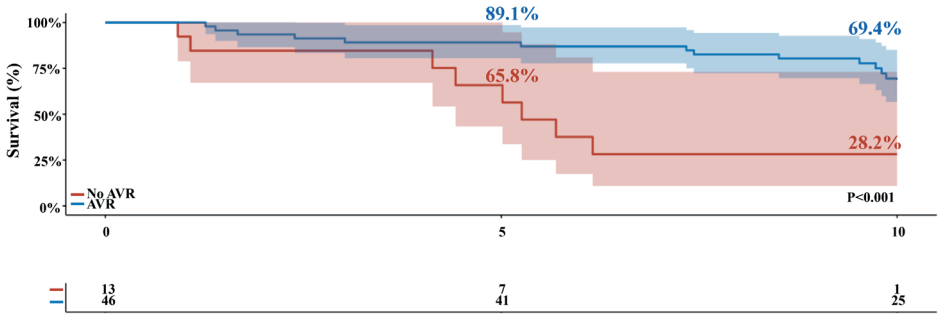


**Figure 1. Cumulative incidence rates in the overall cohort**
A) symptom development, (B) aortic valve replacement (either surgical or transcatehter) and (C) all-cause mortality. *Shaded region represents the 95% confidence interval.*

## Survival

During a mean follow-up time 8.9 ± 0.4 years, 35 patients (59.3%) died. Early (30-day) mortality after AVR occurred in 0 patients. The incidence of all-cause mortality was 38.9% at 10-years in the overall cohort (Figure 1C). The mean 1-year, 2-year, 5-year and 10-year overall survival rates was higher in patients receiving AVR compared to conservatively managed patients (100%, 93.5%, 89.1%, and 69.4% versus 92.3%, 84.6%, 65.8% and 28.2% respectively; p<0.001) (Figure 2). Patients receiving AVR during follow-up had a survival benefit of 31.9 months (95% confidence interval [CI]: 13.27-58.44, p=0.002) compared to conservatively managed patients (Table 2).

**Table 2. Between-group differences in mortality among treatment strategies (conservative versus AVR)**

| **Overall cohort** | | | |
|---|---|---|---|
| **Restricted mean survival time at 10 years** | | 95% CI | p-value |
| **Difference – months** | 31.85 | 13.27-58.44 | 0.002 |
| **Ratio** | 1.51 | 1.11-2.05 | 0.008 |
| **Ratio of restricted mean time lost** | 0.28 | 0.13-0.60 | 0.001 |

***AVR**, aortic valve replacement; **CI**, confidence interval.*

## Predictors of outcome

In univariable analyses, being older (HR 1.11, 95% CI 1.06-1.17), having higher NT-proBNP levels (HR 1.002, 95% CI 1.001-1.004), having diabetes mellitus (HR = 4.57, 95% CI 1.91-10.96), atrial fibrillation (HR 4.98, 95% CI 1.40-17.72), and AVR during follow-up (HR 0.24, 95% CI 0.10-0.58) were predictors of all-cause mortality (Table 3). Age remained the only predictor after multivariable analysis (HR 1.08, 1.01-1.16, p=0.026). Univariate predictors of AVR in asymptomatic patients is shown in Table S2.

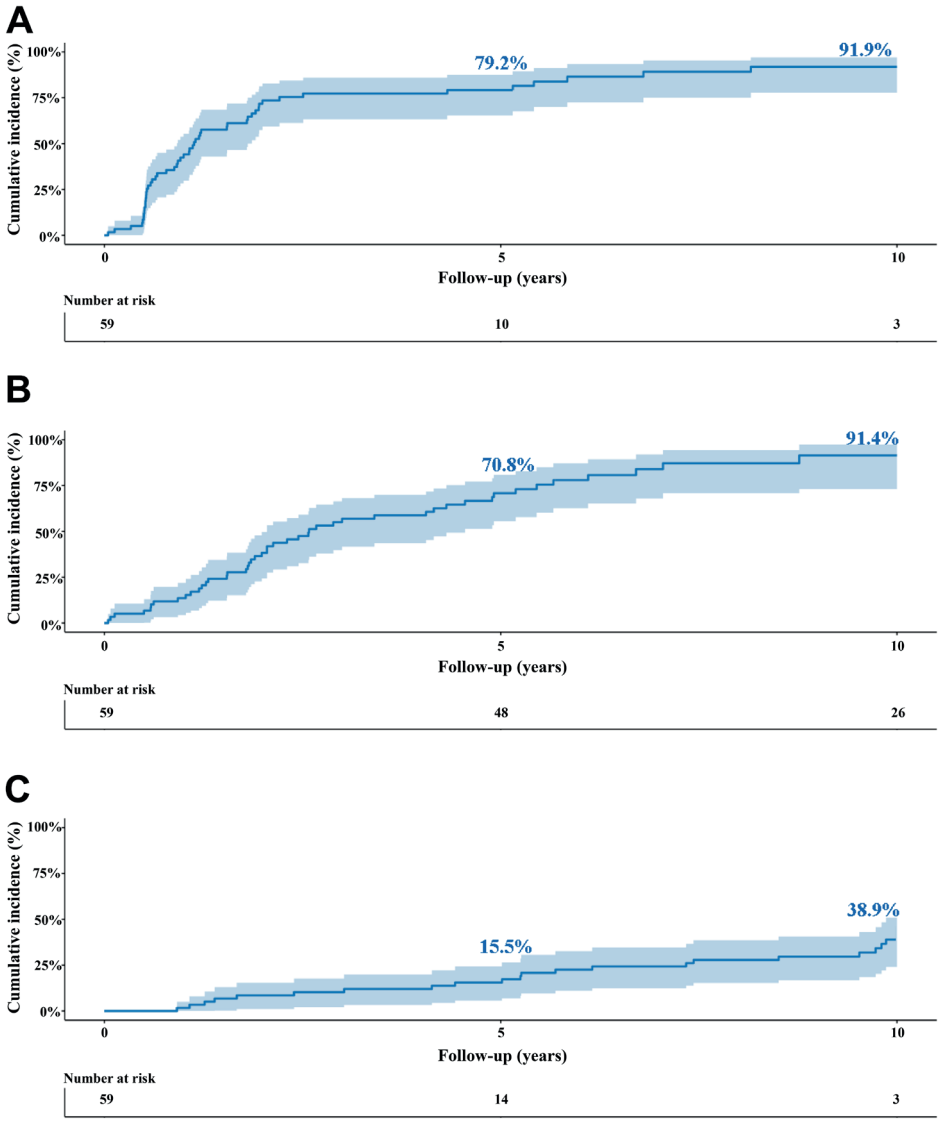


**Figure 2. Survival during follow-up.**

Actual survival of asymptomatic patients according to having received AVR during follow-up. *Blue line represents patients who did undergo AVR during follow-up. Red line represents patients who did not undergo AVR during follow-up. Shaded region represents the 95% confidence interval. AVR, aortic valve replacement.*

**Table 3. Predictors of all-cause mortality in asymptomatic patients during follow-up**

| | Univariable HR (95% CI), p-value | Multivariable HR (95% CI), p-value |
|---|---|---|
| **Age** | 1.11 (1.06-1.17), p<0.001 | 1.08 (1.01-1.16), p=0.026 |
| **Gender (female)** | 0.43 (0.16-1.37), p=0.125 | |
| **Atrial fibrillation** | 4.98 (1.40-17.72), p=0.013 | 3.10 (0.68-14.26), p=0.146 |
| **Coronary artery disease** | 0.62 (0.08-4.59), p=0.639 | |
| **COPD** | 1.60 (0.48-5.39), p=0.446 | |
| **Diabetes mellitus** | 4.57 (1.91-10.96), p<0.001 | 2.36 (0.87-6.44), p=0.094 |
| **Hyperlipidemia** | 1.65 (0.72-3.78), p=0.234 | |
| **Hypertension** | 1.50 (0.66-3.37), p=0.332 | |
| **Myocardial infarction** | 1.14 (0.27-4.86), p=0.862 | |
| **Peripheral arterial disease** | 1.58 (0.46-5.34), p=0.466 | |
| **Stroke** | 2.11 (0.90-.492), p=0.086 | |
| **Exercise test (positive)** | 0.74 (0.27-1.98) p=0.543 | |
| **NT-proBNP** | 1.002 (1.001-1.004) p<0.001 | 1.002 (1.00-1.003), p=0.053 |
| **STS score** | 1.06 (0.99-1.14), p=0.098 | |
| **Logistic EuroSCORE** | 1.22 (1.09-1.35), p<0.001 | 0.98 (0.81-1.18), p=0.830 |
| **AVR** | 0.24 (0.10-0.58) p=0.002 | 1.17 (0.31-4.36), p=0.820 |
| **LVEF** | 0.96 (0.90-1.04), p=0.315 | |
| **Vmax** | 0.95 (0.53-1.70), p=0.851 | |
| **AVA** | 0.19 (0.03-1.11), p=0.065 | |
| **iAVA** | 0.05 (0.00-1.141), p=0.078 | |
| **MAG** | 1.01 (0.99-1.03), p=0.460 | |
| **PAG** | 1.00 (0.98-1.10), p=0.817 | |

***AVA**, aortic valve area; **AVR**, aortic valve replacement; **COPD**: chronic obstructive pulmonary disease; **iAVA**, indexed aortic valve area; **LVEF**, left ventricular ejection fraction; **MAG**, mean aortic gradient; **PAG**, peak aortic gradient; **STS**, Society of Thoracic Surgery; **Vmax**, maximal jet velocity.*



## DISCUSSION

This study describes the natural history of asymptomatic patients with severe AS and the impact of intervention in this patient population. We found that (i) the majority of the patients eventually develop AS related symptoms, (ii) subsequently requiring AVR, and (iii) patients who did receive AVR have a survival benefit of close to three years compared to conservatively managed patients.

Adriana C. Gittenberger-de Groot and her team have performed an extensive number of indispensable studies on the spectrum of aortic valvular disease over the past decades, including histopathological, anatomical and developmental studies on animal as well as human tissue.[10]

Majority of asymptomatic patients develop symptoms within the first 3 years after initial diagnosis[11], with up to 86.4% at 10-years in our cohort. The asymptomatic patient might be 'falsely' labelled as asymptomatic. In our cohort 79.7% underwent exercise stress testing at baseline, of whom 31.9% of the patients had a positive test. Abnormal exercise test is associated with impaired 2-year event-free survival[12-14], and is clear indication for AVR.[3,4] Especially, in elderly patients who are subconsciously adapting their exercise to their tolerance and underrepresent their symptoms. It is still concerning that relatively few asymptomatic patients in practice undergo routine stress testing.[15] Several difficulties of exercise testing exists in the elderly population, including 1) its lower predictive value compared to a younger population, 2) limited exercise capability in the elderly due to non-cardiac conditions limiting mobility, and 3) the differences in exercise protocol and definition of an abnormal exercise test.[16,17] The relevancy and accuracy of exercise testing is therefore still a debated topic.

The majority of the asymptomatic population with severe AS who develop symptoms underwent AVR (91.4%). Our rate is higher in comparison with earlier reports, wherein approximately 57% of the patients underwent AVR at 10-years of follow-up.[11] This discrepancy could be caused due to the recommendation of the physician. The current asymptomatic patient with severe AS does not have a formal indication for intervention, unless the patient has 1) depressed LVEF, or 2) is undergoing concomitant cardiac surgery.[3,4] Yet, it is expected that the degree of AS will gradually increase, and the initially asymptomatic patient eventually will develop symptoms due to disease progression subsequently requiring guideline recommended AVR. The upfront gain obtained by delaying surgery might not outweigh the risk of AVR being delayed with conservative treatment. This is especially the case in patients who are older and subsequently have increased operative risk.[18] In those patients the long-term hemodynamic consequences might outweigh the positive outcomes of an early interventional strategy.[19,20]

Asymptomatic patients with severe AS undergoing AVR during follow-up had better survival compared to conservatively managed patients. In the first randomized controlled trial, a total 145 asymptomatic patients with very severe AS were randomized to early surgery (n=73) and conservative care (n=72).[21] Early surgery resulted in improved survival at 8-years of follow-up compared to patients treated with a conservative approach (90% versus 74%, p=0.003, respectively). However, the this study only provides a perspective on patients with very severe AS. Initial data in asymptomatic patients with severe AS on all-cause mortality at 5-year from the CURRENT AS registry indicates a survival benefit for patients undergoing surgery within 3-months compared to conservative treatment, 26.4% vs. 15.4%; P=0.009, respectively.[20] While pre-emptive strategy seems superior in those with (very) severe AS[21], the exact timing and benefit of AVR in asymptomatic patients with severe AS remains to be defined. Conservative treatment is a solution that almost nobody still considers with the advent of TAVI. The role of mini-

mally invasive techniques in the asymptomatic cohort with severe AS will need to be substantiated in the future (NCT03094143 and NCT03042104, Table S3).

### Limitations

Several limitations need to be acknowledged. First, this is an ambispective study with its inherent shortcomings. Second, the number of patients and subsequent events are relatively low with its shortcomings related to overfitting of multivariable analyses. Given the fact that patients were not randomized into the early surgical management and conservative treatment, potential selection bias cannot be eliminated, wherein the older patient was more unlikely to undergo AVR, as the indication for treatment was left to the discretion of the treating physician.

## CONCLUSION

The vast majority of asymptomatic patients with severe AS develop symptoms during follow-up and subsequently require intervention. Intervention during follow-up is associated with better long-term survival, and early intervention is likely to improve survival. Close clinical follow-up is warranted for all patients, and pre-emptive elective aortic valve procedures may be considered in selected elderly patients at low procedural risk. Further results from the currently ongoing clinical trials will give us more insight on the role of early intervention in asymptomatic patients with severe AS.

## REFERENCES


1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. Circulation. 2014;129(3):e28-e292.
2. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet. 2006;368(9540):1005-11.
3. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739-91.
4. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Fleisher LA, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017;70(2):252-89.
5. Genereux P, Stone GW, O'Gara PT, Marquis-Gravel G, Redfors B, Giustino G, et al. Natural History, Diagnostic Approaches, and Therapeutic Strategies for Patients With Asymptomatic Severe Aortic Stenosis. J Am Coll Cardiol. 2016;67(19):2263-88.
6. Taniguchi T, Morimoto T, Shiomi H, Ando K, Kanamori N, Murata K, et al. Sudden Death in Patients With Severe Aortic Stenosis: Observations From the CURRENT AS Registry. J Am Heart Assoc. 2018;7(11).
7. Heuvelman HJ, van Geldorp MW, Kappetein AP, Geleijnse ML, Galema TW, Bogers AJ, et al. Clinical course of patients diagnosed with severe aortic stenosis in the Rotterdam area: insights from the AVARIJN study. Neth Heart J. 2012;20(12):487-93.
8. American College of Cardiology/American Heart Association Task Force on Practice G, Society of Cardiovascular A, Society for Cardiovascular A, Interventions, Society of Thoracic S, Bonow RO, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. Circulation. 2006;114(5):e84-231.
9. Vahanian A, Baumgartner H, Bax J, Butchart E, Dion R, Filippatos G, et al. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. Eur Heart J. 2007;28(2):230-68.
10. Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, et al. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). Circulation. 2002;106(14):1883-92.
11. Pellikka PA, Sarano ME, Nishimura RA, Malouf JF, Bailey KR, Scott CG, et al. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. Circulation. 2005;111(24):3290-5.
12. Lancellotti P, Lebois F, Simon M, Tombeux C, Chauvel C, Pierard LA. Prognostic importance of quantitative exercise Doppler echocardiography in asymptomatic valvular aortic stenosis. Circulation. 2005;112(9 Suppl):I377-82.
13. Peidro R, Brion G, Angelino A. Exercise testing in asymptomatic aortic stenosis. Cardiology. 2007;108(4):258-64.

14. Rafique AM, Biner S, Ray I, Forrester JS, Tolstrup K, Siegel RJ. Meta-analysis of prognostic value of stress testing in patients with asymptomatic severe aortic stenosis. Am J Cardiol. 2009;104(7):972-7.
15. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Barwolf C, Levang OW, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. Eur Heart J. 2003;24(13):1231-43.
16. Das P, Rimington H, Chambers J. Exercise testing to stratify risk in aortic stenosis. Eur Heart J. 2005;26(13):1309-13.
17. Redfors B, Pibarot P, Gillam LD, Burkhoff D, Bax JJ, Lindman BR, et al. Stress Testing in Asymptomatic Aortic Stenosis. Circulation. 2017;135(20):1956-76.
18. Hussain AI, Auensen A, Brunborg C, Beitnes JO, Gullestad L, Pettersen KI. Age-dependent morbidity and mortality outcomes after surgical aortic valve replacement. Interact Cardiovasc Thorac Surg. 2018;27(5):650-6.
19. Everett RJ, Clavel MA, Pibarot P, Dweck MR. Timing of intervention in aortic stenosis: a review of current and future strategies. Heart. 2018;104(24):2067-76.
20. Taniguchi T, Morimoto T, Shiomi H, Ando K, Kanamori N, Murata K, et al. Initial Surgical Versus Conservative Strategies in Patients With Asymptomatic Severe Aortic Stenosis. J Am Coll Cardiol. 2015;66(25):2827-38.
21. Kang DH, Park SJ, Lee SA, Lee S, Kim DH, Kim HK, et al. Early Surgery or Conservative Care for Asymptomatic Aortic Stenosis. N Engl J Med. 2020;382(2).

## SUPPLEMENTARY MATERIAL

**Table S1 – Baseline characteristics of patients who did not undergo AVR during follow-up**

| | No AVR during follow-up (n=13) | Died (n=8) | Alive (n=5) | P-value |
|---|---|---|---|---|
| **Age (years)** | 74.1 ± 8.9 | 78.0 ± 7.7 | 67.8 ± 7.6 | 0.039 |
| **Female** | 1 (7.7) | 0 | 1 (20.0) | 0.188 |
| **BMI** | 27.5 ± 3.9 | 25.6 ± 2.0 | 30.4 ± 4.7 | 0.027 |
| **BSA** | 2.00 ± 0.12 | 2.0 ± 0.1 | 2.0 ± 0.1 | 0.572 |
| **Previous CABG** | 0 | 0 | 0 | >0.999 |
| **Smoking** | 10 (76.9) | 7 (87.5) | 3 (60.0) | 0.252 |
| **Atrial fibrillation** | 2 (15.4) | 1 (12.5) | 1 (20.0) | 0.715 |
| **Carotid disease** | 1 (7.7) | 1 (12.5) | 0 | 0.411 |
| **Coronary artery disease** | 0 | 0 | 0 | >0.999 |
| **COPD** | 2 (15.4) | 1 (12.5) | 1 (20.0) | 0.715 |
| **Diabetes** | 6 (46.2) | 5 (62.5) | 1 (20.0) | 0.135 |
| **Hyperlipidemia** | 8 (61.5) | 6 (75.0) | 2 (40.0) | 0.207 |
| **Hypertension** | 5 (38.5) | 4 (50.0) | 1 (20.0) | 0.279 |
| **Myocardial infarction** | 0 | 0 | 0 | >0.999 |
| **Peripheral arterial disease** | 0 | 0 | 0 | >0.999 |
| **Stroke** | 3 (23.1) | 2 (25.0) | 1 (20.0) | 0.835 |
| **NT-proBNP (pmol/l)** | 33.0 (12.8-149.3) | 100.5 (19.0-971.5) | 35.0 (31.0-50.0) | 0.425 |
| **Baseline positive stress test** | 4 (30.8) | 3 (37.5) | 1 (20.0) | 0.506 |
| **Logistic EuroSCORE** | 4.7 (3.2-8.1) | 7.1 (4.4-10.5) | 3.0 (2.1-5.7) | 0.121 |
| **STS score** | 5.2 (2.2-8.6) | 5.8 (3.4-9.6) | 3.4 (2.4-6.0) | 0.845 |
| **No medication** | 2 (15.4) | 1 (12.5) | 1 (20.0) | 0.715 |
| **Diuretics** | 3 (23.1) | 2 (25.0) | 2 (40.0) | 0.835 |
| **Ace Inhibitor** | 4 (30.8) | 3 (37.5) | 1 (20.0) | 0.506 |
| **A2 antagonist** | 5 (38.5) | 5 (62.5) | 0 | 0.024 |
| **B blocker** | 1 (7.7) | 1 (12.5) | 0 | 0.411 |
| **Calcium antagonist** | 2 (15.4) | 2 (25.0) | 0 | 0.224 |
| **Digoxine** | 0 | 0 | 0 | >0.999 |
| **Echocardiographic parameters** | | | | |
| **Vmax (m/s)** | 4.28 ± 0.70 | 4.28 ± 0.85 | 4.28 ± 0.45 | >0.999 |
| **AVA ($cm^2$)** | 0.80 ± 0.30 | 0.70 ± 0.26 | 0.95 ± 0.32 | 0.149 |
| **iAVA ($cm^2/m^2$)** | 0.41 ± 0.16 | 0.36 ± 0.14 | 0.48 ± 0.17 | 0.190 |
| **MAG (mmHg)** | 44.3 ± 17.4 | 47.1 ± 21.9 | 39.7 ± 4.8 | 0.476 |
| **PAG (mmHg)** | 75.3 ± 24.1 | 76.1 ± 29.4 | 74.0 ± 15.4 | 0.885 |
| **AR grade I/II** | 6 (46.2) | 4 (50.0) | 2 (40.0) | 0.725 |
| **MR grade I/II** | 4 (30.8) | 3 (37.5) | 1 (20.0) | 0.506 |

**Table S1 – Baseline characteristics of patients who did not undergo AVR during follow-up** (*continued*)

| | No AVR during follow-up (n=13) | Died (n=8) | Alive (n=5) | P-value |
|---|---|---|---|---|
| **LVEF** | 61.1 ± 5.9 | 59.9 ± 6.4 | 63.1 ± 5.1 | 0.376 |
| **LF/LG AS (%)** | 0 | 0 | 0 | >0.999 |
| **LVH (%)** | 2 (16.7) | 2 (100.0) | 0 | 0.190 |
| **TAPSE (mm)** | 23.6 ± 2.8 | 23.0 ± 2.6 | 24.6 ± 3.3 | 0.345 |
| **LVEDD (mm)** | 49.6 ± 5.1 | 48.4 ± 6.1 | 51.6 ± 1.8 | 0.288 |
| **LVESD (mm)** | 30.3 ± 5.7 | 32.7 ± 4.7 | 26.4 ± 5.2 | 0.044 |
| **LVFS (%)** | 38.6 ± 11.0 | 32.2 ± 6.6 | 48.9 ± 9.0 | 0.002 |
| **LA (mm)** | 42.2 ± 6.8 | 44.9 ± 6.4 | 37.9 ± 5.4 | 0.072 |
| **IVSd (mm)** | 12.5 ± 2.0 | 13.0 ± 2.1 | 11.6 ± 1.5 | 0.231 |
| **IVCd (mm)** | 16.4 ± 2.7 | 15.9 ± 3.1 | 16.5 ± 5.0 | 0.542 |
| **PWd (mm)** | 11.5 ± 1.7 | 11.3 ± 1.1 | 12.0 ± 2.4 | 0.448 |
| **E' (cm/s)** | 69.1 ± 29.9 | 69.1 ± 33.9 | 69.0 ± 21.6 | 0.997 |
| **A' (cm/s)** | 104.2 ± 59.9 | 88.0 ± 33.1 | 136.6 ± 92.2 | 0.198 |
| **E'A' ratio** | 0.8 ± 0.5 | 0.9 ± 0.6 | 0.6 ± 0.4 | 0.377 |
| **LVET (ms)** | 312.6 ± 43.9 | 321 ± 29.5 | 300 ± 63.0 | 0.491 |
| **DT (ms)** | 217.5 ± 52.6 | 228.4 ± 55.7 | 188.3 ± 34.8 | 0.283 |

values are presented as mean ± SD or n (%)

***A'**, peak velocity of diastolic mitral annular motion; **AR**, aortic regurgitation; **AVA**, aortic valve area; **BMI**, body mass index; **BSA**, body surface area; **COPD**, chronich obstructive pulmonary disease; **DT**, deceleration time; **iAVA** , indexed aortic valve area; **E'**, peak velocity of early diastolic mitral annular motion; **E'A' ratio**, ratio of E' to A'; **IVCd**, inferior vena cava dimension; **IVSd**, interventricular septum dimension; **LA**, left atrium; **LF/LG AS**, low-flow/low-grade AS; **LVEDD**, left ventricular end diastolic diameter; **LVEF**, left ventricular ejection fraction; **LVESD**, left ventricular end systolic diameter; **LVET**, left ventricular ejection time; **LVFS**, left ventricular fractional shortening; **LVH**, left ventricular hypertrophy; **MAG** , mean aortic gradient; **MR**, mitral regurgitation; **PAD**, peripheral arterial disease; **PAG**, peak aortic gradient; **PWd**, posterior wall dimension, **TAPSE**, tricuspid annular plane systolic excursion; **Vmax**, maximal velocity*

**Table S2. Predictors of AVR in asymptomatic patients during follow-up**

| | Univariable HR (95% CI), P value |
|---|---|
| **Age** | 0.98 (0.95-1.01), p=0.125 |
| **Gender (female)** | 1.52 (0.80-2.90), p=0.200 |
| **LVEF** | 1.01 (0.97-1.06), p=0.556 |
| **Atrial fibrillation** | 0.51 (0.12-2.15), p=0.362 |
| **Coronary artery disease** | 1.15 (0.41-3.27), p=0.790 |
| **COPD** | 0.88 (0.31-2.46) p=0.806 |
| **Diabetes mellitus** | 0.57 (0.24-1.36) p=0.206 |
| **Hyperlipidemia** | 0.68 (0.38-1.23) p=0.205 |
| **Hypertension** | 1.25 (0.70-2.23) p=0.457 |
| **Myocardial infarction** | 2.07 (0.73-5.85), p=0.172 |
| **Peripheral arterial disease** | 1.33 (0.52-3.38), p=0.553 |
| **Stroke** | 0.80 (0.39-1.67), p=0.557 |
| **Exercise test (positive)** | 1.24 (0.62-2.48), p=0.540 |
| **NT-proBNP** | 1.00 (1.00-1.00) p=0.182 |
| **STS** | 1.00 (0.92-1.08), p=0.938 |
| **Logistic EuroSCORE** | 0.97 (0.88-1.07), p=0.593 |
| **LVEF** | 1.01 (0.97-1.06), p=0.556 |
| **Vmax** | 1.52 (0.99-2.32), p=0.056 |
| **AVA** | 0.51 (0.17-1.50), p=0.219 |
| **iAVA** | 0.38 (0.05-2.85), p=0.344 |
| **MAG** | 1.02 (1.00-1.03), p=0.093 |
| **PAG** | 1.01 (1.00-1.02), p=0.100 |

***AVA**, aortic valve area; **AVR**, aortic valve replacement; **COPD**: chronic obstructive pulmonary disease; **iAVA**, indexed aortic valve area; **LVEF**, left ventricular ejection fraction; **MAG**, mean aortic gradient; **PAG**, peak aortic gradient; **STS**, Society of Thoracic Surgery; **Vmax**, maximal jet velocity.*

**Table S3. Current on-going RCTs in the asymptomatic population**

| Name study | Source | SAVR or TAVR |
|---|---|---|
| **RECOVERY** | (https://clinicaltrials.gov/ct2/show/NCT01161732) | SAVR |
| **AVATAR** | (https://clinicaltrials.gov/ct2/show/NCT02436655) | SAVR |
| **ESTIMATE** | (https://clinicaltrials.gov/ct2/show/NCT02627391) | SAVR |
| **EVoLVeD** | (https://clinicaltrials.gov/ct2/show/NCT03094143) | SAVR/TAVR |
| **EARLY TAVR** | (https://clinicaltrials.gov/ct2/show/NCT03042104) | TAVR |

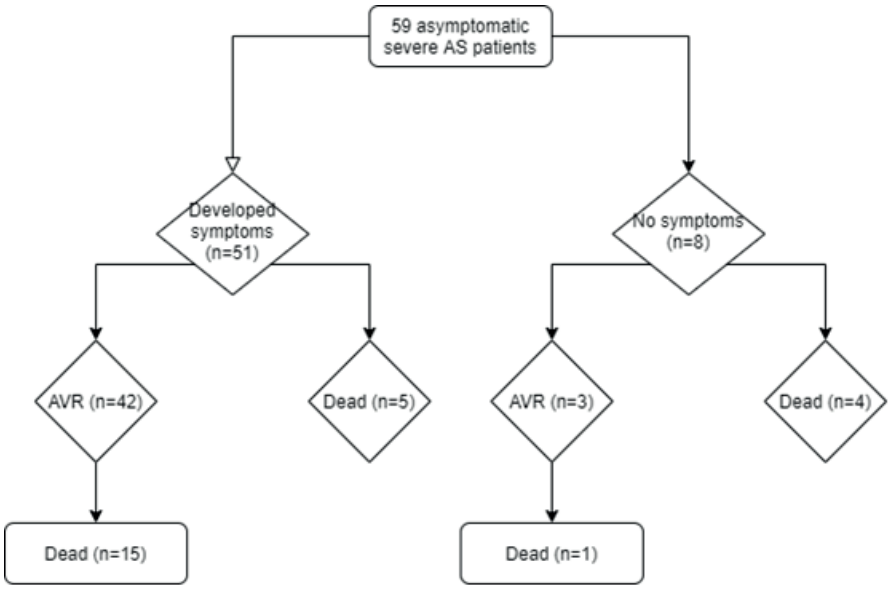


**Figure S1. Flowchart of the patients during follow-up**
A total of 59 asymptomatic patients with severe AS were included. Total of 51 patients did develop symptoms and 8 did not. Of whom who did develop symptoms underwent 42 AVR, and 15 patients died after AVR. Of whom who did not develop symptoms 3 underwent AVR, and 1 died after AVR. Five patients died after symptoms without undergoing AVR. Four patients died with no symptoms without undergoing AVR.

# 12 The Natural History of Asymptomatic Severe Aortic Stenosis and the Association of Early Intervention With Outcomes: A Systematic Review and Meta-analysis

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## KEY POINTS

**Question:** What is the natural history of asymptomatic severe aortic stenosis (AS), which variables predict prognosis, and can early intervention improve outcomes?
**Findings:** In this meta-analysis, the rate of all-cause death was 5 per 100 conservatively treated patients per year, of which 3 and 1 were of cardiac and sudden cause, respectively. Twenty per 100 patients per year developed an indication for intervention. Early intervention was significantly associated with improved survival.
**Meaning:** Many patients with asymptomatic severe AS develop indication for intervention while experiencing deaths that are mostly cardiac, but not only sudden. Early intervention is associated with improved survival.

## ABSTRACT

**Importance:** Whether intervention should be performed in patients with asymptomatic severe aortic stenosis (AS) remains debated.

**Objective:** Meta-analyze the natural history of asymptomatic severe AS and examine the association of early intervention on survival.

**Data sources:** PubMed, Embase and Cochrane databases were searched on February 1st, 2020.

**Study selection:** Observational studies of adult patients with asymptomatic severe AS .

**Data extraction and synthesis:** Two investigators independently extracted study and patient characteristics, follow-up time and events, and prognostic indicators of events. Random-effects model were used to derive pooled estimates.

**Main outcomes:** The meta-analysis on natural history was performed on the primary end point of all-cause death occurring during a conservative treatment period, with secondary end points consisting of cardiac death, death due to heart failure, sudden death, development of symptoms, development of an indication for aortic valve intervention, and aortic valve intervention. The primary end point for the meta-analysis of early intervention versus a conservative strategy was all-cause death during long-term follow-up. Finally, we performed a meta-analysis on the association of prognostic indicators with the composite of death or aortic valve intervention found in multivariable models.

**Results:** We included 30 studies with 4075 patients with 11901 years of follow-up. Pooled rates per 100 patients per year were 4.8 (95% CI 3.6-6.4) for all-cause death, 3.0 (95%CI 2.2-4.1) for cardiac death, 2.0 (95%CI 1.3-3.1 for death due to heart failure, 1.1 (95%CI 0.6-2.1) for sudden death, 17.5 (95%CI 12.8-24.0) for an indication for aortic valve intervention, 17.9 (95%CI 13.1-24.3) for development of symptoms, and 19.2 (95%CI 15.5-23.8) for aortic valve intervention. Early intervention was associated with a significant reduction in long-term mortality (HR 0.38, 95%CI 0.25-0.58). Factors associated with worse prognosis were severity of AS, low-flow AS, left ventricular damage, and atherosclerotic risk factors.

**Conclusions and relevance:** Data from observational studies and a recent randomized trial suggests that many patients with asymptomatic severe AS develop an indication for aortic valve intervention while experiencing deaths that are mostly cardiac, but not only sudden. Other endpoints besides sudden death should be considered during the decision to perform early intervention that are associated with improved survival.


**Keywords:** asymptomatic; severe aortic stenosis; symptoms; surgery; intervention; aortic valve replacement; transcatheter aortic valve replacement; transcatheter aortic valve intervention; death; sudden death; heart failure; early intervention; review; meta-analysis

## INTRODUCTION

Patients with symptomatic severe aortic stenosis (AS) have an indication for surgical aortic valve replacement (SAVR) or transcatheter aortic valve replacement (TAVR). The role of intervention is less clear in patients with asymptomatic severe AS. North American and European guidelines agree on a class I indication for SAVR in patients with a reduced left ventricular ejection fraction (LVEF <50%), but are inconsistent for patients with other disease or comorbid factors.[1,2,3]

Studies suggest that as many as 50% of patients with asymptomatic severe AS progress to a symptomatic status and require surgery within the first 2 years of follow-up[4], and that this waiting period increases the risk of sudden cardiac death and congestive heart failure.[5,6] In light of these results, the concept of early intervention has raised increasing interest.[5,7] However, advocators of a conservative approach argue that the procedural risk does not balance against the potential benefits of early intervention, and that many patients will never become symptomatic.[8] Such arguments come mainly from single-center observational studies with few patients and based on events that occur infrequently.[1]

The natural history should be better quantified to improve our understanding of potential benefits and harms of intervention versus conservative treatment. Moreover, risk factors of a poor prognosis should be identified to evaluate which patients are at highest risk and may particularly benefit from early intervention. Therefore, we have performed a systematic review and meta-analysis of studies evaluating the natural history of patients with asymptomatic severe AS and determined whether early intervention improves long-term survival.

## METHODS

This study complies with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.[9]

### Search strategy and study inclusion

The PubMed, Embase and Cochrane databases were searched from their inception to February 1st, 2020, for full-length, English-language, observational studies that reported on patients with asymptomatic severe AS who were initially treated conservatively. We searched among titles and abstracts using the keywords “asymptomatic” AND “aortic” AND “stenosis”. No search software was used. Authors were not contacted for studies that did not fulfill inclusion criteria or if data were unclear.

Two investigators (S.J.H. and M.C.) independently reviewed the search result in duplicate. In case of disagreement, consensus was reached through discussion. The title and abstract were reviewed during the first stage, after which the remaining articles were reviewed in-depth during the second stage. Reference lists of potentially valid studies and review articles were checked to ensure no relevant studies were missed. Abstracts from meetings were not considered.

Studies were included if they fulfilled the following criteria: i) the study included adult patients with severe AS quantified by at least an aortic valve area (AVA) of <1.0 $cm^2$ or an indexed AVA (iAVA) <0.6 $cm^2/m^2$, a jet velocity of >4.0 m/s, or a mean gradient of >40 mmHg; ii) patients were considered to be asymptomatic if reported as such, which was left to the discretion of the physicians and investigators of the individual studies and performance of exercise testing was not considered mandatory to confirm absence of symptoms; and iii) at least the event of death during follow-up, and the mean/median duration of follow-up, was reported. Studies with a combined inclusion of patients with moderate and severe AS were excluded unless results were separately reported for patients with severe AS. In case there was overlap in the patient populations in different studies from the same center, we included only the study with the longest follow-up or largest patient cohort. A list of excluded papers is available upon request.

### Data extraction

Two investigators (S.J.H. and M.C.) independently extracted and cross-checked clinically relevant data and data necessary for study inclusion and meta-analysis (Supplementary Text 1). Inconsistencies were resolved by discussion.

### Endpoints

For the meta-analysis on the natural history, the primary end point was all-cause death. Secondary end points consisted of cardiac death, sudden death, death due to congestive heart failure, the development of an indication for aortic valve intervention, the development of symptoms, and aortic valve intervention by either SAVR or TAVR. For the meta-analysis of early intervention versus conservative treatment, the primary end point was all-cause death. For the meta-analysis of predictors, the primary endpoint consisted of the composite of all-cause death and aortic valve intervention (or development of symptoms), but allowing for studies to include hospitalization or congestive heart failure as additional end point in the composite.

### Statistical analyses

We calculated the log rate of events per 100 patients per year of observation time and the corresponding standard error within studies, and then used a DerSimonian and Laird random-effects model to derive pooled estimates and corresponding limits of the 95%

CI[10] and back transformed pooled estimates and limits of the 95% CI to rates per 100 patient-years throughout. If the total amount of follow-up time was not reported, this was calculated by multiplying the number of patients by the mean follow-up time. In case of zero events, we derived the upper end of the 95% confidence interval (CI) of the rate as described by Hanley and Lippman-Hand, adding a continuity correction of 0.01 to the numerator, and a continuity correction of 0.01 multiplied by the average follow-up time to the denominator to derive rates.[11] We explored heterogeneity across studies using the DerSimonian and Laird between-study variance $\tau^2$ statistic,[12] and calculated 95% prediction intervals for the pooled rates in addition to conventional confidence intervals taking into account the between study variance to reflect residual uncertainty.[13] Our analysis on the natural history consisted of pooling the studies that reported events occurring only during a period of time in which patients were asymptomatic and no aortic valve intervention took place. Pre-specified subgroup analyses were restricted to the 26 studies with follow-up until aortic valve intervention, investigating heterogeneity by: study design (prospective versus retrospective), year of initiation of patient recruitment (before 1999 versus 1999 or later), number of patients included in the study (<100 versus ≥100 patients), length of average follow-up time (<2 versus ≥2 years), length of accumulated follow-up patient-time (<200 versus ≥200 patient-years), and whether or not good left ventricular ejection fraction (defined as ≥50%, ≥55%, or "normal") was an inclusion criterion of the study. Subgroup analyses were accompanied by a test for interaction from random-effects meta-regression.

For the comparison of all-cause mortality following early intervention versus conservative treatment, we included studies that did not censor patients at the time of intervention and evaluated long-term mortality. We pooled studies using the study-level HRs in a random-effects model with Knapp-Hartung modification of the variance as the number of cohort studies that reported HRs for this comparison was low.

For the pooling of the effect of prognostic indicators on events, whenever two or more studies reported the HRs of the association between prognostic indicators and events during follow-up, we pooled them across studies using a random-effects Bayesian meta-analysis. Details are provided in Supplementary Text 2. Analyses were performed in Stata version 14.2 (StataCorp, College Station, TX, USA) and WinBUGS version 14.

## RESULTS

### Study inclusion

The literature search yielded 2,370 studies that were potentially relevant for inclusion in the meta-analysis, and 30 studies were included in our meta-analysis on the natural history (Supplementary Figure 1). All studies were observational. A total of 4,075 pa-

tients with a median follow-up of 2.3 years (interquartile range (IQR), 1.6-3.3 years) were included in the natural history analysis (Table 1). In addition, 9 studies were included in our meta-analysis comparing an early surgical treatment strategy with watchful waiting, of which 1 was a randomized controlled trial (Supplementary Figure 1). A total of 3,904 patients with a median follow-up of 5.0 years (IQR, 3.7-5.7 years) were included in our analyses comparing an early surgical treatment strategy with watchful waiting (Table 1).

## Meta-analysis on death

*Mortality*

The rate of all-cause death was 4.8 (95% CI 3.6-6.4) per 100 patients per year in 21 studies with 3,041 patients with a median follow-up of 2.3 years (IQR, 1.7-3.4 years) (Figure 1A). Cardiac death occurred at a rate of 3.0 (95% CI 2.2-4.1) per 100 patients per year in 18 studies with 2,813 patients with a median follow-up of 2.1 years (IQR, 1.4-2.9 years) (Figure 1B). The rate of death due to congestive heart failure was 2.0 (95% CI 1.3-3.1) per 100 patients per year in 11 studies with 1,809 patients with a median follow-up of 2.3 years (IQR, 1.9-2.9 years) (Figure 1C). Sudden death occurred at a rate of 1.1 (95% CI 0.6-2.1) per 100 patients per year in 12 studies with 1,767 patients with a median follow-up of 2.3 years (IQR, 1.7-3.1 years) (Figure 1D).

*Progression to aortic valve intervention*

An indication for aortic valve intervention was reported in 11 studies with 1,754 patients with a median follow-up of 2.3 years (IQR 1.8-3.2) and occurred in 18.1 (95% CI 12.8-25.4) per 100 patients per year (Figure 2A). There were 16 studies with 2,234 patients and median follow-up of 1.9 years (IQR 1.3-3.1) that reported the number of patients that developed symptoms, with a pooled rate of 18.5 (95% CI 13.4-25.5) per 100 patients per year (Figure 2B). Aortic valve intervention was performed in 19.2 (95% CI 15.5-23.8) per 100 patients per year (21 studies with 3,494 patients with a median follow-up of 2.3 years (IQR 1.7-3.0) (Figure 2C).

*Subgroup analyses*

Supplementary Table 1 shows results of subgroup analyses. Studies with shorter total follow-up were associated with higher rates of all-cause death. Studies with shorter mean and total follow-up were associated with higher rates of symptom development and aortic valve interventions. Rates of an indication for aortic valve intervention (p=0.022) and development of symptoms (p=0.007) were markedly higher in prospective versus retrospective studies. There were no interactions with subgroups by LVEF.

**Table 1. Study characteristics**

| Study | Design | Patient inclusion | AS criteria | LVEF criteria | Mean LVEF (%) | Stress test | Number of patients | Mean age | Abnormal stress test* | Mean follow-up (years) | Total patient-years of follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Censored at aortic valve intervention** | | | | | | | | | | | |
| Suzuki et al,[14] 2018 | Retrospective | 2006-2015 | AVA < 1.0 $cm^2$ | >50% | 68 ± 8 | No | 63 | 87 ± 5 | … | 2.2 | 138.6 |
| Wu et al,[15] 2018 | Prospective | 2012-2013 | iAVA < 0.6 $cm^2/m^2$ | ≥50% | 60 ± 6 | No | 124 | 80 ± 9 | … | 0.6 | 78.5 |
| González Gómez et al,[16] 2017 | Retrospective | 2012-2015 | iAVA < 0.6 $cm^2/m^2$ | ≥50% | 70.0 | No | 442 | 80 ± 11 | … | 1.7 | 755.1 |
| Christensen et al,[17] 2017 | Prospective | 2014-2016 | AVA < 1.0 $cm^2$ or $V_{max}$ > 3.5 m/s | >50% | 62 ± 7 | yes | 92 | 74 ± 8 | 0% | 1 | 90.5 |
| Zilberszac et al,[18] 2017 | Prospective | 1999-2009 | $V_{max}$ ≥ 4.0 m/s | ≥55% | 61.0 ± 5.9 | No | 103 | 77.3 ± 4.8 | … | 1.6 | 166.5 |
| Nishimura et al,[19] 2016 | Retrospective | 1994-2013 | AVA ≤ 1.0 $cm^2$ | ≥50% | 70.2 ± 10.0 | No | 140 | 73.6 ± 8.6 | … | 3.9 | 548.3 |
| Maréchaux et al,[20] 2016 | Retrospective | 2000-2012 | AVA ≤ 1.0 $cm^2$ | ≥50% | †65 (58-71) | Yes | 199 | 69 ± 14 | 0% | 4 | 796 |
| Shibayama et al,[21] 2016 | Retrospective | 2000-2012 | AVA < 1.0 $cm^2$ or $V_{max}$ > 4.0 m/s | ≥50% | 67 ± 10 | No | 230 | 72 ± 11 | … | 2.8 | 632.5 |
| Todaro et al,[22] 2016 | Prospective | 2009-2014 | AVA ≤ 1.0 $cm^2$ | ≥50% | 60 ± 5 | Yes | 82 | 73 ± 10 | 0% | 1.3 | 109.3 |
| Nagata et al,[23] 2015 | Prospective | 2011-2014 | iAVA < 0.6 $cm^2/m^2$ | >50% | 60 ± 5 | No | 104 | 78 ± 10 | … | 1 | 106.6 |
| Jander et al,[24] 2014 | Prospective | 2001-2004 | AVA <1.0 $cm^2$ and $V_{max}$ ≥ 2.5 - ≤ 4.0 m/s and $P_{mean}$ ≤ 40 mmHg | ≥55% | 66.6 ± 6 | No | 435 | 69.8 ± 9 | … | 3.5 | 1522.5 |
| Zuern et al,[25] 2014 | Prospective | 2009-2012 | AVA < 1.0 $cm^2$ or $V_{max}$ > 4.0 m/s or $P_{mean}$ > 40 mmHg | None | 55.0 | No | 71 | 74† | … | 1.2 | 85.2 |

**Table 1. Study characteristics** (*continued*)

| Study | Design | Patient inclusion | AS criteria | LVEF criteria | Mean LVEF (%) | Stress test | Number of patients | Mean age | Abnormal stress test* | Mean follow-up (years) | Total patient-years of follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Levy et al,[26] 2014 | Prospective | … | AVA < 1.0 $cm^2$ or iAVA ≤ 0.6 $cm^2/m^2$ | >50% | 62 ± 7 | Yes | 43 | 69 ± 13 | 28% | 2.3 | 100.3 |
| Cho et al,[27] 2013() | Prospective | 2007-2012 | AVA < 1.0 $cm^2$ or $V_{max}$ > 4.0 m/s or $P_{mean}$ > 40 mmHg | >50% | 65.8 | Yes | 31 | 62 ± 11 | 0% | 1.7 | 51.7 |
| Yingchoncharoen et al,[28] 2012 | Prospective | 2004-2010 | AVA < 1.0 $cm^2$ or $V_{max}$ > 4.0 m/s | ≥50% | 63.4 ± 7.9 | No | 79 | 77 ± 12 | … | 1.9 | 151.4 |
| Saito et al,[29] 2012 | Retrospective | 2001-2007 | AVA < 1.0 $cm^2$ | None | 60.0 ± 9.6 | No | 103 | 72 ± 11 | … | 3 | 309 |
| Lancellotti et al,[30] 2012 | Prospective | … | AVA < 1.0 $cm^2$ | ≥55% | 66.6 ± 7.6 | Yes | 150 | 69.7 ± 8.0 | 0% | 2.3 | 337.5 |
| Perera et al,[31] 2011 | Retrospective | 2005-2009 | AVA ≤ 1.0 $cm^2$ or $V_{max}$ > 4.0 m/s or $P_{mean}$ > 40 mmHg | None | … | No | 25 | 81.7 ± 14.4 | … | 2.9 | 72.9 |
| Kitai et al,[32] 2011 | Retrospective | 1999-2009 | AVA < 1.0 $cm^2$ or $P_{mean}$ > 40 mmHg | ≥50% | 65 ± 8 | No | 76 | 70 ± 11 | … | 5.5 | 418 |
| Cioffi et al,[33] 2011 | Prospective | 2003-2008 | AVA < 1.0 $cm^2$ or $P_{mean}$ ≥ 50 mmHg | None | 59.2 ± 10.4 | No | 218 | 75 ± 11 | … | 1.8 | 399.7 |
| Rosenhek et al,[34] 2010 | Prospective | 1995-2008 | $V_{max}$ ≥ 5.0 m/s | None | … | No | 116 | 67 ± 15 | … | 3.4 | 396.3 |
| Hristova-Antova et al,[35] 2009 | Prospective | 2004 | AVA ≤ 1.0 $cm^2$ and $V_{max}$ > 4.0 m/s and $P_{mean}$ > 60 mmHg | >50% | 69.9 ± 5.5 | No | 49 | 59 ± 13 | … | 1.8 | 89.8 |
| Lafitte et al,[36] 2009 | Prospective | … | AVA < 1.0 $cm^2$ | >55% | 64 ± 7 | Yes | 60 | 70 ± 12 | 65% | 1 | 60 |

**Table 1. Study characteristics** (*continued*)

| Study | Design | Patient inclusion | AS criteria | LVEF criteria | Mean LVEF (%) | Stress test | Number of patients | Mean age | Abnormal stress test* | Mean follow-up (years) | Total patient-years of follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Weisenberg et al,[37] 2008 | Retrospective | 2001-2005 | AVA < 1.0 $cm^2$ or $P_{mean}$ ≥ 50 mmHg | Normal | … | Yes | 101 | 69 ± 10 | 68% | 2.9 | 294.6 |
| Avakian et al,[38] 2008 | Prospective | … | $P_{mean}$ ≥ 60 mmHg | Normal | 72.7 ± 6.0 | No | 133 | 66.2 ± 13.6 | … | 3.3 | 438.9 |
| Le Tournea et al,[39 and] Pellikka et al,[40] 2005‡ | Retrospective | 1984-1995 | $V_{max}$ ≥ 4.0 m/s | None | 64.3 ± 7.3 | No | 622 | 72 ± 11 | … | 5.4 | 3358.8 |
| Amato et al,[40] 2001 | Prospective | 1987-1992 | AVA ≤ 1.0 $cm^2$ | None | … | Yes | 66 | 49.7 ± 14.9 | 67% | 1.2 | 81.4 |
| Pierri et al,[41] 2000 | Prospective | 1981-1993 | AVA < 0.9 $cm^2$ or $P_{mean}$ > 50 mmHg | None | … | No | 12 | 81.1 | … | 6 | 72 |
| Rosenhek et al,[42] 2000 | Prospective | 1994 | $V_{max}$ ≥ 4.0 m/s | None | … | No | 106 | 57 ± 19 | … | 2.3 | 238.5 |
| **Watchful waiting versus intervention** | | | | | | | | | | | |
| Kang et al,[43] 2020 | Prospective | 2010-2015 | AVA ≤ 0.75 cm2 and (JV ≥ 4.5 m/s or MG ≥ 50 mmHg) | ≥50% | 64.8 ± 4.1 | No | 72 | 63.4 ± 10.7 | … | 5.8 | 4998.7 |
| Kim et al,[44] 2019 | Retrospective | 2000-2015 | AVA ≤ 1.0 $cm^2$ or iAVA ≤ 0.6 $cm^2/m^2$ or $V_{max}$ ≥ 4.0 m/s or $P_{mean}$ ≥ 40 mmHg | ≥50% | 63.1 ± 5.1 | No | 247 | 67.1 ± 13.1 | … | 5.1 | 1253.5 |
| Campo et al,[45] 2019 | Retrospective | 2005-2013 | AVA ≤ 1.0 $cm^2$ or $V_{max}$ ≥ 4.0 m/s or $P_{mean}$ ≥ 40 mmHg | None | 61 ± 8.1 | Yes | 161 | 73.0 ± 12.6 | 18% | … | … |
| Bohbot et al,[46] 2018 | Retrospective | 2000-2015 | $P_{mean}$ ≥ 40 mmHg | ≥50% | … | Yes | 247 | … | 64% | 3.5 | 864.5 |

**Table 1. Study characteristics** (*continued*)

| Study | Design | Patient inclusion | AS criteria | LVEF criteria | Mean LVEF (%) | Stress test | Number of patients | Mean age | Abnormal stress test* | Mean follow-up (years) | Total patient-years of follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Masri et al,[47] 2016 | Prospective | 2001-2012 | iAVA ≤ 0.6 $cm^2/m^2$ | ≥50% | 58 ± 4 | Yes | 533 | 66 ± 13 | 44% | 6.9 | 3677.7 |
| Taniguchi et al,[5] 2015 | Retrospective | 2003-2011 | AVA < 1.0 $cm^2$ or $V_{max}$ > 4.0 m/s or $P_{mean}$ > 40 mmHg | None | 65.7 ± 11.1 | No | 1517 | 77.8 ± 9.4 | … | 3.7 | 5650.8 |
| Le Tourneau et al,[39] 2010 | Retrospective | 1994-1995 | $V_{max}$ ≥ 4.0 m/s | None | 64 ± 7 | No | 694 | 71 ± 11 | … | 5.5 | 3817 |
| Kang et al,[48] 2010(322) | Prospective | 1996-2006 | AVA ≤ 0.75 $cm^2$ and $V_{max}$ > 4.5 m/s or $P_{mean}$ ≥ 50 mmHg | ≥50% | 63 ± 7 | No | 95 | 63 ± 12 | … | 4.8 | 460 |
| Pai et al,[49] 2006 | Retrospective | 1993-2003 | AVA ≤ 0.8 $cm^2$ | None | 59 ± 17 | No | 338 | 71 ± 15 | … | 3.5 | 1183 |

*Occurrence of symptoms, abnormal blood pressure response, ST-segment depression, or ventricular arrhythmia.

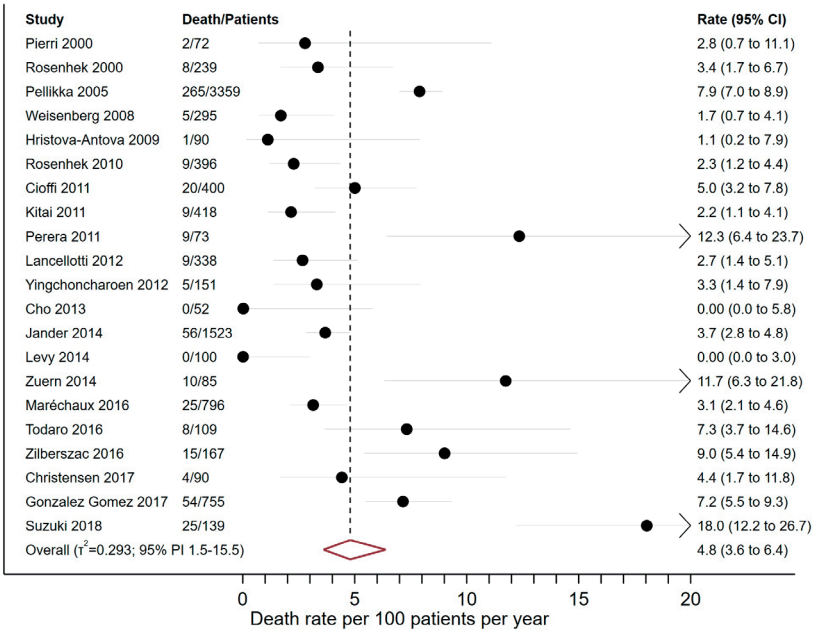
†Median instead of mean, with interquartile ranges in between brackets if provided.

‡There is overlap between the study by Pellikka et al[40] and Le Tourneau et al.[39] The study characteristics in this table are from Pellikka et al.[40] The study by Le Tourneau et al. was used for the comparison of conservative treatment versus early surgery.[39]

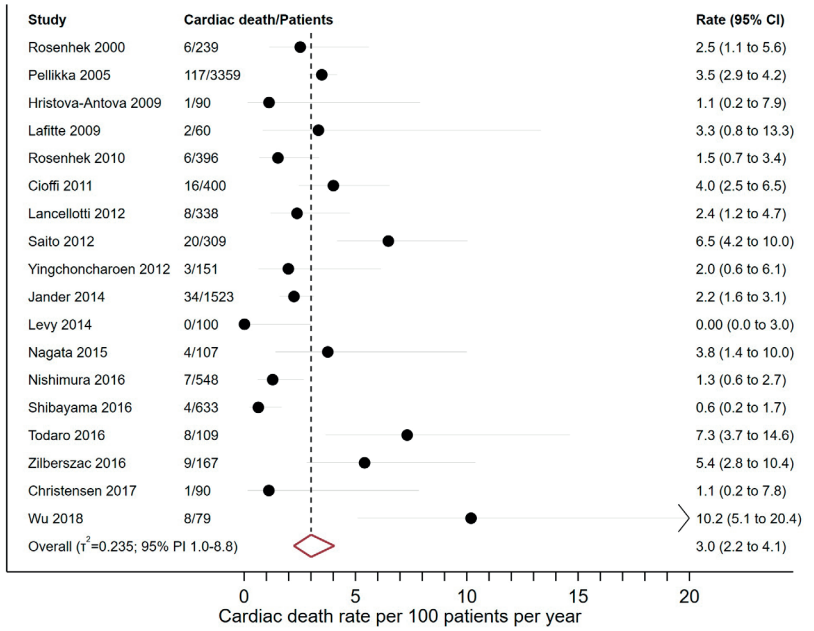
AS, aortic stenosis; (i)AVA, (indexed) aortic valve area; LVEF, left ventricular ejection fraction; $P_{mean}$, mean gradient; $V_{max}$, jet velocity

**Figure 1. Meta-analysis of studies on death.**

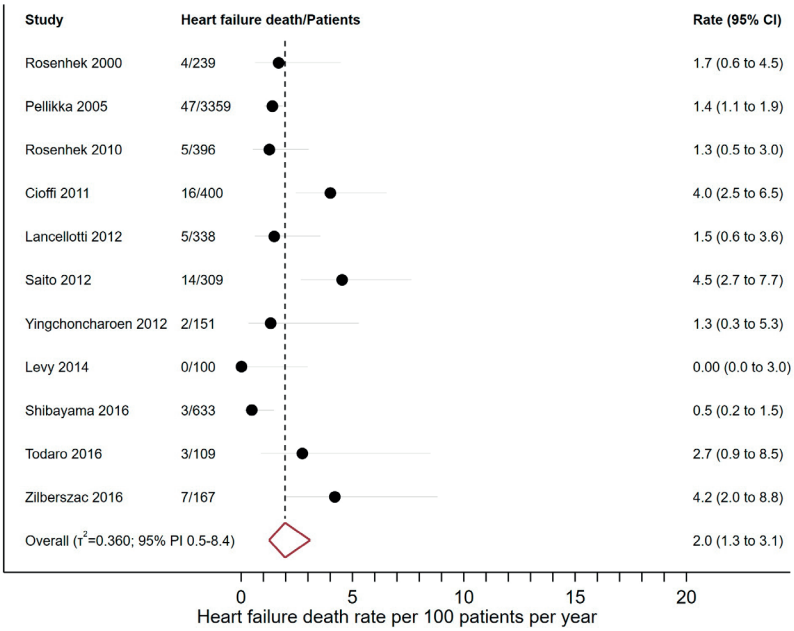
**A. All-cause death**




**B. Cardiac death**



**C. Death due to heart failure**




**D. Sudden death**

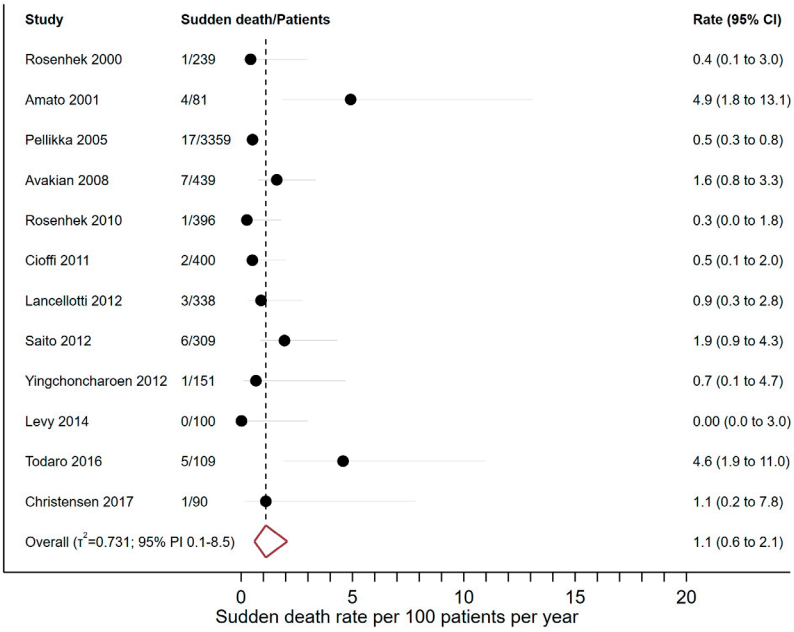
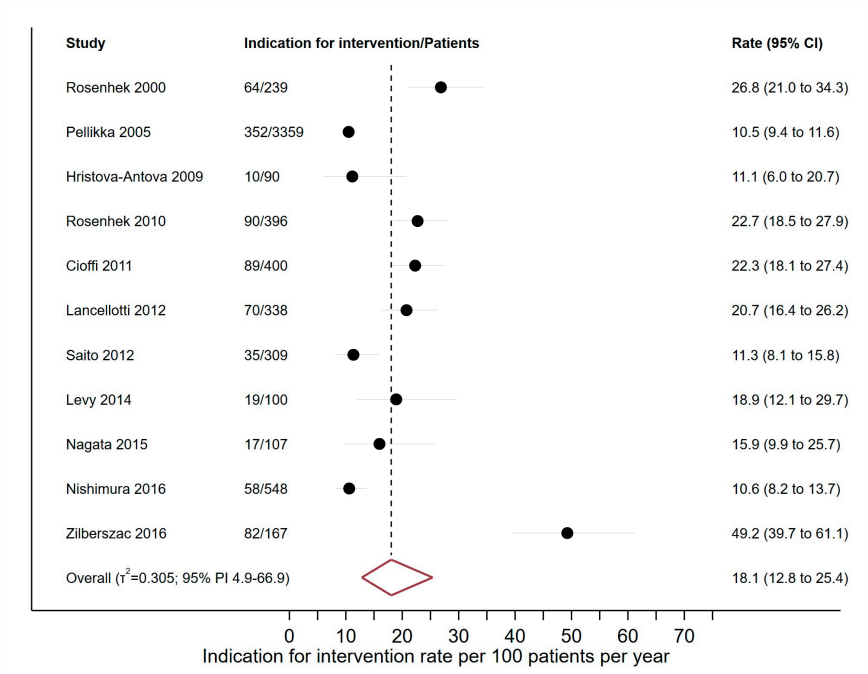
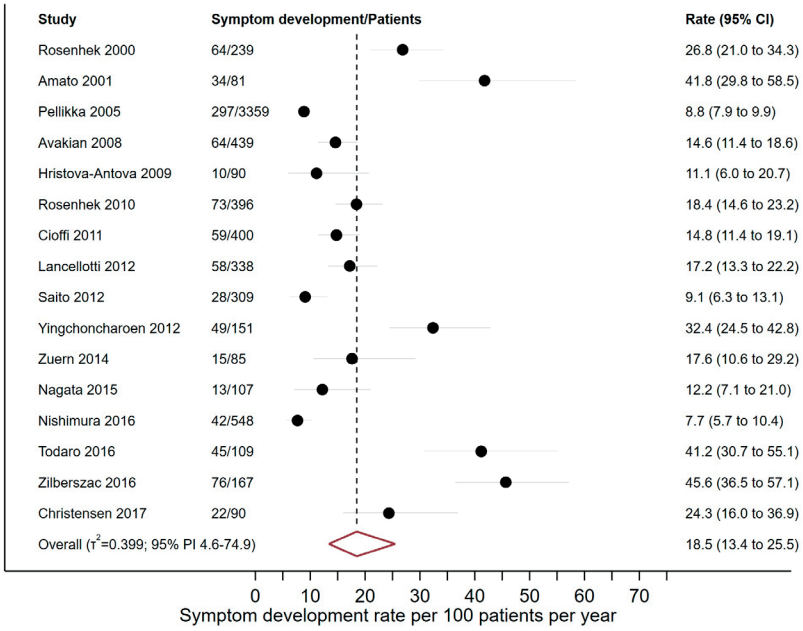


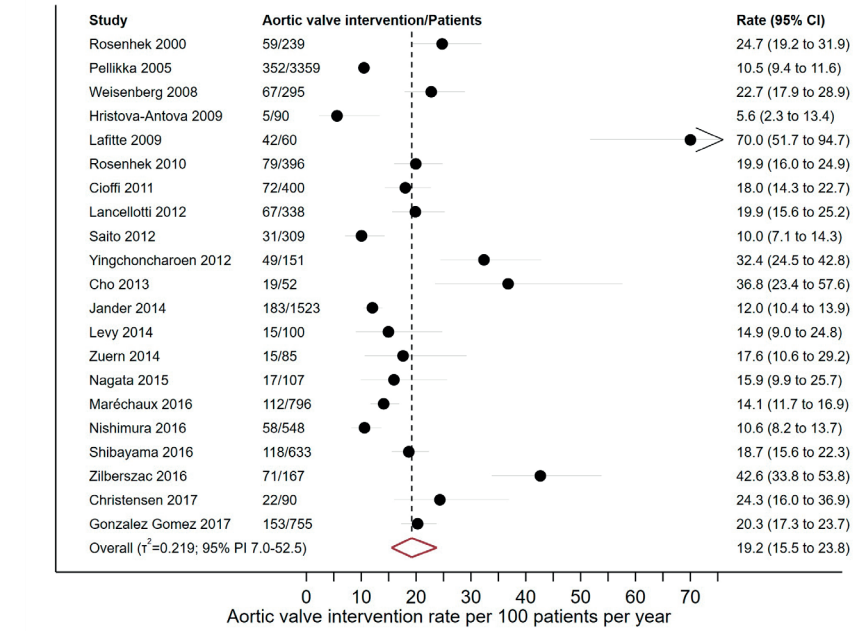
**Figure 2. Meta-analysis of studies on progression to aortic valve intervention.**
**A. Indication for aortic valve intervention**




**B. Development of symptoms**



**C. Aortic valve intervention**



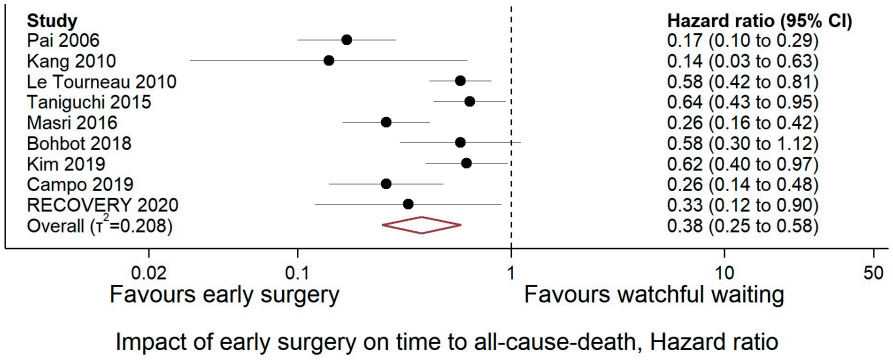




**Figure 3. Meta-analysis on all-cause mortality of surgery versus an initial conservative treatment strategy.**

CI = confidence interval; IV = inverse variance; SE = standard error

*Adverse events*

Fifteen studies performed a multivariable analysis on the composite of death or aortic valve intervention. Outcomes were largely associated with measurements of the severity of AS and left ventricular dysfunction, with clinical factors being limited to atherosclerotic risk factors (Supplementary Table 2). There was inconsistency in how variables and cut-offs were used in multivariable models, but pooling consistent variables with 2 or more results in multivariable analyses resulted in a set of independent variables (Table 2). Heterogeneity was low for all pooled analyses. Results were consistent in sensitivity analyses using different assumptions for the prior distribution of $\tau$ (Supplementary Table 3).

## Meta-analysis on the impact of early intervention

There were 9 studies that compared patients who underwent early intervention versus an initial conservative treatment strategy, which included a combined 3904 patients with a median follow-up of 5.0 years (IQR of 3.7-5.7) (Supplementary Table 4).[5,39,43,47-49] All but one randomized trial used either propensity-score matching or multivariable models to adjust for differences in baseline characteristics between treatment groups. Intervention consisted of surgery in the vast majority of cases. Our meta-analysis indicates that intervention was associated with a significant reduction in all-cause mortality during follow-up (HR 0.38, 95% CI 0.25-0.58), with moderate heterogeneity ($\tau^2$=0.21) (Figure 3).

**Table 2. Factors associated with death or aortic valve intervention**

| Characteristic | HR (95% CrI) | $\tau^2$ (95% CrI) | References |
|---|---|---|---|
| **Peak pressure gradient, per 10mmHg** | 1.22 (1.03 to 1.44) | 0.002 (0.000 to 0.067) | [28,33] |
| **Peak aortic jet velocity ≥ 4.0 m/s** | 1.93 (1.17 to 3.18) | 0.006 (0.000 to 0.131) | [19,29] |
| **Aortic valve area ≤ 0.6 cm2** | 1.68 (1.13 to 2.53) | 0.010 (0.000 to 0.146) | [20,34] |
| **Aortic valve calcification ≥ grade 3** | 2.65 (1.71 to 4.25) | 0.006 (0.000 to 0.115) | [28,19,42] |
| **Female gender** | 0.97 (0.72 to 1.33) | 0.006 (0.000 to 0.113) | [34,42] |
| **Hypertension** | 0.66 (0.48 to 0.93) | 0.005 (0.000 to 0.089) | [18,21,42] |
| **Dyslipidemia** | 1.45 (1.09 to 1.93) | 0.006 (0.000 to 0.097) | [18,19,34,42] |
| **Diabetes** | 1.64 (1.09 to 2.41) | 0.044 (0.000 to 0.272) | [33,18,34,42] |
| **Coronary artery disease** | 1.32 (0.90 to 1.91) | 0.012 (0.000 to 0.161) | [18,34,42] |
| **Global longitudinal strain on speckle** | 1.12 (1.02 to 1.28) | 0.002 (0.000 to 0.049) | [28,22,30] |
| **Valvulo-arterial impedance** | 1.35 (1.03 to 1.76) | 0.005 (0.000 to 0.100) | [28,22] |
| **Left ventricular mass Index, per 10 units** | 1.1 (0.87 to 1.39) | 0.004 (0.000 to 0.089) | [23,33] |

CrI, credible interval; HR, hazard ratio

## DISCUSSION

In this systematic review and meta-analysis of 30 studies on the natural history of patients with asymptomatic severe AS, we found that there were overall 5 deaths per 100 patients per year during a conservative treatment strategy, with a high rate of progressing to a symptomatic state and developing an indication for aortic valve intervention. Particularly patients with more severe AS, abnormal LV characteristics, and atherosclerotic clinical factors were at a higher risk of death or an indication for intervention. Moreover, among another 9 studies that investigated performing early intervention, consisting of surgery in the majority of cases within these studies, was associated with a significant reduction in all-cause death during follow-up. While it has been argued that many patients do not develop an indication for intervention and that the risk of death is low during conservative treatment, the results of the current meta-analysis suggest otherwise. Indeed, most studies focus on sudden death, but this meta-analysis demonstrates that sudden death accounts for only part of cardiac deaths that occur in asymptomatic patients with severe AS, and that the risk of death may therefore be underestimated. These data suggest that early intervention may need to be considered in a greater proportion of patients with asymptomatic severe AS.

Currently, the largest and only available randomized controlled trial on asymptomatic patients with severe AS analysed 145 patients and found that initial surgery versus an initial conservative treatment significantly reduced the all-cause death and operative or cardiovascular death, even when 74% of patients in the conservative group required SAVR during follow-up.[43] This study is pivotal in the debate on treating asymptomatic patients, but it only provides a perspective on patients with very severe AS, applying inclusion criteria of an AVA of ≤0.75 $cm^2$ with either a jet velocity of ≥4.5 m/s or a mean gradient of ≥50 mm Hg, while lacking evidence on the much broader patient population with asymptomatic AS. Further data from observational studies as summarized in the current meta-analysis provides these additional insights. The largest available observational study analyzed 291 propensity-matched pairs and found that early surgery versus an initial conservative treatment significantly reduced the 5-year rates of all-cause death and hospitalization for heart failure, even when 41% of patients in the conservative group required SAVR during follow-up.[5] When pooling multiple studies on the impact of intervention on survival, we found that intervention versus conservative treatment was associated with significantly improved survival with a HR of 0.38. While this may be a true impact, considering the high rates of death and progression to an indication for aortic valve intervention (e.g. symptoms or left ventricular dysfunction) among conservatively treated patients in this meta-analysis, most of the observational studies may be biased because physicians could have opted for a conservative treatment strategy for patients due to a high risk for surgery, as was often the case before the introduction of

TAVR, when most of these studies were performed.[50] Moreover, not all studies specifically evaluated the impact of intervention within a short (for example, 3 months) period after the diagnosis of severe AS. Patients that went on to have intervention at a later follow-up time are inherently a selected group with a better prognosis, since the highest risk patients may have died within the early follow-up period. Indeed, Le Tourneau and coauthors[39] found that the point estimate of the HR in favor of surgery was much larger if conservative treatment was compared with surgery being performed within 1 year of presentation as opposed to surgery at any time during follow-up (HR = 0.58 versus HR = 0.39). Data from the RECOVERY trial are consistent with that of these observational studies,[43] but additional results from ongoing randomized trials comparing an early interventional treatment strategy and a conservative strategy in asymptomatic patients with severe AS will add significant knowledge and provide important insight to substantiate the role of early intervention (Supplementary Table 5).

The decision to undergo early intervention should depend on a critical assessment of symptoms and careful and individualized consideration of potential benefits and harms. Cardiac magnetic resonance to detect LV damage furthermore helps identify patients that may benefit from early intervention.[51] Apart from LV dysfunction as an indication to perform SAVR in patients with asymptomatic severe AS, current clinical guidelines provide several additional recommendations to consider intervention in patients with asymptomatic severe AS.[1] Our meta-analysis of variables associated with mortality related outcomes, indicate that prognosis is significantly worse if global longitudinal strain or valvulo-arterial impedance is present even with a preserved LV function[22,23,28,33,] if AS is more severe as measured by higher valve gradient and lower valve area, and if atherosclerotic risk factors, such as dyslipidemia or diabetes are present. These additional disease and comorbid characteristics are not considered in current guidelines or are inconsistently recognized in North American and European guidelines. We therefore suggest that cardiologists and surgeons take these additional factors into account when deciding to perform early intervention or initiate a conservative treatment strategy. Of note, our subgroup analysis could not confirm that LVEF was associated with worse outcomes, which is most likely related to the criteria used in the individual manuscripts; almost all studies included patients with preserved LVEF.

### Strengths and Limitations

An important strength is that a large number of studies could be pooled in a random-effects model with moderate statistical heterogeneity, increasing the validity of the results. The included studies consisted exclusively of patients with asymptomatic severe AS, unlike many other studies and reviews that have not stratified results according to the severity of AS in asymptomatic patients.[7,52] Lastly, using Bayesian methods for meta-analyses of a low number of studies allowed a more reliable estimation of between-trial

variance and its uncertainty to identify particular disease and patient factors that impact the prognosis of asymptomatic severe AS. This resulted in identifying several variables that are currently not included in clinical guidelines.

This is a meta-analysis of observational studies, which is dependent on the quality of the individual studies that were included. Many of the studies were single-center, retrospective, and it may therefore have been difficult to adjudicate events related to the development of symptoms and indications for intervention during follow-up. Secondly, only a few studies routinely performed stress testing in patients with asymptomatic severe AS, and we were therefore not able to determine whether all patients in these studies were truly asymptomatic. In addition, studies mainly reported that patients with severe AS referred to their clinic were included, but did not clarify whether patients already had severe AS a certain time before primarily being evaluated in the clinic (e.g. prevalent cases) or had mild or moderate AS when primarily being evaluated and progressed to severe AS just before a later check (e.g. incident cases). Nevertheless, there was considerable heterogeneity in our meta-analyses of event rates. Although subgroup analyses to detect heterogeneity within meta-analyses of observational studies should be interpreted with caution, our subgroup analyses revealed that the type of study (prospective versus retrospective) and the duration of follow-up (short versus long mean and total follow-up time) were associated with differences in event rates. This may have been the result of more closely monitoring of patients that were prospectively followed, with earlier recognition of symptoms and timely referral for intervention, as opposed to a less strict follow-up regimen in retrospective studies. Moreover, the higher rates of symptom development, (an indication for) aortic valve intervention, all-cause death and sudden death in studies with a shorter mean and total length of follow-up of a conservative strategy is most likely related to shorter follow-up due to the occurrence of these events, and publication bias may also play a role. Lastly, the effect of the associations between variables from multivariable analysis of several studies could not be pooled due to different definitions or cut-offs used in the models. Initiatives like the Valve Academic Research Consortium can further standardize studies to improve meta-analyses.[53]



## CONCLUSIONS

In this meta-analysis, asymptomatic severe AS was associated with a high rate of developing an indication for aortic valve intervention, while all-cause, cardiac, and sudden death occurred in respectively 4.8, 3.0, and 1.1 of 100 patients per year during a conservative strategy. It is therefore important to consider not only sudden death but also cardiac death due to heart failure or other causes. Patients with higher severity of AS,

low-flow AS, evidence of left ventricular damage, and atherosclerotic risk factors are at particular high risk of death or requiring intervention. Moreover, our meta-analysis also suggested that surgery versus an initial conservative treatment strategy is associated with long-term survival. Although existing guidelines provide some guidance on when to perform SAVR in patients with asymptomatic severe AS, this meta-analysis provides additional data to support a recommendation to consider early intervention in patients at high risk of adverse events. Further results from the ongoing randomized trials are required to substantiate the role of early intervention in patients with asymptomatic severe AS.

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## REFERENCES


1. Falk V, Baumgartner H, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur J Cardiothorac Surg.* 2017;52(4):616-664.
2. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;129(23):e521-643.
3. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation.* 2017;135(25):e1159-e1195.
4. Heuvelman HJ, van Geldorp MW, Kappetein AP, et al. Clinical course of patients diagnosed with severe aortic stenosis in the Rotterdam area: insights from the AVARIJN study. *Neth Heart J.* 2012;20(12):487-493.
5. Taniguchi T, Morimoto T, Shiomi H, et al. Initial Surgical Versus Conservative Strategies in Patients With Asymptomatic Severe Aortic Stenosis. *J Am Coll Cardiol.* 2015;66(25):2827-2838.
6. Amato MC, Moffa PJ, Werner KE, Ramires JA. Treatment decision in asymptomatic aortic valve stenosis: role of exercise testing. *Heart.* 2001;86(4):381-386.
7. Genereux P, Stone GW, O'Gara PT, et al. Natural History, Diagnostic Approaches, and Therapeutic Strategies for Patients With Asymptomatic Severe Aortic Stenosis. *J Am Coll Cardiol.* 2016;67(19):2263-2288.
8. Owen A, Henein MY. Challenges in the management of severe asymptomatic aortic stenosis. *Eur J Cardiothorac Surg.* 2011;40(4):848-850.
9. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA.* 2000;283(15):2008-2012.
10. Head SJ, da Costa BR, Beumer B, et al. Adverse events while awaiting myocardial revascularization: a systematic review and meta-analysis. *Eur J Cardiothorac Surg.* 2017;52(2):206-217.
11. Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? Interpreting zero numerators. *JAMA.* 1983;249(13):1743-1745.
12. da Costa BR, Juni P. Systematic reviews and meta-analyses of randomized trials: principles and pitfalls. *Eur Heart J.* 2014;35(47):3336-3345.
13. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *J R Stat Soc Ser A Stat Soc.* 2009;172(1):137-159.
14. Kang DH, Park SJ, Rim JH, et al. Early surgery versus conventional treatment in asymptomatic very severe aortic stenosis. *Circulation.* 2010;121(13):1502-1509.
15. Le Tourneau T, Pellikka PA, Brown ML, et al. Clinical outcome of asymptomatic severe aortic stenosis with medical and surgical management: importance of STS score at diagnosis. *Ann Thorac Surg.* 2010;90(6):1876-1883.
16. Pai RG, Kapoor N, Bansal RC, Varadarajan P. Malignant natural history of asymptomatic severe aortic stenosis: benefit of aortic valve replacement. *Ann Thorac Surg.* 2006;82(6):2116-2122.
17. Masri A, Goodman AL, Barr T, et al. Predictors of Long-Term Outcomes in Asymptomatic Patients With Severe Aortic Stenosis and Preserved Left Ventricular Systolic Function Undergoing Exercise Echocardiography. *Circ Cardiovasc Imaging.* 2016;9(7).
18. Kang DH, Park SJ, Lee SA, et al. Early Surgery or Conservative Care for Asymptomatic Aortic Stenosis. *N Engl J Med.* 2020;382(2):111-119.

19. Iung B, Baron G, Butchart EG, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *Eur Heart J.* 2003;24(13):1231-1243.
20. Everett RJ, Tastet L, Clavel MA, et al. Progression of Hypertrophy and Myocardial Fibrosis in Aortic Stenosis: A Multicenter Cardiac Magnetic Resonance Study. *Circ Cardiovasc Imaging.* 2018;11(6):e007451.
21. Yingchoncharoen T, Gibby C, Rodriguez LL, Grimm RA, Marwick TH. Association of myocardial deformation with outcome in asymptomatic aortic stenosis with normal ejection fraction. *Circ Cardiovasc Imaging.* 2012;5(6):719-725.
22. Todaro MC, Carerj S, Khandheria B, et al. Usefulness of atrial function for risk stratification in asymptomatic severe aortic stenosis. *J Cardiol.* 2016;67(1):71-79.
23. Nagata Y, Takeuchi M, Wu VC, et al. Prognostic value of LV deformation parameters using 2D and 3D speckle-tracking echocardiography in asymptomatic patients with severe aortic stenosis and preserved LV ejection fraction. *JACC Cardiovasc Imaging.* 2015;8(3):235-245.
24. Cioffi G, Faggiano P, Vizzardi E, et al. Prognostic effect of inappropriately high left ventricular mass in asymptomatic severe aortic stenosis. *Heart.* 2011;97(4):301-307.
25. Lancellotti P, Magne J, Dulgheru R, et al. Outcomes of Patients With Asymptomatic Aortic Stenosis Followed Up in Heart Valve Clinics. *JAMA Cardiol.* 2018;3(11):1060-1068.
26. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). *Eur J Cardiothorac Surg.* 2012;42(5):S45-60.
27. Suzuki A, Tajiri K, Ishizu T, et al. Effect of Asymptomatic Severe Aortic Stenosis on Outcomes of Individuals Aged 80 and Older. *J Am Geriatr Soc.* 2018;66(9):1800-1804.
28. Wu VC, Takeuchi M, Nagata Y, et al. Prognostic value of area of calcified aortic valve by 2-dimensional echocardiography in asymptomatic severe aortic stenosis patients with preserved left ventricular ejection fraction. *Medicine (Baltimore).* 2018;97(12):e0246.
29. Gonzalez Gomez A, Fernandez-Golfin C, Monteagudo JM, et al. Severe aortic stenosis patients with preserved ejection fraction according to flow and gradient classification: Prevalence and outcomes. *Int J Cardiol.* 2017;248:211-215.
30. Christensen NL, Dahl JS, Carter-Storch R, et al. Relation of Left Atrial Size, Cardiac Morphology, and Clinical Outcome in Asymptomatic Aortic Stenosis. *Am J Cardiol.* 2017;120(10):1877-1883.
31. Zilberszac R, Gabriel H, Schemper M, Laufer G, Maurer G, Rosenhek R. Asymptomatic Severe Aortic Stenosis in the Elderly. *JACC Cardiovasc Imaging.* 2017;10(1):43-50.
32. Nishimura S, Izumi C, Nishiga M, et al. Predictors of Rapid Progression and Clinical Outcome of Asymptomatic Severe Aortic Stenosis. *Circ J.* 2016;80(8):1863-1869.
33. Marechaux S, Ringle A, Rusinaru D, Debry N, Bohbot Y, Tribouilloy C. Prognostic Value of Aortic Valve Area by Doppler Echocardiography in Patients With Severe Asymptomatic Aortic Stenosis. *J Am Heart Assoc.* 2016;5(5).
34. Shibayama K, Daimon M, Watanabe H, et al. Significance of Coronary Artery Disease and Left Ventricular Afterload in Unoperated Asymptomatic Aortic Stenosis. *Circ J.* 2016;80(2):519-525.
35. Jander N, Hochholzer W, Kaufmann BA, et al. Velocity ratio predicts outcomes in patients with low gradient severe aortic stenosis and preserved EF. *Heart.* 2014;100(24):1946-1953.
36. Zuern CS, Rizas KD, Eick C, et al. Severe autonomic failure as a predictor of mortality in aortic valve stenosis. *Int J Cardiol.* 2014;176(3):782-787.
37. Levy F, Fayad N, Jeu A, et al. The value of cardiopulmonary exercise testing in individuals with apparently asymptomatic severe aortic stenosis: a pilot study. *Arch Cardiovasc Dis.* 2014;107(10):519-528.

38. Cho EJ, Park SJ, Song JE, et al. What is the real practice of exercise echocardiographic testing in asymptomatic patients with severe aortic stenosis? *Chin Med J (Engl).* 2013;126(24):4649-4654.
39. Saito T, Muro T, Takeda H, et al. Prognostic value of aortic valve area index in asymptomatic patients with severe aortic stenosis. *Am J Cardiol.* 2012;110(1):93-97.
40. Lancellotti P, Magne J, Donal E, et al. Clinical outcome in asymptomatic severe aortic stenosis: insights from the new proposed aortic stenosis grading classification. *J Am Coll Cardiol.* 2012;59(3):235-243.
41. Perera S, Wijesinghe N, Ly E, Devlin G, Pasupati S. Outcomes of patients with untreated severe aortic stenosis in real-world practice. *N Z Med J.* 2011;124(1345):40-48.
42. Kitai T, Honda S, Okada Y, et al. Clinical outcomes in non-surgically managed patients with very severe versus severe aortic stenosis. *Heart.* 2011;97(24):2029-2032.
43. Rosenhek R, Zilberszac R, Schemper M, et al. Natural history of very severe aortic stenosis. *Circulation.* 2010;121(1):151-156.
44. Hristova-Antova E, Georgievska-Ismail L, Srbinovska E, Spiroska V, Hristova-Dimceva A, Zanteva-Naumoska M. Annual rate of progression of aortic-jet velocity and survival in cases of severe asymptomatic aortic stenosis. *Prilozi.* 2009;30(1):91-104.
45. Lafitte S, Perlant M, Reant P, et al. Impact of impaired myocardial deformations on exercise tolerance and prognosis in patients with asymptomatic aortic stenosis. *Eur J Echocardiogr.* 2009;10(3):414-419.
46. Weisenberg D, Shapira Y, Vaturi M, et al. Does exercise echocardiography have an added value over exercise testing alone in asymptomatic patients with severe aortic stenosis? *J Heart Valve Dis.* 2008;17(4):376-380.
47. Avakian SD, Grinberg M, Ramires JA, Mansur AP. Outcome of adults with asymptomatic severe aortic stenosis. *Int J Cardiol.* 2008;123(3):322-327.
48. Pellikka PA, Sarano ME, Nishimura RA, et al. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. *Circulation.* 2005;111(24):3290-3295.
49. Pierri H, Nussbacher A, Decourt LV, et al. Clinical predictors of prognosis in severe aortic stenosis in unoperated patients > or = 75 years of age. *Am J Cardiol.* 2000;86(7):801-804, A810.
50. Rosenhek R, Binder T, Porenta G, et al. Predictors of outcome in severe, asymptomatic aortic stenosis. *N Engl J Med.* 2000;343(9):611-617.
51. Kim HJ, Kim JB, Kim HR, et al. Impact of Valve Replacement on Long-Term Survival in Asymptomatic Patients With Severe Aortic Stenosis. *Am J Cardiol.* 2019;123(8):1321-1328.
52. Campo J, Tsoris A, Kruse J, et al. Prognosis of Severe Asymptomatic Aortic Stenosis With and Without Surgery. *Ann Thorac Surg.* 2019;108(1):74-79.
53. Bohbot Y, Pasquet A, Rusinaru D, et al. Asymptomatic Severe Aortic Stenosis With Preserved Ejection Fraction: Early Surgery Versus Conservative Management. *J Am Coll Cardiol.* 2018;72(23 Pt A):2938-2939.

**Supplementary Table 1. Subgroup analyses.**

| | Indication for aortic valve intervention | | Development of symptoms | | Aortic valve intervention | | All-cause death | | Cardiac death | | Heart failure death | | Sudden death | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Rate (95% CI) | p* | Rate (95% CI) | p* | Rate (95% CI) | p* | Rate (95% CI) | p* | Rate (95% CI) | p* | Rate (95% CI) | p* | Rate (95% CI) | p* |
| **Design** | | 0.022 | | 0.007 | | 0.102 | | 0.277 | | 0.528 | | 0.663 | | 0.795 |
| Prospective | 21.0 (15.8 to 28.0) | | 21.2 (16.2 to 27.6) | | 21.4 (16.2 to 28.3) | | 4.0 (2.8 to 5.5) | | 3.2 (2.2 to 4.6) | | 2.2 (1.4 to 3.6) | | 1.2 (0.6 to 2.4) | |
| Retrospective | 10.6 (9.6 to 11.6) | | 8.7 (7.9 to 9.7) | | 14.6 (11.2 to 19.0) | | 5.9 (3.7 to 9.2) | | 2.3 (1.1 to 4.8) | | 1.6 (0.6 to 4.4) | | 1.0 (0.3 to 3.5) | |
| **Patient inclusion†** | | 0.694 | | 0.749 | | 0.425 | | 0.666 | | 0.272 | | 0.238 | | 0.547 |
| 1999 or later | 18.3 (12.0 to 27.9) | | 18.8 (13.1 to 27.0) | | 18.7 (15.3 to 22.9) | | 4.7 (3.3 to 6.7) | | 3.4 (2.2 to 5.2) | | 2.4 (1.4 to 4.2) | | 1.4 (0.7 to 2.9) | |
| Before 1999 | 16.1 (9.8 to 26.4) | | 16.8 (9.3 to 30.6) | | 15.2 (9.9 to 23.4) | | 3.9 (1.8 to 8.4) | | 2.2 (1.3 to 3.8) | | 1.4 (1.1 to 1.8) | | 0.8 (0.2 to 3.3) | |
| **Number of patients** | | 0.406 | | 0.171 | | 0.262 | | 0.676 | | 0.789 | | 0.735 | | 0.073 |
| ≥ 100 | 18.8 (12.8 to 27.4) | | 15.2 (10.4 to 22.2) | | 17.2 (13.9 to 21.3) | | 4.3 (3.1 to 5.9) | | 3.0 (2.2 to 4.2) | | 2.0 (1.2 to 3.4) | | 0.8 (0.5 to 1.5) | |
| < 100 | 13.9 (10.6 to 18.3) | | 22.8 (14.5 to 35.8) | | 22.0 (13.3 to 36.3) | | 4.4 (2.3 to 8.3) | | 2.4 (0.9 to 6.1) | | 1.4 (0.3 to 6.1) | | 2.2 (0.8 to 6.2) | |
| **Mean follow-up** | | 0.246 | | 0.019 | | 0.020 | | 0.304 | | 0.082 | | 0.148 | | 0.166 |
| ≥ 2 years | 15.7 (11.7 to 21.2) | | 13.0 (9.5 to 17.9) | | 15.2 (12.6 to 18.3) | | 3.8 (2.5 to 5.9) | | 2.3 (1.5 to 3.4) | | 1.5 (0.8 to 2.7) | | 0.8 (0.4 to 1.6) | |
| < 2 years | 21.9 (12.0 to 40.2) | | 24.4 (17.1 to 34.7) | | 25.0 (18.0 to 34.8) | | 6.3 (4.6 to 8.7) | | 4.5 (3.0 to 6.7) | | 3.6 (2.5 to 5.2) | | 1.8 (0.7 to 5.0) | |

**Supplementary Table 1. Subgroup analyses.** (*continued*)

| | Indication for aortic valve intervention | Development of symptoms | Aortic valve intervention | All-cause death | Cardiac death | Heart failure death | Sudden death |
|---|---|---|---|---|---|---|---|
| **Total patient years of follow-up** | 0.361 | 0.009 | 0.030 | 0.044 | 0.194 | 0.666 | 0.073 |
| ≥ 200 years | 16.1 (11.9 to 21.8) | 13.2 (9.9 to 17.5) | 15.8 (13.2 to 18.8) | 3.5 (2.5 to 5.0) | 2.5 (1.8 to 3.6) | 1.8 (1.1 to 3.1) | 0.8 (0.5 to 1.5) |
| < 200 years | 20.8 (9.8 to 43.9) | 26.5 (19.2 to 36.7) | 25.1 (17.0 to 37.0) | 6.6 (4.0 to 11.0) | 4.0 (2.3 to 7.0) | 2.3 (0.9 to 6.1) | 2.2 (0.8 to 6.2) |
| **LVEF criteria‡** | 0.969 | 0.789 | 0.371 | 0.360 | 0.590 | 0.495 | 0.568 |
| No cutoff | 17.4 (11.3 to 27.0) | 17.1 (10.9 to 26.7) | 15.9 (11.3 to 22.4) | 5.8 (3.8 to 8.8) | 3.5 (2.4 to 5.1) | 2.3 (1.3 to 4.2) | 0.9 (0.4 to 2.3) |
| Good | 17.5 (10.7 to 28.6) | 18.4 (12.2 to 27.8) | 20.1 (15.7 to 25.8) | 3.9 (2.6 to 5.9) | 2.7 (1.6 to 4.3) | 1.5 (0.7 to 3.5) | 1.5 (0.7 to 3.2) |

*P for interaction

†Start date of the study.

‡Good left ventricular ejection fraction included studies with criteria of ≥ 50%, ≥ 55%, or "normal".

LVEF, left ventricular ejection fraction; CI, confidence interval

**Supplementary Table 2. Predictors from multivariable analyses.**

| Characteristic | Hazard ratio | Confidence interval | Study reference number | Comment |
|---|---|---|---|---|
| **Peak aortic jet velocity** | | | | |
| Continuous | HR not reported (p=0.004) | | [1] | HR with CI not reported |
| | HR 1.82 | 95% CI 1.13-2.90 | [2] | |
| > 4.0 m/s | HR 2.58 | 95% CI 1.15-5.78 | [3] | |
| ≥ 4.0 m/s | HR 1.65 | 95% CI 0.94-2.86 | [4] | |
| ≥ 4.5 m/s | RR 1.1 | 95% CI 0.7-1.9 | [5] | RR instead of HR |
| ≥ 5 m/s | HR 1.93 | 95% CI 1.16-3.23 | [6] | |
| ≥ 5.5 m/s | HR 1.88 | 95% CI 1.19-2.96 | [7] | |
| First-year progression ≥ 0.22 m/s/year | HR 1.85 | 95% CI 1.07-3.21 | [4] | |
| Rate of progression | HR 9.75 | 95% CI 2.24-42.39 | [8] | |
| **Aortic valve area** | | | | |
| Continuous | HR 1.08 | 95% CI 0.24-4.92 | [6] | |
| | RR 1.48 | | [9] | RR instead of HR; CI and p-value not reported |
| Per 0.1 $cm^2$ | HR 1.17 | 95% CI 1.06-1.29 | [10] | |
| ≤ 0.6 $cm^2$ | HR 2.22 | 95% CI 1.41-3.52 | [10] | |
| | HR 1.25 | 95% CI 0.77-2.02 | [7] | |
| < 0.75 $cm^2$ | HR 1.48 | 95% CI 0.79-2.79 | [3] | |
| > 0.6 - ≤ 0.8 $cm^2$ | HR 1.38 | 95% CI 0.93-2.05 | [10] | |
| Indexed, < 0.6 $cm^2/m^2$ | HR 2.62 | 95% CI 1.09-6.33 | [3] | |
| **Pressure gradient** | | | | |
| Mean, continuous | HR 1.02 | 95% CI 1.00-1.04 | [11] | |
| Peak, continuous | HR 1.02 | 95% CI 1.01-1.04 | [12] | |
| | HR 1.02 | 95% CI 1.01-1.03 | [13] | |
| **Aortic valve calcification** | | | | |
| Continuous | HR 1.10 | 95% CI 0.54-2.24 | [6] | |
| ≥ 3 | HR 2.23 | 95% CI 1.22-4.17 | [4] | |
| | HR 2.63 | 95% CI 1.27-5.44 | [12] | |
| | RR 4.6 | 95% CI 1.6-14.0 | [5] | RR instead of HR |
| 4 | HR 2.51 | 95% CI 1.42-4.44 | [13] | |
| **Age** | | | | |
| Continuous | RR 1.16 | | [9] | RR instead of HR; CI and p-value not reported |
| > 70 years | HR 1.04 | 95% CI 0.66-1.62 | [7] | |
| > 50 years | HR 1.1 | 95% CI 0.5-2.6 | [5] | |
| **Female gender** | HR 1.14 | 95% CI 0.72-1.81 | [7] | |
| | RR 0.9 | 95% CI 0.7-1.2 | [5] | RR instead of HR |

**Supplementary Table 2. Predictors from multivariable analyses.** (*continued*)

| Characteristic | Hazard ratio | Confidence interval | Study reference number | Comment |
|---|---|---|---|---|
| **Hypertension** | HR 0.71 | 95% CI 0.40-1.27 | [6] | |
| | HR 0.70 | 95% CI 0.43-1.15 | [7] | |
| | RR 0.6 | 95% CI 0.4-1.1 | [5] | RR instead of HR |
| **Dyslipidemia** | HR 1.42 | 95% CI 0.85-2.37 | [6] | |
| | HR 1.81 | 95% CI 1.09-3.06 | [4] | |
| | HR 1.68 | 95% CI 1.02-2.75 | [7] | |
| | RR 1.0 | 95% CI 0.6-1.7 | [5] | RR instead of HR |
| **Diabetes** | HR 0.68 | 95% CI 0.35-1.33 | [6] | |
| | HR 4.34 | 95% CI 2.15-8.76 | [13] | |
| | HR 1.84 | 95% CI 1.24-2.73 | [7] | |
| | RR 1.3 | 95% CI 0.7-2.5 | [5] | RR instead of HR |
| **Coronary artery disease** | HR 2.15 | 95% CI 1.29-3.60 | [6] | |
| | HR 0.94 | 95% CI 0.55-1.55 | [7] | |
| | RR 1.1 | 95% CI 0.6-1.9 | [5] | RR instead of HR |
| **Smoking** | HR 1.67 | 95% CI 0.98-2.80 | [4] | |
| **Hemodialysis** | HR 2.28 | 95% CI 0.90-5.10 | [4] | |
| **Systolic blood pressure (continuous)** | HR 1.01 | 95% CI 0.992-1.030 | [14] | |
| **Left ventricular mass** | | | | |
| Continuous | HR 0.99 | 95% CI 0.97-1.07 | [14] | |
| Index, continuous | HR 1.01 | 95% CI 0.99-1.03 | [11] | |
| | HR 1.01 | 95% CI 0.98-1.04 | [13] | |
| Inappropriately high (> 110% measured of predicted) | HR 3.08 | 95% CI 1.65-5.73 | [13] | |
| **Strain** | | | | |
| Global longitudinal strain on speckle strain | HR 1.49 | 95% CI 1.11-2.01 | [14] | |
| | HR 1.13 | 95% CI 1.03-1.25 | [12] | |
| | HR 1.06 | 95% CI 0.96-1.17 | [2] | |
| 2D global longitudinal strain | HR 1.10 | 95% CI 0.99-1.23 | [11] | |
| 3D global longitudinal strain | HR 1.41 | 95% CI 1.21-1.66 | [11] | |
| 3D global radial strain | HR 0.93 | 95% CI 0.85-1.02 | [11] | |
| **Valvulo-arterial impedance** | HR 1.35 | 95% CI 0.87-2.10 | [14] | |
| | HR 1.35 | 95% CI 1.08-1.67 | [12] | |
| **Left atrial reservoir** | HR 1.04 | 95% CI 0.95-1.14 | [14] | |
| **Left atrial stiffness** | HR 0.06 | 95% CI 0.01-1.80 | [14] | |
| **Stroke volume** | HR 0.90 | 95% CI 0.79-1.03 | [14] | |
| **E/e'** | HR 1.42 | 95% CI 1.01-1.98 | [14] | |

**Supplementary Table 2. Predictors from multivariable analyses.** (*continued*)

| Characteristic | Hazard ratio | Confidence interval | Study reference number | Comment |
|---|---|---|---|---|
| **STS predicted risk of mortality** | HR 0.95 | 95% CI 0.90-1.00 | [12] | |
| **Left ventricular end-diastolic volume** | HR 1.01 | 95% CI 1.01-1.02 | [2] | |
| **Left ventricular end-systolic volume** | HR 1.01 | 95% CI 0.98-1.03 | [2] | |
| **Mitral A wave** | HR 1.33 | 95% CI 0.62-2.84 | [2] | |
| **Left atrial area index** | HR 1.13 | 95% CI 1.06-1.20 | [2] | |
| **Low flow (< 35 ml/m$^2$)** | HR 1.70 | 95% CI 1.01-2.90 | [2] | |
| **Low gradient (< 40 mmHg)** | HR 2.30 | 95% CI 1.30-4.00 | [2] | |
| **LVEF (continuous)** | HR 0.953 | 95% CI 0.925-0.982 | [15] | |
| | HR not reported (p=0.013) | | [1] | HR with CI not reported |
| **Positive exercise test** | HR 7.43 | | [9] | CI and p-value not reported |

CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; RR, relative risk

**Supplementary Table 3. Sensitivity analysis of predictors of death or aortic valve intervention according to a half-normal prior distribution of τ.**

| Characteristic | HR (95% CrI) | $\tau^2$ (95% CrI) | References |
|---|---|---|---|
| Peak pressure gradient, per 10mmHg | 1.22 (1.02 to 1.46) | 0.004 (0.000 to 0.070) | [12,13] |
| Peak aortic jet velocity ≥ 4.0 m/s | 1.93 (1.16 to 3.23) | 0.009 (0.000 to 0.107) | [3,4] |
| Aortic valve area ≤ 0.6 cm2 | 1.68 (1.14 to 2.52) | 0.013 (0.000 to 0.118) | [7,10] |
| Aortic valve calcification ≥ grade 3 | 2.68 (1.69 to 4.21) | 0.009 (0.000 to 0.099) | [4,5,12] |
| Female gender | 0.97 (0.72 to 1.34) | 0.009 (0.000 to 0.096) | [5,7] |
| Hypertension | 0.67 (0.48 to 0.93) | 0.007 (0.000 to 0.087) | [5-7] |
| Dyslipidemia | 1.44 (1.08 to 1.93) | 0.008 (0.000 to 0.098) | [4-7] |
| Diabetes | 1.65 (1.14 to 2.37) | 0.041 (0.000 to 0.193) | [5-7,13] |
| Coronary artery disease | 1.32 (0.92 to 1.89) | 0.016 (0.000 to 0.129) | [5-7] |
| Global longitudinal strain on speckle | 1.12 (1.01 to 1.3) | 0.003 (0.000 to 0.052) | [2,12,14] |
| Valvulo-arterial impedance | 1.35 (1.03 to 1.79) | 0.007 (0.000 to 0.090) | [12,14] |
| Left ventricular mass Index, per 10 units | 1.11 (0.87 to 1.41) | 0.006 (0.000 to 0.084) | [11,13] |

CrI, credible interval; HR, hazard ratio

In many situations, the available data makes it difficult to estimate the between study heterogeneity, which is captured by the standard deviation τ. As a consequence, the result for the posterior distribution of τ may be sensitive to the choice of the prior distribution for τ. Thus, we conducted the analyses using two different weakly informative prior distributions for τ. Recommendations exist to use plausible priors for τ that put a small probability (e.g., 5%) on scenarios that are basically equivalent to assuming no relationship among the study specific parameters (16, 17).[16,17] Therefore, we used two different versions of weakly informative priors for τ. In version one, we used a beta distribution for τ with shape parameters 1 and 8. In version two, we used a half-normal distribution with a mean of 0 and a standard deviation of 0.15. We report the results of version one in the main body of text and tables. Results of version two are reported here. Results of this sensitivity analysis shows that results, and thus conclusions, are similar between the two different priors for τ.

**Supplementary Table 4. Additional information on studies comparing early surgery versus conservative treatment strategy.**

| Study, year | Patients | Interval that intervention was performed | Hazard ratio adjusted for potential confounders |
|---|---|---|---|
| Pai, 2006[18] | Entire cohort of 338 patients | Mean of 232 days; 4 patients had delay of 2 to 3 years | Multivariable Cox model adjusted for variables significantly different in univariable analyses: age, chronic renal insufficiency, aspirin use and mitral regurgitation grade 3 or 4. Additional variables (beta-blocker use, statin use, digoxin use, LVEF, and AVA) were tested but not included in the multivariable model due to a lack of an association in univariable analysis. |
| Kang, 2010[8] | 104 propensity-matched patients | < 3 months | No adjustment, but comparable groups based on propensity matching. |
| Le Tourneau, 2010[19] | Entire cohort of 674 patients | < 1 year | Multivariable Cox model, variables used for adjustment were not reported. |
| Taniguchi, 2015[20] | 582 propensity-matched patients | All patients within ±8 months, >90% of patients within ±4 months; >70% within 3 months | Within propensity-matched groups where there were some statistically significant differences among baseline characteristics, a multivariable Cox model adjusted for age, dyslipidemia, malignancy currently under treatment, EuroSCORE II, and STS score. |
| Masri, 2016[21] | Entire cohort of 533 patients | Median duration after stress test was 147 days, and within 60 days if the test was abnormal. | Multivariable Cox model adjusted for STS score, % age-sex-predicted METs, and heart rate recovery. Additional variables (peak rate-pressure product, indexed LV mass, resting mean aortic valve gradient, moderate or more than moderate resting aortic regurgitation, ischemic LV response to stress, resting right ventricular systolic pressure) were tested but not included in the multivariable model due to a lack of an association in univariable analysis. |
| Bohbot, 2018[22] | Entire cohort of 439 patients | < 3 months | Multivariable Cox model adjusted for age, sex, body surface area, hypertension, coronary artery disease, atrial fibrillation, Charlson Comorbidity Index, AVA, peak aortic jet velocity, LVEF, and LV mass. |
| Kim, 2019[23] | Entire cohort of 468 patients | Median of 49 (IQR 12-581) days; 58.8% within 3 months. | Multivariable Cox model adjusted for age, body mass index, anemia, severe chronic kidney disease, previous stroke, coronary artery disease, previous malignancy, left atrium diameter, left ventricular mass index, peak tricuspid regurgitation pressure gradient. Additional variables (hypertension, diabetes, atrial fibrillation, peripheral arterial disease, previous PCI, rheumatic etiology, significant mitral regurgitation, significant tricuspid regurgitation) were tested but not included in the multivariable model due to a lack of an association in univariable analysis. |

**Supplementary Table 4. Additional information on studies comparing early surgery versus conservative treatment strategy.** (*continued*)

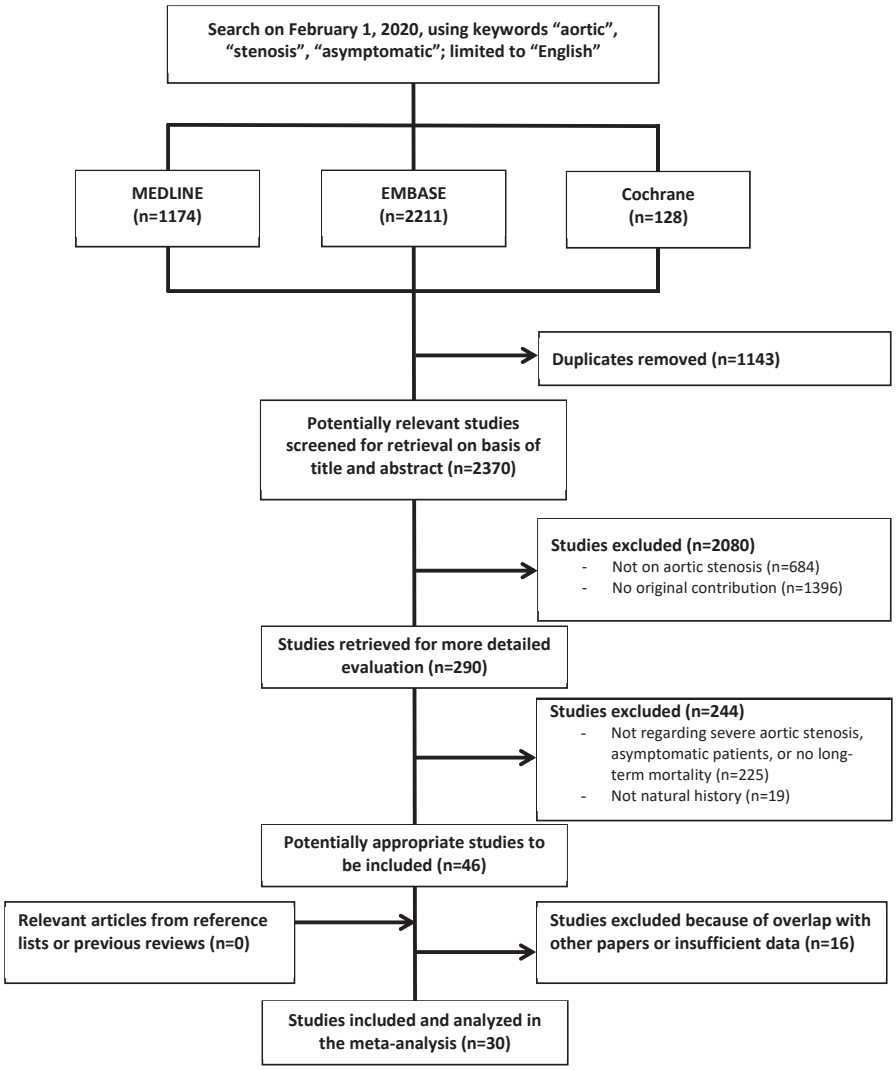
| Study, year | Patients | Interval that intervention was performed | Hazard ratio adjusted for potential confounders |
|---|---|---|---|
| Campo, 2019[24] | Entire cohort of 265 patients | Intervention at 1 year was 90.2% of patients in the intervention group versus 11.7% in the watchful waiting group. | Multivariable Cox model adjusted for age, LVEF, and renal failure. Additional variables (not all variables reported) were tested but not included in the multivariable model due to a lack of an association in univariable analysis. |
| Kang, 2020[25] | Entire cohort of 145 patients | Median of 23 (IQR 10-36) days. | No adjustment, but comparable groups based on randomized controlled design. |

AVA, aortic valve area; AR, aortic regurgitation; IQR, interquartile range; LV, left ventricular; LVEF, left ventricular ejection fraction; METs, metabolic equivalents; PCI, percutaneous coronary intervention

**Supplementary Table 5. Ongoing randomized trials evaluating early intervention versus conservative treatment.**

| | AVATAR[26]<br>NCT02436655 | ESTIMATE<br>NCT02627391 | EVoLVeD<br>NCT03094143 | EARLY TAVR<br>NCT03042104 |
|---|---|---|---|---|
| Sample size | 312 patients | 360 patients | 1000 patients | 1109 patients |
| Age | ≥ 18 years old | 18 – 80 years old | ≥ 18 years old | ≥ 65 years old |
| Aortic stenosis | Severe AS:<br>1. AVA ≤ 1 $cm^2$ or iAVA ≤ 0.6 $cm^2/m^2$<br>AND<br>2. $V_{max}$ ≥ 4 m/s or $P_{mean}$ ≥ 40 mmHg<br>AND<br>3. No very severe AS ($V_{max}$ > 5.5 m/s at rest) | Severe AS:<br>1. $V_{max}$ ≥ 4 m/s<br>OR<br>2. $P_{mean}$ ≥ 40 mmHg<br>AND<br>3. No more than mild AR (grade 2/4) | Severe AS ($V_{max}$ ≥ 4 m/s, or iAVA ≤ 0.6 $cm^2/m^2$ with $V_{max}$ ≥ 3.5 m/s) with mid wall fibrosis on MRI and no severe AR | Severe AS:<br>1. AVA ≤ 1 $cm^2$ or iAVA ≤ 0.6 $cm^2/m^2$<br>AND<br>2. $V_{max}$ ≥ 4 m/s or $P_{mean}$ ≥ 40 mmHg<br>AND<br>3. No severe AR (grade 3+) |
| Symptomatic | No reported AS-related symptoms | No symptoms potentially attributable to AS: dyspnea, angina or syncope during exercise | No symptoms attributable to AS that require SAVR | Negative treadmill stress test or per physician assessment if not able to perform a treadmill stress test (NYHA ≥ 2, syncope, angina CCS score > 1, hospitalization for heart failure within last 6 months) |
| Exercise test | Negative exercise test:<br>- No angina<br>- No syncope or dizziness<br>- No decrease in systolic blood pressure ≥20 mmHg<br>- No malignant arrhythmia | Negative exercise test:<br>- No angina<br>- No syncope or dizziness<br>- No dyspnea<br>- No decease in systolic blood pressure | No criteria | Negative exercise test |
| LVEF | ≥ 50% at rest | > 50% | < 50% | ≥ 50% |
| Intervention | Isolated SAVR | Isolated SAVR | SAVR or TAVR with or without coronary revascularization | TAVR |
| Operative risk | STS score < 8% | EuroSCORE II ≤ 5% | No criteria | STS score ≤ 10% |
| Primary outcome | Composite of all-cause death, acute MI, cerebrovascular event, and unplanned hospitalization for heart failure requiring intravenous treatment at 3 years | Composite of all-cause death and cardiac event requiring hospitalization (e.g. symptoms, congestive heart failure, acute coronary syndrome) at 1 year | Composite of all-cause death or unplanned AS-related hospitalization (e.g. syncope, heart failure, angina or ventricular arrhythmia or second or third degree heart block) at a mean follow-up of 2.75 years | Composite of all-cause death, stroke, and unplanned cardiovascular hospitalization at 2 years |

AS, aortic stenosis; AR, aortic regurgitation; (i)AVA, (indexed) aortic valve area; CCS, Canadian Cardiovascular Score; MI, myocardial infarction; MRI, magnetic resonance imaging; NYHA, New York Heart Association; $P_{mean}$, mean gradient; SAVR, surgical aortic valve replacement; STS, Society for Thoracic Surgeons; TAVR, transcatheter aortic valve replacement; $V_{max}$, maximal velocity.




**Supplementary Figure 1. Flow-chart of systematic literature search and study inclusion.**

**Supplementary Text 1. Details on data extraction**

Study description data that was extracted included the location of the study, design of the study, the number of included patients, and time span of patient inclusion. For the assessment of the severity of AS and truly asymptomatic status we extracted data on the criteria used to define severe AS, cut-offs of the LVEF for inclusion in the study, percentage of patients that underwent stress evaluation either through exercise testing or stress echocardiography, and the results of stress evaluation. Mean age and mean LVEF were extracted as patient characteristics. For the analysis we extracted the total follow-up time, mean or median time of follow-up, whether patients were censored at the time of aortic valve intervention during follow-up, and the number of events that occurred during this follow-up for our endpoints of interest. We then extracted the results of multivariable analyses to identify predictors of these events. For studies that compared groups of early intervention with a conservative treatment, we furthermore extracted the hazard ratio (HR) with 95% confidence intervals (CI) of the comparison between treatments and methods of adjusting for potential differences in baseline characteristics between treatment groups.

**Supplementary Text 2. Details on Bayesian meta-analysis of prognostic indicators.**

A Bayesian approach was used as it appropriately takes into account the uncertainty around τ^2 when only a scarce number of studies are available for the analysis, as was the case.[27] Monte-Carlo Markov Chain simulation methods were used to obtain posterior distributions of the HRs of interest and of τ^2. Pooled HRs were estimated from the median of the respective posterior distributions,[28] with 95% credible intervals (CrI) obtained from the 2.5th and the 97.5th percentile of the posterior distribution, which can be interpreted similarly to a conventional 95% confidence interval. We conducted sensitivity analyses according to type of prior distribution for the between-study standard deviation τ (Supplementary Table 3). Between-study heterogeneity in HRs may be considered low if the median of the posterior distribution of τ^2 is 0.04; τ^2 estimates of 0.16 may be interpreted as a moderate and 0.36 as a high degree of heterogeneity between studies.[29] Results were obtained after a burn-in of 30000 iterations, retaining every 20th out of 200000 iterations to address problems with auto-correlation observed in some of the analyses. Model convergence was assessed visually using the trace plots and using Gelman-Rubin plots. For all posterior distributions of parameters of interest we report the median, and the 2.5th and the 97.5th percentile of the posterior distribution.

1. **Supplementary Figure 1. Flow-chart of systematic literature search and study inclusion.**
2. **Supplementary Table 1. Subgroup analyses.**
3. **Supplementary Table 2. Predictors from multivariable analyses.**
4. **Supplementary Table 3. Sensitivity analysis according to prior distribution of τ.**
5. **Supplementary Table 4. Additional information on studies comparing a conservative treatment strategy versus surgery.**
6. **Supplementary Table 5. Ongoing randomized trials evaluating early intervention versus conservative treatment.**
7. **Supplementary Text 1. Details on data extraction.**
8. **Supplementary Text 2. Details on Bayesian meta-analysis of prognostic indicators.**
9. **References in Supplement.**

## REFERENCES IN SUPPLEMENT


1. Pellikka PA, Nishimura RA, Bailey KR, Tajik AJ. The natural history of adults with asymptomatic, hemodynamically significant aortic stenosis. *J Am Coll Cardiol.* 1990;15(5):1012-1017.
2. Lancellotti P, Magne J, Donal E, et al. Clinical outcome in asymptomatic severe aortic stenosis: insights from the new proposed aortic stenosis grading classification. *J Am Coll Cardiol.* 2012;59(3):235-243.
3. Saito T, Muro T, Takeda H, et al. Prognostic value of aortic valve area index in asymptomatic patients with severe aortic stenosis. *Am J Cardiol.* 2012;110(1):93-97.
4. Nishimura S, Izumi C, Nishiga M, et al. Predictors of Rapid Progression and Clinical Outcome of Asymptomatic Severe Aortic Stenosis. *Circ J.* 2016;80(8):1863-1869.
5. Rosenhek R, Binder T, Porenta G, et al. Predictors of outcome in severe, asymptomatic aortic stenosis. *N Engl J Med.* 2000;343(9):611-617.
6. Zilberszac R, Gabriel H, Schemper M, Laufer G, Maurer G, Rosenhek R. Asymptomatic Severe Aortic Stenosis in the Elderly. *JACC Cardiovasc Imaging.* 2016.
7. Rosenhek R, Zilberszac R, Schemper M, et al. Natural history of very severe aortic stenosis. *Circulation.* 2010;121(1):151-156.
8. Kang DH, Park SJ, Rim JH, et al. Early surgery versus conventional treatment in asymptomatic very severe aortic stenosis. *Circulation.* 2010;121(13):1502-1509.
9. Amato MC, Moffa PJ, Werner KE, Ramires JA. Treatment decision in asymptomatic aortic valve stenosis: role of exercise testing. *Heart.* 2001;86(4):381-386.
10. Marechaux S, Ringle A, Rusinaru D, Debry N, Bohbot Y, Tribouilloy C. Prognostic Value of Aortic Valve Area by Doppler Echocardiography in Patients With Severe Asymptomatic Aortic Stenosis. *J Am Heart Assoc.* 2016;5(5).
11. Nagata Y, Takeuchi M, Wu VC, et al. Prognostic value of LV deformation parameters using 2D and 3D speckle-tracking echocardiography in asymptomatic patients with severe aortic stenosis and preserved LV ejection fraction. *JACC Cardiovasc Imaging.* 2015;8(3):235-245.
12. Yingchoncharoen T, Gibby C, Rodriguez LL, Grimm RA, Marwick TH. Association of myocardial deformation with outcome in asymptomatic aortic stenosis with normal ejection fraction. *Circ Cardiovasc Imaging.* 2012;5(6):719-725.
13. Cioffi G, Faggiano P, Vizzardi E, et al. Prognostic effect of inappropriately high left ventricular mass in asymptomatic severe aortic stenosis. *Heart.* 2011;97(4):301-307.
14. Todaro MC, Carerj S, Khandheria B, et al. Usefulness of atrial function for risk stratification in asymptomatic severe aortic stenosis. *J Cardiol.* 2016;67(1):71-79.
15. Avakian SD, Grinberg M, Ramires JA, Mansur AP. Outcome of adults with asymptomatic severe aortic stenosis. *Int J Cardiol.* 2008;123(3):322-327.
16. Neuenschwander B, Capkun-Niggli G, Branson M, Spiegelhalter DJ. Summarizing historical information on controls in clinical trials. *Clin Trials.* 2010;7(1):5-18.
17. Smith TC, Spiegelhalter DJ, Thomas A. Bayesian approaches to random-effects meta-analysis: a comparative study. *Stat Med.* 1995;14(24):2685-2699.
18. Pai RG, Kapoor N, Bansal RC, Varadarajan P. Malignant natural history of asymptomatic severe aortic stenosis: benefit of aortic valve replacement. *Ann Thorac Surg.* 2006;82(6):2116-2122.
19. Le Tourneau T, Pellikka PA, Brown ML, et al. Clinical outcome of asymptomatic severe aortic stenosis with medical and surgical management: importance of STS score at diagnosis. *Ann Thorac Surg.* 2010;90(6):1876-1883.

20. Taniguchi T, Morimoto T, Shiomi H, et al. Initial Surgical Versus Conservative Strategies in Patients With Asymptomatic Severe Aortic Stenosis. *J Am Coll Cardiol.* 2015;66(25):2827-2838.
21. Masri A, Goodman AL, Barr T, et al. Predictors of Long-Term Outcomes in Asymptomatic Patients With Severe Aortic Stenosis and Preserved Left Ventricular Systolic Function Undergoing Exercise Echocardiography. *Circ Cardiovasc Imaging.* 2016;9(7).
22. Bohbot Y, Pasquet A, Rusinaru D, et al. Asymptomatic Severe Aortic Stenosis With Preserved Ejection Fraction: Early Surgery Versus Conservative Management. *J Am Coll Cardiol.* 2018;72(23 Pt A):2938-2939.
23. Kim HJ, Kim JB, Kim HR, et al. Impact of Valve Replacement on Long-Term Survival in Asymptomatic Patients With Severe Aortic Stenosis. *Am J Cardiol.* 2019;123(8):1321-1328.
24. Campo J, Tsoris A, Kruse J, et al. Prognosis of Severe Asymptomatic Aortic Stenosis With and Without Surgery. *Ann Thorac Surg.* 2019;108(1):74-79.
25. Kang DH, Park SJ, Lee SA, et al. Early Surgery or Conservative Care for Asymptomatic Aortic Stenosis. *N Engl J Med.* 2020;382(2):111-119.
26. Banovic M, Iung B, Bartunek J, et al. Rationale and design of the Aortic Valve replAcemenT versus conservative treatment in Asymptomatic seveRe aortic stenosis (AVATAR trial): A randomized multicenter controlled event-driven trial. *Am Heart J.* 2016;174:147-153.
27. Cornell JE, Mulrow CD, Localio R, et al. Random-effects meta-analysis of inconsistent effects: a time for change. *Ann Intern Med.* 2014;160(4):267-270.
28. Warn DE, Thompson SG, Spiegelhalter DJ. Bayesian random effects meta-analysis of trials with binary outcomes: methods for the absolute risk difference and relative risk scales. *Stat Med.* 2002;21(11):1601-1623.
29. da Costa BR, Juni P. Systematic reviews and meta-analyses of randomized trials: principles and pitfalls. *Eur Heart J.* 2014;35(47):3336-3345.

# 13 General Discussion

## Aortic stenosis

The prevalence of aortic stenosis (AS) increases due to the aging of the population and is considered the most common valve disease requiring intervention. Calcific disease of the normal trileaflet valve is the most common cause of AS in adults and accounts for 80% of cases in the United States and Europe, with patients mostly presenting after the sixth decade of life.[1] The majority of the remaining cases are due to bicuspid aortic valves. These patients present are often younger at the time of presentation.[2] Aortic stenosis is characterized by the abnormal flow through the aortic valve and mainly a slowly progressive disease associated with dismal outcomes after symptom development.[3] Symptomatic severe aortic stenosis has a poor prognosis after the development of symptoms.[4] Aortic valve replacement for the treatment of severe AS has been associated with increased survival and reduced symptoms.[5,6] Guidelines recommend intervention for patients with severe high-gradient aortic stenosis (mean transaortic gradient ≥40 mmHg or peak velocity ≥4 m/s, Class I recommendation) and severe low-flow, low-gradient aortic stenosis (<40 mmHg) with reduced ejection fraction (Class I).

Surgery was the only effective treatment strategy for severe AS for decades.[7] However, transcatheter aortic valve implantation (TAVR) has emerged as an effective alternative to surgical aortic valve replacement (SAVR). The first TAVR was implanted in 2000 in a critically ill patient by Professor Alain Cribier.[8] Increasing global expansion, experience, and technological advances in TAVR, the technique has been simplified and become a low-risk therapeutic option, even for patients classified as low-risk. TAVR demonstrated short- and mid-term outcomes comparable to SAVR regardless of the surgical risk of the patients in isolated studies. In the last 15 years, more than 350,000 procedures have been performed in approximately 70 countries, with over 275,000 only in the United States.[9] Major issues regarding the clinical practice in patients with severe AS remain to be discussed: (i) the undertreatment of symptomatic and asymptomatic patients with severe AS, and (ii) the right effective treatment modality for patients with severe AS.

## Current undertreatment of aortic stenosis

Degenerative valve disease is the most prevalent heart valve disease in the western population.[10] However, the Euro Heart survey shows that 68.2% of the patients with severe symptomatic AS undergo intervention. Exercise stress testing is underutilized in asymptomatic patients, which is performed in up to 7.9% of the total population with asymptomatic AS. The undertreatment of aortic stenosis in the U.S. is severe, driven by deep-rooted racial and sex disparities and a disconnect between patients and their clinicians, leading to treatment delay.[11]

Aortic stenosis is diagnosed from cardiological referral for echocardiography, often triggered by symptoms. However, comorbidities such as diabetes mellitus, hypertension, tobacco abuse, and obesity may mask these symptoms and the symptoms may be

misattributed, potentially delaying diagnosis and management. Further, patient refusal and social demographics play a significant role in patient presentation and treatment. Especially in countries with low insurance rates, such as the U.S., Hispanic and Asian patients tend to have higher uninsured rates than white non-Hispanic patients, leading to less treatment due to the associated cost of aortic valve replacement (AVR).[12] On the other hand the number of patients with severe aortic stenosis is projected to increase.[13]

In a large retrospective database, 366.909 patients hospitalized for aortic valve disease between 2012 and 2016 were analyzed for the evolving management of aortic valve disease.[14] In this analysis, the likelihood of patients receiving TAVR increased by 4.57 (relative risk ratio) relative to SAVR and 4.41 relative to medical management. Patients admitted to large academic and urban teaching hospitals were more likely to receive SAVR. Patients in urban nonteaching and rural hospitals and not-for-profit hospitals were more likely to receive TAVR. This may be due to the price of TAVR. The treatment cost of aortic valve stenosis is estimated to be 10.2$ billion in 2016 and is expected to increase toward 2025 due to the expanded indication of TAVR.[15] While the replacement of the valve may lead to higher upfront costs, medical therapy leads to higher delayed costs due to readmission and ongoing medical care.

Sociodemographic factors such as income, education level, and language barrier have been shown to influence access to health care in the United States and Europe.[16,17] Patient-specific factors related to the presentation, comorbidities, and disease perception, and social determinants often result in a lower incidence of aortic valve replacement rates in the underserved minorities. This may have implications for underserved minorities and rural patients, as rural Americans have shown similar challenges.[18] The inequitable distribution of aortic valve replacement, should be addressed.

## The changing landscape

The number of patients hospitalized for aortic valve disease nearly doubled from 57,516 in 2012 to 85,165 in 2016 in the USA.[14] The incidences of SAVR and increased from 24,568 in 1989 to 31,380 in 2011[19] and the incidence of TAVR from 4,627 in 2012 to 24,808 in 2015, with 418 centers participating, respectively.[20] Currently, the incidence is TAVR is increasing while the incidence of SAVR is stable. The incidence of patients treated medically is decreasing.

In **Chapter 2**, we noted an increase of reported comorbidities comorbidity in the SAVR patients during the last decades. Patients undergoing SAVR had an increased frequency of comorbidities in the patient population.[21] The prevalence of diabetes mellitus, hypercholesterolemia, and hypertension have at least doubled during the 30-year observation period. These factors are known to be adversely associated with outcomes in patients undergoing cardiac surgery.

Prosthesis choice is an essential element of treatment decisions in aortic valve disease. Mechanical and bioprosthetic valves are associated with inherent risks. The incidence of bioprosthetic valve use is increasing[22], the incidence of bioprosthetic valves is increasing, and this shift is most prominent between patients aged 60 and 70 years of age, and further initiates the discussion of TAVR.

**Asymptomatic aortic stenosis**

Aortic stenosis is an insidious disease with a long latency (asymptomatic) period. Rapid progression ensues after the onset of symptoms. The mortality rate is up to 50% within the first two years after developing symptoms.[23] Syncope and heart failure are the most significant predictors of mortality.[4] The sudden cardiac mortality is higher than previously anticipated.[24-27] In the current era, conservative treatment for asymptomatic patients with severe aortic stenosis is therefore, a solution that almost nobody still considers, especially with the advent of TAVR.

The first randomized controlled trial by Kang et al.[28] shows the importance of early treatment in patients with asymptomatic very severe AS. The study included 145 patients with very severe aortic stenosis defined as an aortic-valve area of ≤0.75 $cm^2$ with either an aortic jet velocity of ≥4.5 m per second or a mean transaortic gradient of ≥50 mm Hg to either preemptive surgery or watchful waiting. The primary outcome was a composite of mortality during follow-up. Other assessed endpoints included death by any cause and hospitalization for heart failure. The survival was significantly better in patients treated with early intervention, persisting up to 8 years of follow-up compared to patients receiving conservative care (90% versus 68%).

The largest asymptomatic AS registry, the CURRENT AS registry, is a multicentre, retrospective registry enrolling consecutive patients with asymptomatic severe AS among 27 centers (an on-site surgical facility in 20 centers) in Japan between 2003 and 2011.[29] Patients with severe AS (peak aortic jet velocity (Vmax)>4.0 m/s, mean aortic pressure gradient (PG)>40mm Hg, or aortic valve area (AVA) <1$cm^2$) were included.[29] A total of 3813 patients were included, of whom 1808 were asymptomatic. A total of 291 patients were assigned to the initial treatment group, with all of the patients receiving surgical aortic valve replacement, due to TAVR not yet been approved in Japan. Initial AVR was defined as AVR within three months after diagnosis. The all-cause mortality was higher in the conservatively treated patient than patients receiving immediate AVR (26.4% versus 15.4%, p=0.009). This difference disappeared after comparison of initial SAVR and receiving SAVR during follow-up after turning symptomatic. The 5-year overall survival was 86.0% and 84.1% (p=0.34) in patients with AVR within three months and AVR during follow-up, respectively.

In **Chapter 11** we display that the myriad of patients develop symptoms and therefore require aortic valve intervention. In the next chapter (**Chapter 12**), we present the risk

of sudden death is underestimated and accounts for only a part of cardiac mortality occurring in asymptomatic patients with severe AS. The all-cause incidence of death is 4.8 per 100 patients per year.

Although the trial by Kang emphasizes the importance of early treatment in patients with very severe AS, direct correlation with patients with severe AS cannot be made through extrapolation. It only provides a perspective on patients with very severe AS, applying inclusion criteria of an AVA of ≤0.75 $cm^2$ with either a jet velocity of ≥4.5 m/s or a mean gradient of ≥50 mm Hg, while lacking evidence on the much broader patient population with asymptomatic AS. Further randomized trials assessing early surgical and transcatheter treatment are required. The AVATAR (NCT02436655), EVOLVED (NCT03094143), ESTIMATE (NCT02627391), and the EARLY TAVR (NCT03042104) are warranted.

### Heart failure due aortic stenosis

Asymptomatic patients with severe AS present with better left ventricular function. These patients present with a lower degree of combined valve disease.[30] However, the incidence of heart failure and mortality due to heart failure is higher than previously anticipated under conservative management.[27] In the CURRENT AS registry, the prognosis of patients with severe AS complicated by acute heart failure (AHF) is poor, with extremely high rates of all-cause death and hospitalization due to heart failure.[31] AHF is associated with an increased risk of mortality compared to patients with chronic heart failure, even after aortic valve replacement.[31] TAVR was associated with a relative risk reduction of 54% of all-cause mortality compared to watchful waiting[32,33] and a significant decrease in the incidence of hospitalization due heart failure.

In Chapter 14, we describe that the rate of congestive heart failure associated mortality is 2.0 per 100 patients per year.[24] Early intervention may therefore be considered in a greater proportion of patients with asymptomatic severe AS. Early treatment was associated with a 3x increase of survival (Hazard ratio of 0.38), yet a caveat may be placed at patients treated conservatively might have been assessed as inoperable, which was most often the case before the introduction of TAVR.[1]

### Heart valve team

The Heart Team concept is introduced in 2010 and integrated into the European Society of Cardiology revascularization guidelines.[34] Since then, the Heart Team has expanded toward structural and valvular heart diseases. The most recent American College of Cardiology and European Society of Cardiology on coronary revascularization and valvular guideline recommend Heart Team consultation (Class IC).[3,35-37] Patients for aortic valve surgery need careful assessment to help determine the operative risk.[38,39] Operative risk is affected by underlying comorbidities and might even affect the symptoms and

long-term outcome more than the underlying valvular disease. The assessment of operative risk has been facilitated by scoring systems to estimate the risks of cardiac surgery, e.g., the Society for Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) and EuroSCORE II risk scoring systems. However, although these are accurate in identifying higher-risk patients, it has been argued that these scores overestimate mortality for patients requiring TAVR.[40] Newer scores have been developed to predict outcomes after TAVR, but widespread use and validation remain warranted.[41-43]

A recent consensus report has emphasized the importance of a multidisciplinary Aortic Heart Valve Team based within a heart valve center for the management of patients with aortic valve disease.[44] TAVR is now recommended in an ever-growing population. The majority of patients discussed in the Heart Team undergo TAVR.[45] Bicuspid anatomy favors SAVR, as TAVR shows suboptimal, non-circular valve expansion in those patients.[46] Patients with pure bicuspid aortic valves are currently considered for SAVR, yet specialized transcatheter systems are developed and are currently investigated (NCT02732704). Further points to discuss within the Heart Team are patients with small aortic annulus might require annuloplasty and therefore have permanent pacemaker implantation post-TAVR and are better off with initial SAVR.[47] In addition, patients with heavy annular and LVOT calcification are associated with increased annular rupture, increased rate of ≥ moderate PVL, and stroke due to calcium embolization.[48-51]

**Newer surgical approaches**

The SAVR devices are improving promptly. The advent of minimally invasive procedures requires diligent technical improvements, i.e., the Perceval sutureless valve and rapid deployments valves have changed the landscape of surgical aortic valve pathology treatment.[52-57] The minimal invasive character of the intervention is expected to improve the patient's quality of life. Further comparative trials comparing minimally invasive surgery such as transcatheter aortic valve replacement remains warranted due to the increasing adoption of both techniques.

*Minimal invasive and rapid deployment aortic valves*

The minimal invasive AVR consists of either an upper mini-sternotomy or a limited right anterior thoracotomy through the second intercostal space. Patients are discharged earlier and have a better quality of life.[58,59] However, minimal invasive AVR is associated with increased complexity, and the main obstacles to the wide adoption of minimal invasive AVR are i) increased operative times, ii) technical difficulty, iii) and steep learning curves. Rapid-deployment (also known as sutureless aortic valve prostheses) is specially developed to facilitate minimally invasive surgery and reduce cardiopulmonary bypass time. This valve can be implanted without the need for circumferential sutures. Currently,

there are two rapid-deployment valves in use: the Perceval (self-expandable; LivaNova) and INTUITY (balloon-expandable; Edwards Lifesciences).

In a large cohort with 22062 from the German Aortic Valve Registry (GARY) between 2011 and 2015, rapid deployment valves had lower procedural, cardiopulmonary bypass and cross-clamp time, and decreased incidence of postoperative bleeding and atrial fibrillation, yet resulted in an increased risk of permanent pacemaker implantation, with an incidence of up to 9.1%[60-62], worse than standard AVR (3.0%), paravalvular leakage[63], and more importantly an increased risk of disabling stroke.[64-66] Other significant complications include neurological events (transient ischemic attack or disabling stroke), myocardial infarction, kidney failure, and surgical site infections[67,68], which counterattacks the purpose of competing with TAVR.[66] Specific patient populations may benefit from rapid deployment valves, such as patients with a small aortic root or with calcified homograft, avoiding the need for annular decalcification and patients undergoing multiple cardiac surgical procedures.[69-74] An International Expert Consensus Panel recommends sutureless valves as the first choice of valve prosthesis for patients who require concomitant procedures or who have a small aortic annulus and might be recommended in patients requiring redo operation.[75]

*New generation mechanical valves with lower-intensity coagulation*

Specially designed valves, such as the on-x, to support low-intensity anticoagulation and subsequently reducing the risk for bleeding in patients is developed. The PROACT (Prospective Randomized On-X Anticoagulation Clinical Trial) assessed the safety of dual antiplatelet therapy or reduced anticoagulation therapy for patients with an On-X® AVR.[76] This study investigated the non-inferiority of a lowered target INR (range 1.5 to 2.0) over standard anticoagulation with warfarin in patients undergoing mechanical aortic valve replacement (AVR) with the On-X valve. The incidence of bleeding was lower with reduced versus standard intensity warfarin (2.86%/py vs. 7.43%/py respectively; P<0.001) without affecting the incidences of valve thrombosis (0.21%/py vs. 0.18%/py; P=0.90), stroke (0.74%/py vs. 0.64%/py; P=0.80), transient ischemic attack (1.27%/py vs. 1.01%/py; P=0.60), peripheral thromboembolism (0.42%/py vs. 0.09%/py; P=0.20) or all cause-mortality (1.38%/py vs. 1.56%/py; P=0.70) in patients with reduced and standard anticoagulation, respectively. The recent newer Further PROACT Xa trial (NCT04142658) might improve further usage if beneficial results are yielded for the apixaban group. Currently, this is the only aortic valve prosthesis the Food and Drug Administration has approved with a lower INR goal of 1.5-2.0. If lower INR targets can be achieved, patients with a contraindication for anticoagulation, who receive bioprosthetic valves, may receive a mechanical substitute.

### Transcatheter aortic valve replacement

Patients considered inoperable were historically rejected therapy, with the prevalence being up to ¼ of the patients. The inoperable patient initially benefitted from transcatheter aortic valve implantation (TAVR). However, with advanced technology and TAVR being simplified, TAVR is now an alternative treatment strategy for patients at low- and intermediate-surgical risk.[52-56]

Recent advancements of the TAVR devices lead to gradual improvements in survival, hemodynamic performance, and a better safety profile.[77] The improvement of survival is partly caused by i) patient selection, ii) increasing operator experience, iii) improvement in devices and iv) lower-risk patients receiving TAVR.[78] Subsequently, this led to decreased risk and incidence of TAVR related complications, amplifying and easing the expansion of TAVR. A recent meta-analysis summarizing data within randomized controlled trials regarding mortality showed decreased incidence of mortality in patients receiving TAVR compared to SAVR.[79] Additional analyses show the significant favor of TAVR over SAVR is limited to the first year after implantation due to the minimally invasive nature of the intervention.[80] However, the time-varying effect of TAVR on the all-cause mortality is evident during follow-up in patients at high-risk, showing a hazard ratio of 1.32 (1.03-1.70, p=0.03) in the interval of 40 and 60 months. TAVR remains a feasible option in the high-risk population, with the 5-year outcomes showing an all-cause mortality of 55.3% and 55.4% for TAVR and SAVR, respectively.[81] In this population, the incidence of major stroke was 12.3% and 13.2%, respectively.

In contrast, emerging evidence shows the disadvantages of TAVR at 5 years in real-world practice in low- and intermediate-risk patients.[82] Barbanti and colleagues report 5-year all-cause mortality in low- and intermediate-risk patients with severe symptomatic aortic stenosis of 35.8% versus 44.5% (HR 1.38 [95% CI 1.12-1.69], p=0.002) in SAVR and TAVR, respectively. This was also noted in major adverse cardiac and cardiovascular events during follow-up, with 42.5% and 54.0% (HR 1.35 [95% CI 1.11-1.63], p=0.003) patients having MACCE in SAVR and TAVR, respectively. Our meta-analysis (**Chapter 6**), consisting of all to date data regarding low-risk populations, found an incidence for mortality of 30.7% versus 21.4% for patients receiving TAVR and SAVR at 5-years follow-up, respectively (hazard ratio 1.19 [95% CI 0.96-1.48]), P=0.104). These results emphasize the importance of caution while aggressively expanding the indications of TAVR for younger low-risk patients.

Further expansion of TAVR is limited due to the occurrence of cerebrovascular events, affecting both the morbidity and mortality of patients post-TAVR. The occurrence of cerebrovascular events is multifactorial and includes embolic debris liberated from the native aortic valve and manipulation of the valve.[83] These events most often occur very shortly after TAVR. Yet, the new generation valves have a yearly incidence as low as 1% at one year.[84] Cerebrovascular protection devices even further decrease the incidence of

cerebrovascular events and have become increasingly important.[85,86] Research regarding the effects of silent ischemia, only detectable by brain magnetic resonance imaging, on cognitive function has to be cleared.[87]

Proponents of TAVR in the younger population have argued for future Valve in Valve TAVR as a novel, less invasive approach for the treatment of bioprosthetic aortic valve degeneration and even lowering the age of surgical bioprosthetic valve use, especially in patients deemed high surgical risk for reoperation.[88,89] Data from the valve in valve international data (VIVID) registry show the feasibility of implantation of TAVR in patients with high risk after previous SAVR. The 30-day all-cause mortality was 5.3%, and the 30-day cardiovascular death was 4.8%.[90] The overall 1-year survival is 83.2% and is lower in patients with previous small valve implantation and those with degeneration due to aortic stenosis.[91] At 3-years of follow-up, TAVR for degenerated bioprosthetic valves resulted in a survival of 67.3% and a very low repeat aortic valve intervention of 1.9% at 3-years. Acceptable post-intervention gradients are noted.

### Patients with bicuspid aortic valves

Patient with bicuspid aortic valves requiring aortic valve intervention may benefit from SAVR until long-term data regarding TAVR is available. The incidence of bicuspid aortic valves (BAV) is higher in the younger population requiring aortic valve intervention. This younger population with BAV also presents with a better cardiovascular risk profile (**Chapter 7**). BAV is also three times more prevalent among men than women.[92] Anatomical men have more frequently type 1 BAV with a fusion between left and right coronary cusp than women, 81.5% vs. 69.0, p=0.03, respectively. Female patients tend to have more right and noncoronary cusp fusion (31.0% vs 18.5%, p=0.03). No differences were noted in patients with type 2 BAV.[93]

Furthermore, patients with bicuspid aortic valves tend to have a higher incidence of aortopathy, with male preponderance.[94] Male patients tend to have greater aortic dimensions than female patients, even after adjusting for age and BSA. Aortic distensibility and elasticity can affect aortic dilatation in the BAV population.[95] In cardiac MRI studies, women had higher aortic distensibility than men.[96] The higher frequency of aortic complications among men with BAV compared with women suggests the need for close control of aortic dimensions over time.

In an era where TAVR indications are expanding and becoming an alternative treatment for younger patients with low surgical risk, the knowledge regarding the prevalence of bicuspid valvular morphology in the current SAVR population is of utmost importance. Patients with BAV more often have (pure) AS and fewer cardiovascular risk factors than patients with tricuspid aortic valves. Yoon and colleagues include in BAV patients with severe AS, TAVR 1034 patients were included.[97] During a follow-up of 360 days, 86 patients had died in the overall cohort. The all-cause mortality at 2-years was 12.5%. Patients

with type 1 calcified raphe had higher 2-year mortality than patients with noncalcified raphe or type 0 Sievers patients (17.7% vs. 9.3 vs. 2.4, p=0.001). Therefore, anatomical risk should be further assessed, and the excellent outcomes of the recent low-risk TAVR clinical trials should not be extrapolated to the whole bicuspid aortic valve population.

## CONCLUSION

This dissertation gives an overview of the knowledge regarding the clinical outcomes following surgical aortic valve replacement in symptomatic and asymptomatic patients with severe aortic stenosis. We further identified predictors for early and very long-term mortality following SAVR. In addition, we showed that early surgical intervention at asymptomatic stage did not increase the risk for morbidity and mortality and even did result in a decrease of sudden death during follow-up. We present data comparing SAVR and TAVR in low-risk patients with follow-up and show critical research worthy areas before further allocating and expanding TAVR indications. High expectations are being set for future SAVR and TAVR devices. It is anticipated that these advancements will also further improve the distribution and subsequent outcomes in SAVR patients.

## REFERENCES


1. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Barwolf C, Levang OW, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. Eur Heart J. 2003;24(13):1231-43.
2. Celik M, Milojevic M, Durko AP, Oei FBS, Bogers A, Mahtab EAF. Differences in baseline characteristics and outcomes of bicuspid and tricuspid aortic valves in surgical aortic valve replacement. Eur J Cardiothorac Surg. 2021.
3. Writing Committee M, Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, 3rd, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2021;77(4):450-500.
4. Ross J, Jr., Braunwald E. Aortic stenosis. Circulation. 1968;38(1 Suppl):61-7.
5. Sharabiani MT, Fiorentino F, Angelini GD, Patel NN. Long-term survival after surgical aortic valve replacement among patients over 65 years of age. Open Heart. 2016;3(1):e000338.
6. Glaser N, Persson M, Jackson V, Holzmann MJ, Franco-Cereceda A, Sartipy U. Loss in Life Expectancy After Surgical Aortic Valve Replacement: SWEDEHEART Study. J Am Coll Cardiol. 2019;74(1):26-33.
7. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739-91.
8. Cribier A, Eltchaninoff H, Bash A, Borenstein N, Tron C, Bauer F, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. Circulation. 2002;106(24):3006-8.
9. Carroll JD, Mack MJ, Vemulapalli S, Herrmann HC, Gleason TG, Hanzel G, et al. STS-ACC TVT Registry of Transcatheter Aortic Valve Replacement. J Am Coll Cardiol. 2020;76(21):2492-516.
10. Iung B, Cachier A, Baron G, Messika-Zeitoun D, Delahaye F, Tornos P, et al. Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? Eur Heart J. 2005;26(24):2714-20.
11. Matthew Brennan J, Leon MB, Sheridan P, Boero IJ, Chen Q, Lowenstern A, et al. Racial Differences in the Use of Aortic Valve Replacement for Treatment of Symptomatic Severe Aortic Valve Stenosis in the Transcatheter Aortic Valve Replacement Era. J Am Heart Assoc. 2020;9(16):e015879.
12. Reynolds MR, Magnuson EA, Lei Y, Wang K, Vilain K, Li H, et al. Cost-effectiveness of transcatheter aortic valve replacement compared with surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results of the PARTNER (Placement of Aortic Transcatheter Valves) trial (Cohort A). J Am Coll Cardiol. 2012;60(25):2683-92.
13. Osnabrugge RL, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, LeReun CM, et al. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. J Am Coll Cardiol. 2013;62(11):1002-12.
14. Goldsweig AM, Tak HJ, Chen LW, Aronow HD, Shah B, Kolte DS, et al. The Evolving Management of Aortic Valve Disease: 5-Year Trends in SAVR, TAVR, and Medical Therapy. Am J Cardiol. 2019;124(5):763-71.
15. Moore M, Chen J, Mallow PJ, Rizzo JA. The direct health-care burden of valvular heart disease: evidence from US national survey data. Clinicoecon Outcomes Res. 2016;8:613-27.
16. Braveman P, Egerter S, Williams DR. The social determinants of health: coming of age. Annu Rev Public Health. 2011;32:381-98.
17. Stronks K, Snijder MB, Peters RJ, Prins M, Schene AH, Zwinderman AH. Unravelling the impact of ethnicity on health in Europe: the HELIUS study. BMC Public Health. 2013;13:402.

18. Weisgrau S. Issues in rural health: access, hospitals, and reform. Health Care Financ Rev. 1995;17(1):1-14.
19. Barreto-Filho JA, Wang Y, Dodson JA, Desai MM, Sugeng L, Geirsson A, et al. Trends in aortic valve replacement for elderly patients in the United States, 1999-2011. JAMA. 2013;310(19):2078-85.
20. Grover FL, Vemulapalli S, Carroll JD, Edwards FH, Mack MJ, Thourani VH, et al. 2016 Annual Report of The Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. J Am Coll Cardiol. 2017;69(10):1215-30.
21. Head SJ, Celik M, Kappetein AP. Mechanical versus bioprosthetic aortic valve replacement. Eur Heart J. 2017;38(28):2183-91.
22. Goldstone AB, Chiu P, Baiocchi M, Lingala B, Patrick WL, Fischbein MP, et al. Mechanical or Biologic Prostheses for Aortic-Valve and Mitral-Valve Replacement. N Engl J Med. 2017;377(19):1847-57.
23. Braunwald E. Aortic Stenosis: Then and Now. Circulation. 2018;137(20):2099-100.
24. Gahl B, Celik M, Head SJ, Vanoverschelde JL, Pibarot P, Reardon MJ, et al. Natural History of Asymptomatic Severe Aortic Stenosis and the Association of Early Intervention With Outcomes: A Systematic Review and Meta-Analysis. JAMA Cardiol. 2020.
25. Minners J, Rossebo A, Chambers JB, Gohlke-Baerwolf C, Neumann FJ, Wachtell K, et al. Sudden cardiac death in asymptomatic patients with aortic stenosis. Heart. 2020;106(21):1646-50.
26. Taniguchi T, Morimoto T, Shiomi H, Ando K, Kanamori N, Murata K, et al. Sudden Death in Patients With Severe Aortic Stenosis: Observations From the CURRENT AS Registry. J Am Heart Assoc. 2018;7(11).
27. Lancellotti P, Magne J, Dulgheru R, Clavel MA, Donal E, Vannan MA, et al. Outcomes of Patients With Asymptomatic Aortic Stenosis Followed Up in Heart Valve Clinics. JAMA Cardiol. 2018;3(11):1060-8.
28. Kang DH, Park SJ, Lee SA, Lee S, Kim DH, Kim HK, et al. Early Surgery or Conservative Care for Asymptomatic Aortic Stenosis. N Engl J Med. 2020;382(2):111-9.
29. Taniguchi T, Morimoto T, Shiomi H, Ando K, Kanamori N, Murata K, et al. Initial Surgical Versus Conservative Strategies in Patients With Asymptomatic Severe Aortic Stenosis. J Am Coll Cardiol. 2015;66(25):2827-38.
30. Genereux P, Stone GW, O'Gara PT, Marquis-Gravel G, Redfors B, Giustino G, et al. Natural History, Diagnostic Approaches, and Therapeutic Strategies for Patients With Asymptomatic Severe Aortic Stenosis. J Am Coll Cardiol. 2016;67(19):2263-88.
31. Nagao K, Taniguchi T, Morimoto T, Shiomi H, Ando K, Kanamori N, et al. Acute Heart Failure in Patients With Severe Aortic Stenosis- Insights From the CURRENT AS Registry. Circ J. 2018;82(3):874-85.
32. Takeji Y, Taniguchi T, Morimoto T, Saito N, Ando K, Shirai S, et al. Transcatheter Aortic Valve Implantation vs. Surgical Aortic Valve Replacement for Severe Aortic Stenosis in Real-World Clinical Practice. Circ J. 2020;84(5):806-14.
33. Takeji Y, Taniguchi T, Morimoto T, Saito N, Ando K, Shirai S, et al. Transcatheter aortic valve implantation versus conservative management for severe aortic stenosis in real clinical practice. PLoS One. 2019;14(9):e0222979.
34. Task Force on Myocardial Revascularization of the European Society of C, the European Association for Cardio-Thoracic S, European Association for Percutaneous Cardiovascular I, Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. Eur Heart J. 2010;31(20):2501-55.
35. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med. 2009;360(10):961-72.

36. Dehmer GJ, Badhwar V, Bermudez EA, Cleveland JC, Jr., Cohen MG, D'Agostino RS, et al. 2020 AHA/ACC Key Data Elements and Definitions for Coronary Revascularization: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Clinical Data Standards for Coronary Revascularization). J Am Coll Cardiol. 2020;75(16):1975-2088.
37. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019;40(2):87-165.
38. Lindman BR, Patel JN. Multimorbidity in Older Adults with Aortic Stenosis. Clin Geriatr Med. 2016;32(2):305-14.
39. Thyregod HG, Holmberg F, Gerds TA, Ihlemann N, Sondergaard L, Steinbruchel DA, et al. Heart Team therapeutic decision-making and treatment in severe aortic valve stenosis. Scand Cardiovasc J. 2016;50(3):146-53.
40. Wolff G, Shamekhi J, Al-Kassou B, Tabata N, Parco C, Klein K, et al. Risk modeling in transcatheter aortic valve replacement remains unsolved: an external validation study in 2946 German patients. Clin Res Cardiol. 2021;110(3):368-76.
41. Capodanno D, Barbanti M, Tamburino C, D'Errigo P, Ranucci M, Santoro G, et al. A simple risk tool (the OBSERVANT score) for prediction of 30-day mortality after transcatheter aortic valve replacement. Am J Cardiol. 2014;113(11):1851-8.
42. Ribeiro HB, Rodes-Cabau J. The multiparametric FRANCE-2 risk score: one step further in improving the clinical decision-making process in transcatheter aortic valve implantation. Heart. 2014;100(13):993-5.
43. Schiller W, Barnewold L, Kazmaier T, Beckmann A, Masseli F, Welz A, et al. The German Aortic Valve Score II. Eur J Cardiothorac Surg. 2017;52(5):881-7.
44. Nishimura RA, O'Gara PT, Bavaria JE, Brindis RG, Carroll JD, Kavinsky CJ, et al. 2019 AATS/ACC/ASE/SCAI/STS Expert Consensus Systems of Care Document: A Proposal to Optimize Care for Patients With Valvular Heart Disease: A Joint Report of the American Association for Thoracic Surgery, American College of Cardiology, American Society of Echocardiography, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2019;73(20):2609-35.
45. Rea CW, Wang TKM, Ruygrok PN, Sidhu K, Ramanathan T, Nand P, et al. Characteristics and Outcomes of Patients With Severe Aortic Stenosis Discussed by the Multidisciplinary "Heart Team" According to Treatment Allocation. Heart Lung Circ. 2020;29(3):368-73.
46. Tchetche D, de Biase C, van Gils L, Parma R, Ochala A, Lefevre T, et al. Bicuspid Aortic Valve Anatomy and Relationship With Devices: The BAVARD Multicenter Registry. Circ Cardiovasc Interv. 2019;12(1):e007107.
47. Herrmann HC, Daneshvar SA, Fonarow GC, Stebbins A, Vemulapalli S, Desai ND, et al. Prosthesis-Patient Mismatch in Patients Undergoing Transcatheter Aortic Valve Replacement: From the STS/ACC TVT Registry. J Am Coll Cardiol. 2018;72(22):2701-11.
48. Langer NB, Hamid NB, Nazif TM, Khalique OK, Vahl TP, White J, et al. Injuries to the Aorta, Aortic Annulus, and Left Ventricle During Transcatheter Aortic Valve Replacement: Management and Outcomes. Circ Cardiovasc Interv. 2017;10(1).
49. Pasic M, Unbehaun A, Buz S, Drews T, Hetzer R. Annular rupture during transcatheter aortic valve replacement: classification, pathophysiology, diagnostics, treatment approaches, and prevention. JACC Cardiovasc Interv. 2015;8(1 Pt A):1-9.

50. Pibarot P, Hahn RT, Weissman NJ, Arsenault M, Beaudoin J, Bernier M, et al. Association of Paravalvular Regurgitation With 1-Year Outcomes After Transcatheter Aortic Valve Replacement With the SAPIEN 3 Valve. JAMA Cardiol. 2017;2(11):1208-16.
51. Pollari F, Dell'Aquila AM, Sohn C, Marianowicz J, Wiehofsky P, Schwab J, et al. Risk factors for paravalvular leak after transcatheter aortic valve replacement. J Thorac Cardiovasc Surg. 2019;157(4):1406-15 e3.
52. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med. 2016;374(17):1609-20.
53. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet. 2015;385(9986):2477-84.
54. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. N Engl J Med. 2019;380(18):1695-705.
55. Makkar RR, Thourani VH, Mack MJ, Kodali SK, Kapadia S, Webb JG, et al. Five-Year Outcomes of Transcatheter or Surgical Aortic-Valve Replacement. N Engl J Med. 2020;382(9):799-809.
56. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. N Engl J Med. 2019;380(18):1706-15.
57. Laborde F, Fischlein T, Hakim-Meibodi K, Misfeld M, Carrel T, Zembala M, et al. Clinical and haemodynamic outcomes in 658 patients receiving the Perceval sutureless aortic valve: early results from a prospective European multicentre study (the Cavalier Trial)dagger. Eur J Cardiothorac Surg. 2016;49(3):978-86.
58. Shehada SE, Elhmidi Y, Mourad F, Wendt D, El Gabry M, Benedik J, et al. Minimal access versus conventional aortic valve replacement: a meta-analysis of propensity-matched studies. Interact Cardiovasc Thorac Surg. 2017;25(4):624-32.
59. Tokarek T, Siudak Z, Dziewierz A, Sobczynski R, Zasada W, Sorysz D, et al. Assessment of quality of life in patients after surgical and transcatheter aortic valve replacement. Catheter Cardiovasc Interv. 2016;88(3):E80-8.
60. Vogt F, Moscarelli M, Nicoletti A, Gregorini R, Pollari F, Kalisnik JM, et al. Sutureless Aortic Valve and Pacemaker Rate: From Surgical Tricks to Clinical Outcomes. Ann Thorac Surg. 2019;108(1):99-105.
61. Vogt F, Pfeiffer S, Dell'Aquila AM, Fischlein T, Santarpino G. Sutureless aortic valve replacement with Perceval bioprosthesis: are there predicting factors for postoperative pacemaker implantation? Interact Cardiovasc Thorac Surg. 2016;22(3):253-8.
62. Lazkani M, Yerasi C, Prakash S, Pershad A, Fang K. Permanent pacemaker implantation and paravalvular leak rates following sutureless aortic valve operations. J Card Surg. 2018;33(12):808-17.
63. Kocher AA, Laufer G, Haverich A, Shrestha M, Walther T, Misfeld M, et al. One-year outcomes of the Surgical Treatment of Aortic Stenosis With a Next Generation Surgical Aortic Valve (TRITON) trial: a prospective multicenter study of rapid-deployment aortic valve replacement with the EDWARDS INTUITY Valve System. J Thorac Cardiovasc Surg. 2013;145(1):110-5; discussion 5-6.
64. Madhavan S, Chan SP, Tan WC, Eng J, Li B, Luo HD, et al. Cardiopulmonary bypass time: every minute counts. J Cardiovasc Surg (Torino). 2018;59(2):274-81.
65. Salsano A, Giacobbe DR, Sportelli E, Olivieri GM, Natali R, Prevosto M, et al. Aortic cross-clamp time and cardiopulmonary bypass time: prognostic implications in patients operated on for infective endocarditis. Interact Cardiovasc Thorac Surg. 2018;27(3):328-35.

66. Ensminger S, Fujita B, Bauer T, Mollmann H, Beckmann A, Bekeredjian R, et al. Rapid Deployment Versus Conventional Bioprosthetic Valve Replacement for Aortic Stenosis. J Am Coll Cardiol. 2018;71(13):1417-28.
67. Powell R, Pelletier MP, Chu MWA, Bouchard D, Melvin KN, Adams C. The Perceval Sutureless Aortic Valve: Review of Outcomes, Complications, and Future Direction. Innovations (Phila). 2017;12(3):155-73.
68. Liakopoulos OJ, Gerfer S, Weider S, Rahmanian P, Zeriouh M, Eghbalzadeh K, et al. Direct Comparison of the Edwards Intuity Elite and Sorin Perceval S Rapid Deployment Aortic Valves. Ann Thorac Surg. 2018;105(1):108-14.
69. Coti I, Haberl T, Scherzer S, Shabanian S, Binder T, Kocher A, et al. Rapid-Deployment Aortic Valves for Patients With a Small Aortic Root: A Single-Center Experience. Ann Thorac Surg. 2020;110(5):1549-56.
70. Hanedan MO, Yuruk MA, Parlar AI, Ziyrek U, Arslan AK, Sayar U, et al. Sutureless versus Conventional Aortic Valve Replacement: Outcomes in 70 High-Risk Patients Undergoing Concomitant Cardiac Procedures. Tex Heart Inst J. 2018;45(1):11-6.
71. Baran C, Durdu MS, Gumus F, Cakici M, Inan MB, Sirlak M, et al. Sutureless aortic valve replacement with concomitant valvular surgery. J Thorac Cardiovasc Surg. 2018;155(6):2414-22.
72. Glauber M, Moten SC, Quaini E, Solinas M, Folliguet TA, Meuris B, et al. International Expert Consensus on Sutureless and Rapid Deployment Valves in Aortic Valve Replacement Using Minimally Invasive Approaches. Innovations (Phila). 2016;11(3):165-73.
73. Lu Y, Wang J, Chen Z, Wei J, Li F, Cai Z. Does Quicker Mean Better? Comparison of Rapid Deployment Versus Conventional Aortic Valve Replacement. Int Heart J. 2020;61(5):951-60.
74. Chang C, Raza S, Altarabsheh SE, Delozier S, Sharma UM, Zia A, et al. Minimally Invasive Approaches to Surgical Aortic Valve Replacement: A Meta-Analysis. Ann Thorac Surg. 2018;106(6):1881-9.
75. Gersak B, Fischlein T, Folliguet TA, Meuris B, Teoh KH, Moten SC, et al. Sutureless, rapid deployment valves and stented bioprosthesis in aortic valve replacement: recommendations of an International Expert Consensus Panel. Eur J Cardiothorac Surg. 2016;49(3):709-18.
76. Puskas JD, Gerdisch M, Nichols D, Fermin L, Rhenman B, Kapoor D, et al. Anticoagulation and Antiplatelet Strategies After On-X Mechanical Aortic Valve Replacement. J Am Coll Cardiol. 2018;71(24):2717-26.
77. Winter MP, Zbiral M, Kietaibl A, Sulzgruber P, Kastner J, Rosenhek R, et al. Normal values for Doppler echocardiographic assessment of prosthetic valve function after transcatheter aortic valve replacement: a systematic review and meta-analysis. Eur Heart J Cardiovasc Imaging. 2018;19(4):361-8.
78. Winter MP, Bartko P, Hofer F, Zbiral M, Burger A, Ghanim B, et al. Evolution of outcome and complications in TAVR: a meta-analysis of observational and randomized studies. Sci Rep. 2020;10(1):15568.
79. Siontis GCM, Overtchouk P, Cahill TJ, Modine T, Prendergast B, Praz F, et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of symptomatic severe aortic stenosis: an updated meta-analysis. Eur Heart J. 2019;40(38):3143-53.
80. Barili F, Freemantle N, Pilozzi Casado A, Rinaldi M, Folliguet T, Musumeci F, et al. Mortality in trials on transcatheter aortic valve implantation versus surgical aortic valve replacement: a pooled meta-analysis of Kaplan-Meier-derived individual patient data. Eur J Cardiothorac Surg. 2020;58(2):221-9.

81. Gleason TG, Reardon MJ, Popma JJ, Deeb GM, Yakubov SJ, Lee JS, et al. 5-Year Outcomes of Self-Expanding Transcatheter Versus Surgical Aortic Valve Replacement in High-Risk Patients. J Am Coll Cardiol. 2018;72(22):2687-96.
82. Barbanti M, Tamburino C, D'Errigo P, Biancari F, Ranucci M, Rosato S, et al. Five-Year Outcomes of Transfemoral Transcatheter Aortic Valve Replacement or Surgical Aortic Valve Replacement in a Real World Population. Circ Cardiovasc Interv. 2019;12(7):e007825.
83. Armijo G, Nombela-Franco L, Tirado-Conte G. Cerebrovascular Events After Transcatheter Aortic Valve Implantation. Front Cardiovasc Med. 2018;5:104.
84. Khatri PJ, Webb JG, Rodes-Cabau J, Fremes SE, Ruel M, Lau K, et al. Adverse effects associated with transcatheter aortic valve implantation: a meta-analysis of contemporary studies. Ann Intern Med. 2013;158(1):35-46.
85. Cubero-Gallego H, Pascual I, Rozado J, Ayesta A, Hernandez-Vaquero D, Diaz R, et al. Cerebral protection devices for transcatheter aortic valve replacement. Ann Transl Med. 2019;7(20):584.
86. Auffret V, Regueiro A, Del Trigo M, Abdul-Jawad Altisent O, Campelo-Parada F, Chiche O, et al. Predictors of Early Cerebrovascular Events in Patients With Aortic Stenosis Undergoing Transcatheter Aortic Valve Replacement. J Am Coll Cardiol. 2016;68(7):673-84.
87. Ghanem A, Dorner J, Schulze-Hagen L, Muller A, Wilsing M, Sinning JM, et al. Subacute Subclinical Brain Infarctions after Transcatheter Aortic Valve Implantation Negatively Impact Cognitive Function in Long-Term Follow-Up. PLoS One. 2017;12(1):e0168852.
88. Nalluri N, Atti V, Munir AB, Karam B, Patel NJ, Kumar V, et al. Valve in valve transcatheter aortic valve implantation (ViV-TAVI) versus redo-Surgical aortic valve replacement (redo-SAVR): A systematic review and meta-analysis. J Interv Cardiol. 2018;31(5):661-71.
89. Webb JG, Murdoch DJ, Alu MC, Cheung A, Crowley A, Dvir D, et al. 3-Year Outcomes After Valve-in-Valve Transcatheter Aortic Valve Replacement for Degenerated Bioprostheses: The PARTNER 2 Registry. J Am Coll Cardiol. 2019;73(21):2647-55.
90. Aziz M, Simonato M, Webb JG, Abdel-Wahab M, McElhinney D, Duncan A, et al. Mortality prediction after transcatheter treatment of failed bioprosthetic aortic valves utilizing various international scoring systems: Insights from the Valve-in-Valve International Data (VIVID). Catheter Cardiovasc Interv. 2018;92(6):1163-70.
91. Dvir D, Webb JG, Bleiziffer S, Pasic M, Waksman R, Kodali S, et al. Transcatheter aortic valve implantation in failed bioprosthetic surgical valves. JAMA. 2014;312(2):162-70.
92. Siu SC, Silversides CK. Bicuspid aortic valve disease. J Am Coll Cardiol. 2010;55(25):2789-800.
93. Kong WK, Regeer MV, Ng AC, McCormack L, Poh KK, Yeo TC, et al. Sex Differences in Phenotypes of Bicuspid Aortic Valve and Aortopathy: Insights From a Large Multicenter, International Registry. Circ Cardiovasc Imaging. 2017;10(3).
94. Roberts WC. The structure of the aortic valve in clinically isolated aortic stenosis: an autopsy study of 162 patients over 15 years of age. Circulation. 1970;42(1):91-7.
95. Grotenhuis HB, Ottenkamp J, Westenberg JJM, Bax JJ, Kroft LJM, de Roos A. Reduced aortic elasticity and dilatation are associated with aortic regurgitation and left ventricular hypertrophy in nonstenotic bicuspid aortic valve patients. J Am Coll Cardiol. 2007;49(15):1660-5.
96. Kim EK, Chang SA, Jang SY, Kim Y, Kim SM, Oh JK, et al. Assessment of regional aortic stiffness with cardiac magnetic resonance imaging in a healthy Asian population. Int J Cardiovasc Imaging. 2013;29 Suppl 1:57-64.
97. Yoon SH, Kim WK, Dhoble A, Milhorini Pio S, Babaliaros V, Jilaihawi H, et al. Bicuspid Aortic Valve Morphology and Outcomes After Transcatheter Aortic Valve Replacement. J Am Coll Cardiol. 2020;76(9):1018-30.

# 14 English summary
# Nederlandse samenvatting

## SUMMARY

**Chapter 1** is a general introduction and gives an overview and outline of this thesis. **Chapter 2** provides an overview of the current results after surgical aortic valve replacement (SAVR). In this study, 4404 consecutive patients undergoing surgical aortic valve replacement were included. In a cohort with ever-increasing comorbidity and complexity over the last 30 years, the trends of short- and long-term survival improved. **Chapter 3** introduces the technical aspect of aortic valve surgery. In this multimedia tutorial, we describe surgical aortic valve implantation using single interrupted annular sutures, the most used technique worldwide. Surgical aortic valve replacement is the standard treatment for patients with aortic valve disease. The choice of valve type translates to postoperative valve function. **Chapter 4** provides an overview of the current rationale for valve choice for aortic valve surgery. This overview discusses the risks and benefits of mechanical and bioprosthetic aortic valves, the current data on the use of mechanical and bioprosthetic valves, and the new developments in aortic valve replacement. One of the complications of aortic valve replacement is postoperative bleeding. **Chapter 5** highlights the importance of anticoagulation-related complications after mechanical aortic valve replacements and the need for newer valves with decreased need for anticoagulation. Surgical aortic valve replacement is the standard treatment for patients with aortic stenosis. The advent of transcatheter aortic valve replacement led to patients being treated which were initially conservatively treated, and the indications for transcatheter aortic valve replacement are expanding. The expanding indications have led to an increase in allocation of TAVR for patients considered low-risk, yet long-term results remain scarce regarding this topic. This is investigated in **Chapter 6**. The increased incidence of younger patients receiving transcatheter aortic valve replacement has resulted in a patient population with an increased bicuspid prevalence to undergo transcatheter aortic valve replacement. The long-term results of patients with bicuspid aortic valves (BAV) undergoing surgical aortic valve replacement is elaborated in **Chapter 7.** Patients with BAV were younger at the time of surgery (59.1 vs. 68.1 years, $p<0.001$) and present with a better cardiovascular risk profile, which even persisted after accounting for age. In patients with BAV, the relative survival in the age-, sex- and calendar year-matched Dutch population is 89.0% after 20-years of SAVR, which is close to that of the general Dutch population. We further elaborate on the specific patient BAV patient population with concomitant aortic surgery in **Chapter 8**. The positive results of the randomized trials lead to widespread enthusiasm around transcatheter aortic valve replacement. However, coronary access post transcatheter aortic valve replacement may be difficult due to the positioning of the transcatheter valve. In **Chapter 9,** we analyzed the incidence of coronary revascularization post-SAVR. The competing cumulative incidence of coronary revascularization was 6.9% at 20-years of follow-up, with a linearized rate

of 6.2 per 1000 patient-years. Patients who already have undergone coronary revascularization before SAVR had the highest risk for post-SAVR coronary revascularization. Gender was not a predictor of revascularization. However, female patients tend to have better short-term outcomes after TAVR. In **Chapter 10**, we analyzed gender-associated differences in patients requiring SAVR. Patients with symptomatic severe AS have an indication for surgical aortic valve replacement. The role of intervention is less evident in patients with asymptomatic severe AS. However, the incidence of asymptomatic patients is underestimated, and patients are misclassified as asymptomatic, yet being symptomatic and lowering the symptom threshold. In **Chapter 11,** we describe the natural history of asymptomatic severe aortic stenosis. In this study, we see an incidence of symptom development of 91.9% before AVR or death, and therefore develop an indication for AVR. We further see a survival benefit of 32 months in patients undergoing AVR during follow-up compared to patients treated conservatively. In **Chapter 12,** we further elaborate on the association of the natural history and the outcomes in patients and substantiate the role of early intervention in patients with asymptomatic severe aortic stenosis. In a systematic review and meta-analysis of 29 studies, we found that there were overall 5 deaths per 100 patients per year during a conservative treatment strategy. In addition, in the 9 trials investigating early intervention in asymptomatic patients with severe AS, early intervention was associated with a significant reduction of all-cause mortality during follow-up (HR, 0.38; 95% CI, 0.25-0.58).

## NEDERLANDSE SAMENVATTING

**Hoofdstuk 1** is een algemene introductie van dit proefschrift. Dit hoofdstuk geeft een overzicht van de huidige ontwikkelingen op het gebied van aortaklepvervanging. In dit hoofdstuk wordt het doel en opzet van dit proefschrift nader toegelicht. In **Hoofdstuk 2** geven wij een overzicht van de huidige resultaten en trends na chirurgische aortaklepvervanging. In deze studie werden 4404 patiënten geïncludeerd die chirurgisch een aortaklepvervanging hebben gehad. Bij een stijgende trend in comorbiditeit over de laatste 30 jaar, zagen we verbeterende trends in korte- en lange-termijn overleving. In **Hoofdstuk 3** geven wij een inzicht in de technische aspect van chirurgische aortaklepvervanging, dit doen we door middel van de 'single interrupted annular sutures', wereldwijd de meest voorkomende techniek voor aortaklepvervanging.

Chirurgische aortaklepvervanging is de therapie van keuze voor patiënten met aortaklep pathologie. De keuze voor klepprothese vertaalt zich in postoperatieve klepfunctie. **Hoofdstuk 4** geeft een overzicht van de huidige inzichten voor klepkeuze bij aortaklepchirurgie. De incidentie van aortaklepvervanging dan wel –implantatie is stijgende. In dit overzicht bediscussiëren we de voor- en nadelen van de mechanische en biologische aortaklepvervanging, de huidige resultaten, toekomstige ontwikkelen.

Een van de complicaties na aortaklepvervanging is het ontstaan van postoperatieve bloeding. **Hoofdstuk 5** belicht het belang van anticoagulatie gerelateerde complicaties na mechanische aortaklepvervanging en de noodzaak voor nieuwere aortakleppen met een verminderde noodzaak voor anticoagulantia gebruik.

Chirurgische aortaklepvervanging is de standaard therapie voor patiënten met AS. Door de ontwikkelingen rondom transcatheter aortaklepvervanging (TAVR), welke heeft geleid tot het behandelen van patiënten die initieel alleen medicamenteus behandelend konden worden. Bovendien heeft dit er toe geleid dat uiteindelijk laag-risico patiënten ook zijn opgenomen in de huidige richtlijnen, echter de lange-termijn resultaten zijn nog schaars. In **Hoofdstuk 6** wordt een vergelijking gemaakt chirurgische en TAVR in laag-risico patiënten door middel van reconstructed Kaplan-Meier curves. Door de stijgende incidentie van jongere patiënten die voor TAVR gaan, heeft dit als gevolg dat de incidentie van patiënten met bicuspide aortakleppen ook een TAVR ondergaan. Derhalve, hebben wij de lange-termijn resultaten van de bicuspide aortakleppopulatie die chirurgische aortaklepvervangingen ondergaan in **Hoofdstuk 7** benoemd. Patiënten met een bicuspide aortaklep waren jonger op het moment van chirurgie (59.1 vs. 68.1 years, $p<0.001$) en presenteerden zich met een beter cardiovasculair risicoprofiel, welke persisteerde na rekening houden met leeftijd. De relatieve overleving in een voor leeftijd-, geslacht- en jaar van operatie gematchte Nederlandse groep was 89.0% 20-jaar na aortaklepvervanging, welk dichtbij de algemene Nederlandse populatie zit. In **Hoofdstuk 8** gaan wij dieper in op de specifieke patiëntenpopulatie met bicuspide aortaklep-

pen en concomitante aortachirurgie. De positieve resultaten van de gerandomiseerde controlled trials. Echter, door de stijging in incidentie van het gebruik van transcatheter aortakleppen, is er een geanticipeerde post-TAVR coronaire access door de positie van de TAVR-klep. In **Hoofdstuk 9** analyseren wij de incidentie van coronaire revascularisatie na SAVR. De cumulatieve incidentie van coronaire revascularisatie is 6.9% na 20-jaar van follow-up in a competing-risk model, met een lineaire ratio van 6.2 per 1000 patienten-jaren. Patiënten die eerder coronaire revascularisatie hebben ondergaan, hebben een verhoogd risico op post-SAVR coronaire revascularisatie. Geslacht was geen voorspeller van de incidentie van coronaire revascularisatie. In **Hoofdstuk 10** analyzeren wij de lange-termijn uitkomsten geassocieerd met geslacht post-SAVR.

Patiënten met symptomatische ernstige AS hebben een indicatie voor aortaklepvervanging. De noodzaak van aortaklepvervanging is minder evident bij patiënten met asymptomatische aortaklepvervanging. De incidentie van asymptomatische patiënten met ernstige AS wordt ernstig onderschat, en de patiënten worden onterecht als asymptomatisch bestempeld. In **Hoofdstuk 11** beschrijven wij het natuurlijk beloop van asymptomatische patiënten met ernstige AS. Hierbij zien wij dat 91.9% van de patiënten symptomen ontwikkelt voor AVR of doodgaan en daardoor een indicatie ontwikkelen voor AVR. Hierin zien wij ook dat patiënten die gedurende follow-up AVR hebben ondergaan een overlevingswinst van 32 maanden hadden ten opzichte van patiënten die geen AVR hebben ondergaan. In **Hoofdstuk 12** gaan wij hier verder op in en associëren het natuurlijk beloop met de uitkomsten in patiënten en substantiëren de rol van eerdere therapiemogelijkheden bij asymptomatische patiënten met ernstige AS. In de systematische review en meta-analyse van 29 studies, zien wij dat de gehele mortaliteit 5 per 100 patiënten per jaar is gedurende conservatieve behandeling. In additie, in de 9 trials die ook naar vroege interventie hebben gekeken in asymptomatische patiënten met ernstige AS, was vroege interventie geassocieerd met een significante reductie van overlijden gedurende de follow-up tegenover conservatieve behandeling (HR, 0.38; 95% CI, 0.25-0.58).

# 15

PhD portfolio
List of publications
Acknowledgements
About the author

| | |
|---|---|
| Erasmus MC Department: | Cardio-Thoracic Surgery |
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| Promotor: | Prof. Dr. A.J.J.C. Bogers |
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| | Year | ECTS |
|---|---|---|
| **Conferences (1.5)** | | |
| Dutch Association for Cardiothoracic Surgery (Maastricht) | 2020 | 1.0 |
| Transcatheter Interventions Online Congress 2021 | 2021 | 0.2 |
| Dutch Association for Cardiothoracic Surgery, voorjaarswebinar | 2021 | 0.3 |
| **Teaching (5.5)** | | |
| Supervising students | 2019-2021 | 2.0 |
| Supervising master students writing master's thesis | 2020-2021 | 3.0 |
| Lecture SAVR versus TAVR in low-risk patients | 2019 | 0.3 |
| Invited lecture on aortic valve surgery (VCMS) | 2021 | 0.2 |
| **General courses (10.3)** | | |
| NIHES Course Biostatistical Methods I: Basic Principles [CC02] | 2019 | 5.7 |
| NIHES Course Biostatistical Methods II: Classical Regression Models [EP03] | 2019 | 4.6 |
| **Academic courses (7.7)** | | |
| OpenClinica Course | 2017 | 0.5 |
| Networked Sciences | 2019 | 0.2 |
| Research integrity | 2019 | 0.3 |
| BROK course | 2020 | 3.0 |
| FCCS course | 2020 | 3.0 |
| ABCDE course | 2020 | 0.5 |
| BLS/PBLS course | 2020 | 0.2 |
| **Courses and seminars (5.0)** | | |
| COEUR - Dilemma's in orgaandonatie | 2019 | 0.1 |
| COEUR - The (un)paved road of heart transplantation | 2019 | 0.4 |
| COEUR - Sex and gender in cardiovascular research | 2019 | 0.5 |
| COEUR - Advanced decision making in vascular care | 2020 | 0.5 |
| COEUR - Ischemic heart disease | 2020 | 0.5 |
| Local scientific meetings department of cardiothoracic surgery | 2019-2020 | 3.0 |
| **Peer review (0.5)** | | |
| Lancet | 2020 | 0.5 |

1. **Outcomes of surgical aortic valve replacement over three decades.**
   Çelik M, Durko AP, Bekkers JA, Oei FBS, Mahtab EAF, Bogers AJJC.
   *J Thorac Cardiovasc Surg. 2021 Apr 28;(21).*

2. **Technique of surgical aortic valve implantation using single interrupted annular sutures.**
   Çelik M, Durko AP, Schouten GN, Bogers AJJC, Mahtab EAF.
   *MMCTS. 2020.*

3. **Mechanical versus bioprosthetic aortic valve replacement.**
   Head SJ, Çelik M, Kappetein AP.
   *Eur Heart J. 2017 Jul 21;38(28):2183-2191.*

4. **Anticoagulation after mechanical aortic valve implantation: is it time to act after PROACT?**
   Çelik M, Durko AP, Head SJ.
   *Ann Trans Med. 2018 Nov;6(Suppl 1):S16.*

5. **Preventing prosthesis-patient mismatch: with the correct valve, with a correct formula, or with both?**
   Durko AP, Çelik M, Head SJ.
   *J Thorac Cardiovasc Surg. 2019 Mar;157(3):e119.*

6. **Mortality in low-risk patients with aortic stenosis undergoing transcatheter or surgical aortic valve replacement: a reconstructed individual patient data meta-analysis.**
   Çelik M, Milojevic M, Durko AP, Oei FBS, Bogers AJJC, Mahtab EAF.
   *Interact Cardiovasc Thorac Surg. 2020 Sep; 31(5): 587-594.*

7. **Differences in baseline characteristics and outcomes of bicuspid versus tricuspid aortic valve in surgical aortic valve replacement.**
   Çelik M, Milojevic M, Durko AP, Oei FBS, Bogers AJJC, Mahtab EAF.
   *Eur J CardioThor Surgery. 2021 Jun 14;59(6):91-1199.*

8. **Surgical Aortic Valve Replacement with Concomitant Aortic Surgery in Patients with Purely Bicuspid Aortic Valve and Associated Aortopathies.**
   Çelik M, Mahtab EAF, Bogers AJJC.
   *J Cardiovasc Dev Disc. 2021, 8(2), 16.*

9. **Coronary revascularization after surgical aortic valve replacement.**
Çelik M, Durko AP, Head SJ, Mahtab EAF, Mieghem NM, Cummins PA, Kappetein AP, Bogers AJJC.
*J Thorac Cardiovasc Surg Open. 3 (2020), pp. 91-101*

10. **Comparative study of male versus female undergoing surgical aortic valve replacement.**
Çelik M, Milojevic M, Durko AP, Oei FBS, Bogers AJJC, Mahtab EAF.

11. **Asymptomatic patients with severe aortic stenosis and the impact of intervention, 10-year outcomes.**
Çelik M, Durko AP, Milojevic M, Oei FBS, Mahtab EAF, Bogers AJJC.
*J Cardiovasc Dev Disc 2021. 8(4), 35.*

12. **The Natural history of asymptomatic severe aortic stenosis and the association of early intervention with outcomes: a systematic review and meta-analysis.**
Çelik M *, Gahl B*, Head SJ, Vanoverschelde JL, Pibarot P, Reardon MJ, Mieghem NM, Kappetein AP, Jüni P**, da Costa BR**. (* and ** equal contribution)
*JAMA Cardiol.* 2020;5(10):1102–1112

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Mevlüt Çelik was born August 8, 1994 in Schiedam, The Netherlands. After graduating Cum Laude from high school in 2012, he started medical school at the Erasmus University Rotterdam, The Netherlands in 2012. During the time of his medical studies, academic involvement also led to the start of his PhD project at the Department of Cardiothoracic Surgery of the Erasmus University Medical Center. He graduated from medical school at the Erasmus University Rotterdam in 2020.

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"When everyone is trying to be something,
be nothing."

*Shams-i Tabrïzï*