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Female Underrepresentation and Higher Mortality in Aortic Valve Replacements Remain. Part 1 - SAVR

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Keywords:

Surgical aortic valve replacement (SAVR); Gender disparities; Women; Risk factors

Abbreviations:

AMI: Acute myocardial infarction; ANOVA: Analysis of variation; AS: Aortic Stenosis; AVR: Aortic valve replacement; CABG: Coronary artery bypass grafting; CPB: Cardiopulmonary bypass; CPR: Central person registry; CR: Cardiac rehabilitation; PPM: Patient prosthesis mismatch; RBC: Red blood cells; SAVR: Surgical aortic valve replacement; IHD: Ischemic Heart Disease; TAVR: Transcatheter aortic valve replacement; VF: Ventricular fibrillation; VT: Ventricular tachycardia; WDHR: West Denmark Heart Registry

1. Abstract

1.1. Background: Aortic valve replacement is second only to coronary artery bypass grafting in number of cardiac surgeries performed annually. Despite an almost equal prevalence of aortic stenosis the referral to surgical aortic valve replacement (SAVR) of females is lower and unexplained, although some refer to differences in risk and outcome. However, still unsolved and the impact of SAVR compared to the population survival remains.

1.2. Methods and Results: Data of 6,708 stand-alone SAVR patients from 2000-2020 was obtained from the mandatory West Denmark Heart Registry. The fraction of females declined gradually from 42.9% in first to 31.8% in the last 5-year period. Females less often received mechanical valves (24% vs. 36%; $p<0.0001$). Females were older but significant more were without comorbidity (47.8% vs. 41.4%; $p<0.0001$). Significant differences were found in most pre-operative parameters, both between valve-types and gender. Raw data implied worse outcome after bioprosthetic compared to mechanical valves but was not different correlating for age and gender. Females more often were treated with dialysis and inotropes. In-hospital and 5-year mortality was significantly higher in females than men while 1-year was marginally higher, but not significant. Women had independent of valve-types consistently lower survival than the background population.

1.3. Conclusion: Female referral for SAVR is still substantially less than men and continuous to fall. Both short- and long-term mortality is higher in females. Female underrepresentation and higher mortality in aortic valve replacements remains.

2. Introduction

Aortic stenosis (AS) is the most common progressive and degenerative cardiac valve disease that necessitates valve replacement [1], making aortic valve replacement (AVR) second only to coronary artery bypass grafting (CABG) in number of cardiac surgeries performed annually [2]. Undoubtedly, surgical aortic valve replacement (SAVR) reduces morbidity and mortality related to aortic stenosis and has been the procedure of choice for younger low to intermediate risk patients [3]. As mechanical prosthesis was associated with a significantly lower risk of reoperation compared to biologic prosthesis, the present recommendation in young low risk patients is a mechanical valve [4]. However, due to the lifelong oral anticoagulants, several centres have moved towards increased use of bioprosthetic valves [5-6].

Significant differences have been described between the genders in incidence, risk, treatment, and outcome of especially IHD [7], but also in severe aortic stenosis [1, 8-11]. Aortic stenosis accounts for more than 40 % of valvular diseases and is reported with equal prevalence in men and women [12]. However, reports show disagreement with approximately only half the number of women treated with SAVR compared to men [9, 13]. It was suggested that this lower referral rate, was likely the result of more unfavourable pre-operative baseline characteristics in women [9] and is expected to change in the future with transcatheter aortic valve replacement (TAVR), showing better outcome and survival in women than men [8, 10, 14].

However, it seems that the TAVR procedure adds to the total number of patients undergoing aortic valve replacement, thereby not significantly reducing the number of patients scheduled for SAVR. Thus, the gender specifics in risk and outcome are still not solved and further the SAVR valve types and impact on survival compared to the background population survival remains.

Using data from the West Denmark Heart Registry (WDHR) during 2000 till 2020, the present study aimed to analyse the various aspects of SAVR treatment strategies with focus on gender difference.

3. Materials and Methods

3.1. Data Source

Data of all adult patients undergoing stand-alone AVR surgery from 2000-2020 was retracted from WDHR, to which reporting has been mandatory for all adult cardiovascular procedures since year 2000. WDHR covers three public and one semi-public cardiac surgery centre, catering approximately 60% of the Danish population. The WDHR holds detailed patient-, risk-, procedure-, care-related data and in-hospital postoperative complications. Data are collected and registered prospectively and is an integral part of clinical practice [15]. Data quality is warranted by automatic validation rules at data entry combined with systematic validation procedures, random spot checks and regular major and minor updates, and data related to this study has been obligatory since 2006. In procedures registered before 2006 data fields were considered as 0 or negative, if any other data was registered on the specific formulas.

Patients submitted to standard SAVR were considered eligible for the study. Patients without valid personal identification number from the Central Personal Registry (CPR), previous cardiac surgery were, together with a small number with incomplete data registration, excluded from the analysis revealing a cohort of 6,708 first time procedures (Figure 1). The study was registered by the Danish Data Protection Agency (1-16-02-455-21). The agency's rules for the use and handling of data were met and written consent is not required for registry-based studies according to Danish legislation.

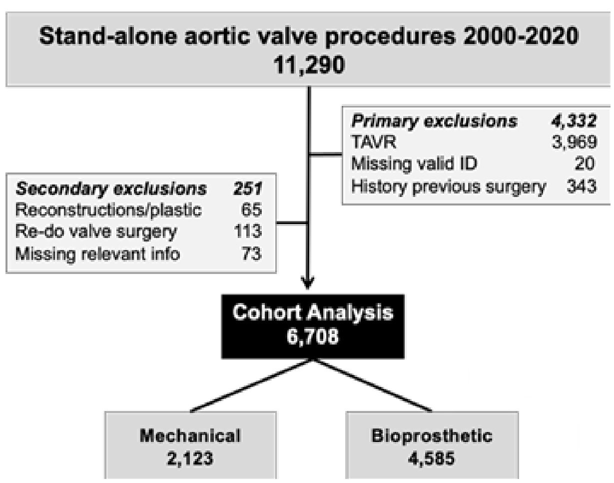


Figure 1: Stand-alone aortic valve procedures from 2000 to 2020 with primary and secondary exclusions.

3.2. Perioperative Procedures

According to hospital protocols, all preoperative cardiac medications, except anticoagulation, were continued until the morning of surgery. Anaesthesia was either based on intravenous propofol or inhalation of sevoflurane together with fentanyl or sufentanil. In the operating room, patients received standard anaesthesiologic monitoring, and routine surgical and cardioprotective techniques were used, including crystalloid or cold blood cardioplegia, closed cardiopulmonary bypass (CPB) systems with surface-modifying additive coated tubing and hollow fibre-membrane oxygenator and heparin coated filters and cardiotomy reservoir. Peroperative transfusion and medication beyond standards and routines were at the discretion of the attending anaesthesiologist and/or surgeon.

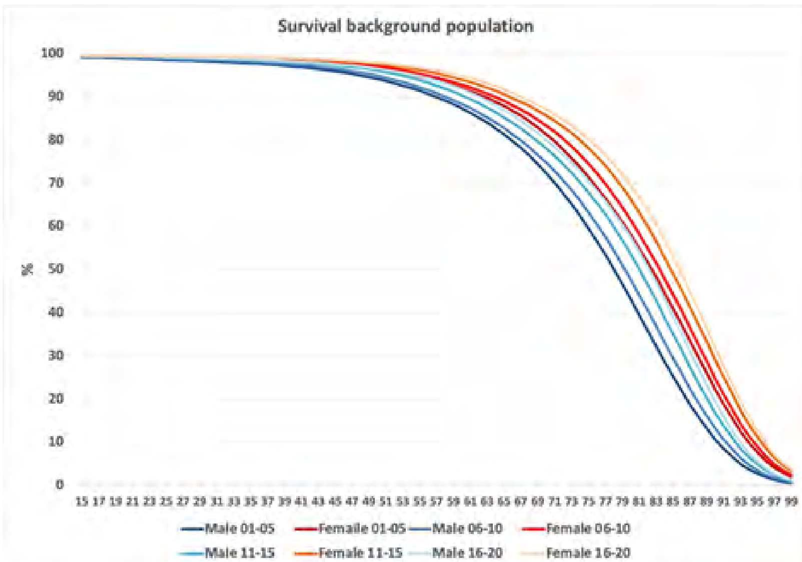
3.3. Factors and Outcome

The analysis was based on valve type, age, gender, comorbidity, and registered perioperative complications, including re-exploration due to bleeding, stroke, acute myocardial infarction, new dialysis, ventricular fibrillation/tachycardia, together with treatments massive blood transfusion (≥ 8 units), inotropes and vasoconstrictors indicating a complicated postoperative path. The comorbidity score was based on the EuroSCORE I [16] retracted the score for age and gender score and supplemented with one point for tablet treated diabetes and two points for insulin treated diabetes.

The primary outcome was all cause mortality. All Danish citizens have a unique civil personal registration (CPR) number assigned at birth and kept throughout life, enabling cross-linking between different health and civil registries. Data on mortality were obtained daily from this system, which has kept updated records of the entire Danish population regarding vital status, date of death, residence, and migration since 1968.

3.4. Background Population Mortality

Due to great differences between men and women in average living age, great changes in population survival in the primary surgical timespan (60-80 years of age) and the relatively large observation time, all patients were assigned the supposed risk of death, founded on the official 5-year life tables from Statistics Denmark (Supplement 1) [17]. Thus, all patients were allocated an expected individual 1- and 5-year mortality, based on the time of surgery, age and gender. Following, the study groups actual mortality can be analyzed against background population mortality in a 1:1 ratio in subgroups of gender, and selected factors in question.



Supplement 1: Population background survival divided on 5-year periods and gender. Survival curves based on one year mortality of the actual ages (15-99 years; Data from Danish Statistics). https://www.dst.dk/en/

3.5. Statistical Analyses

The detailed statistical analysis was primarily based on patients divided on gender, comorbidity, and perioperative complications. Where appropriate data was gathered in time- and outcome groups. Categorical variables were primarily analysed using the $\chi 2$-test. Depending on data-normality longitudinal data was carried out with Mann-Whitney independent test or students-independent t-test and ANOVA or Kruskal-Wallis for comparisons between parameter and subgroups. The analysis of outcomes over time was based on Kaplan–Meier survival curves and compared to the individual assigned population mortality. Analyses were performed with MedCalc® software version 20.008 (Mariakerke, Belgium). A probability value of <0.05 was used to define statistical significance.

4. Results

The WDHR contained 11,290 stand-alone aortic valve procedures from 2000-2020. TAVR (3,969) was not part of detailed final analysis and was excluded, together with 20 foreigners or refugees without a valid CPR-ID preventing follow-up after discharge and 343 with a history of previous surgery. Secondary exclusions was 65 scheduled for reconstruction or homograft, 73 with missing relevant data and 113 re-do valve surgery leaving an eligible cohort of 6,708 first time stand-alone SAVR (Figure 1).

The overall yearly number of stand-alone AVR developed noticeably from 197 in 2000 to 912 in 2020 as shown supplement 2, which also demonstrate height and changes in EuroSCORE during the period. The total number of SAVR was a little higher in early period due to combined CABG and SAVR, which in the first decade was yearly 200-250 and in the last decade 75-150, further enhancing the fall in SAVR in the last 5-6 years. The surgery-, gender-, age- and comorbidity-factors (patient factors) generating the EuroSCORE, demonstrate a stable EuroSCORE in the first decade with slightly increased age factor and diminished comorbidity factor. After introducing of TAVR age factor continued to increase, while the comorbidity stabilized. Despite introduction of TAVR the overall female fraction in AVR did not really change in the observation period being 0.39-0.41 in most years.

The patient characteristics show relatively great differences over time in most registered parameters (Table 1). Although statistically significant, the difference in mean age in SAVR patients was low.

The increasing age factors in supplement 2, the lower number of SAVR and the fall in average age of SAVR patients in the last period, indicate that the oldest AVR patients likely are pushed from SAVR to TAVR.

Significant differences were found in most parameters, both between valve types and gender. Overall mechanical valves and females carried less risk factors and further, females less often received a mechanical valve (24% vs. 36%; p<0.0001, χ2-test).

The fraction of females in SAVR declined gradually from 42.9% in first five-year period to 31.8% in the last 5-year period (Table 1). The comorbidity-score, both with and without diabetes factor, was lower in the last decade than the first 5-years period (13.6% vs. 19.7 %, P<0.001; χ2-test), and further demonstrated by the increasing number of patients without comorbidity over the observation period (P>0.0001; χ2-test; Figure 2). The female group had overall significant more patients without comorbidity (47.8% vs. 41.4%) and less with high comorbidity (3.0% vs. 5.8%; P<0.0001; χ2-test).

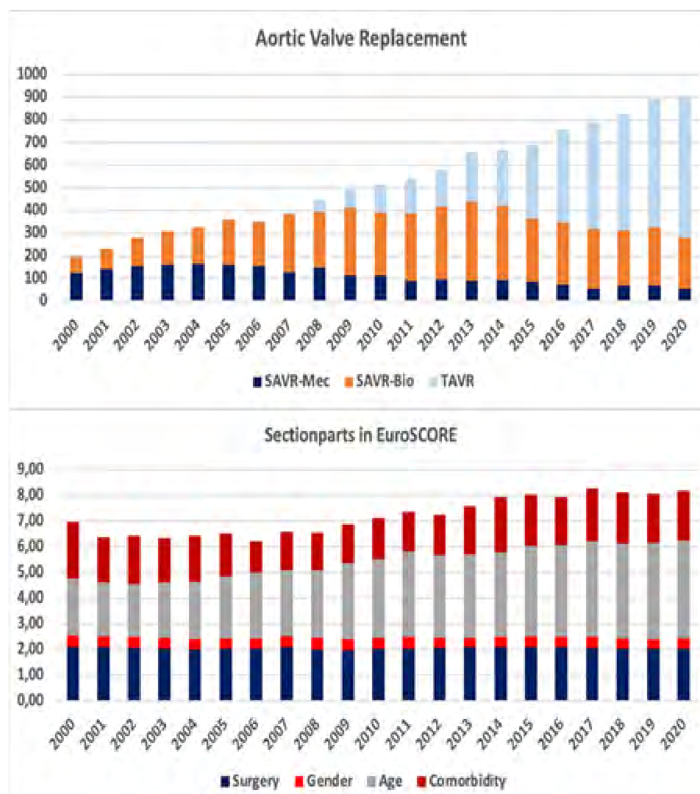
Patients with diabetes as well as patients not discontinuing their antiplatelet drugs increased during the period. The fraction of patient with previous AMI and dialysis before surgery was different between the periods, although without trend (Table 1). Thus, according to EuroSCORE, factors with both positive and negative impact on the outcome changed during the observation time. In general, the risk evaluated by EuroSCORE was significantly higher in females (6.05 vs. 5.77), mainly due to the age and gender score and the “raw” comorbidity in the study group was significantly lower in females (1.21 vs. 1.55) (Table 1).

Comorbidity as well as postoperative complications had significant impact on mortality (Figure 3). Concerning comorbidity, the 1-year mortality increased from 2.9% with none to 17.6% with high comorbidity and the 5-year mortality from 12.1% to 38.1%. The bioprosthetic valve had higher both 1- and 5-year mortality (P<0.001). No difference was found between genders in 1-year mortality (P=0.707), in contrast to 5-year showing higher mortality in females (P=0.002, 2-way ANOVA).

The impact of postoperative complication was more pronounced as 1-year mortality increased from 2.9% with no complication to 56.5% with 3 or more postoperative complications, further increasing to 66.7% after 5-year. The differences in both valve-types and genders were statistically significant both 1- and 5-year mortality.

Postoperative complications are shown in Table 2. Except for higher frequency of postoperative new dialysis and use of inotropes, no difference was found between valve types. Females more often received postoperative dialysis and treated with inotropes. In-hospital and 5-year mortality was significantly higher in females than men, while 1-year was marginal, but not significant higher. Regarding valve type, a significant drop was seen in both actual and population mortality (Figure 4), and although raw data showed a higher in-hospital, 1- and 5-year mortality after bioprosthetic valves (Table 2), correlating to age groups attenuated the difference to not statistically significant (Figure 4).

The actual survival compared to the population survival is shown in Figure 5. Comparing valves, the population survival is very different, following the difference in indication and age at the time of the procedure. The Kaplan-Meier survival plot showed no differences between genders in neither mechanical valves (P=0.493) nor bioprosthetic valves (P=0.759). The difference in population mortality is governed by women’s longer life expectancy and the age differences at the time of the surgery procedure. Women had in both valve types a consistently lower survival than the population. Regarding mechanical valves, men had a lower survival than population, while in bioprosthetic valves the actual survival in men, was better than population after 6-7 years. Considering patients without comorbidity or postoperative complications, the actual survival was consistently better in men, while in women it was only the first eight years (Figure 6).



Supplement 2: Single aortic valve replacement procedures 2000-2020 divided on procedure types (top panel) and the surgery-, gender-, age- and comorbidity-factors generating the EuroSCORE.

Table 1: Preoperative demographic and treatment factors divided on periods and gender. AMI: acute myocardial infarction; NoneP=non-paused; Mech=mechanical valve; Biopro=bioprosthetic valve. Statistics: *) χ2-test, #) ANOVA;!) Students independent t-test.

Period	2000-2005	2006-2010	2011-2015	2016-2020	*p-value*	Male	Female	*p-value*	Mech	Biopro	*p-value*
Number procedures	**1541**	**1715**	**1935**	**1517**		**4135**	**2573**		**2123**	**4584**	
Females fraction	42.9	41	37.5	31.8	*<0.0001*)*				29.5	42.4	*<0.0001*)*
Age (Years)	65.9 ± 12.7	67.7 ± 12.7	68.5 ± 11.8	66.6 ± 11.0	*<0.001#)*	65.6 ± 12.4	70.1 ± 11.7	*<0.001!)*	55.4 ± 11.3	72.8 ± 7.7	*<0.001!)*
EuroSCORE	6.17 ± 2.59	6.06 ± 2.64	6.17 ± 2.61	5.77 ± 2.55	*<0.001#)*	5.77 ± 2.64	6.05 ± 2.32	*<0.001!)*	4.21 ± 2.15	6.91 ± 2.34	*<0.001!)*
Age SCORE	2.22 ± 1.76	2.51 ± 1.84	2.59 ± 1.78	2.22 ± 1.58	*<0.001#)*	2.13 ± 1.71	2.83 ± 1.73	*<0.0001!)*	0.68 ± 1.99	3.2 ± 1.42	*<0.001!)*
Comorbidity Score	1.52 ± 1.68	1.14 ± 1.82	1.21 ± 1.89	1.23 ± 1.93	*<0.001#)*	1.40 ± 1.96	1.06 ± 1.61	*<0.001!)*	1.24 ± 1.24	1.28 ± 1.28	*0.003!)*
Comorbidity Score incl diabetes	1.62 ± 1.74	1.28 ± 1.90	1.38 ± 1.98	1.41 ± 2.01	*<0.001#)*	1.55 ± 2.03	1.21 ± 1.70	*<0.001!)*	1.36 ± 1.36	1.45 ± 1.45	*0.002!)*
Previous AMI	60 (3.9)	103 (6.1)	206 (10.6)	131 (8.6)	*<0.0001*)*	361 (8.7)	139 (5.4)	*<0.001*)*	90 (4.2)	410 (8.9)	*<0.0001*)*
Pre-dialysis	18 (1.2)	38 (2.2)	28 (1.5)	18 (1.2)	*0.019*)*	75 (1.8)	27 (1.1)	*0.027*)*	42 (2.0)	60 (1.3)	*0.021*)*
NoneP-Coagulation inhibitor	1 (0.1)	164 (9.6)	235 (12.1)	282 (18.6)	*<0.0001*)*	448 (10.8)	234 (9.1)	*0.021*)*	118 (5.6)	564 (12.3)	*<0.0001*)*
Pre-arrhythmias	869 (12.5)	693 (12.9)	649 (13.3)	422 (8.8)	*<0.0001*)*	541 (13.1)	265 (210.3)	*0.003*	201 (9.5)	605 (13.2)	*<0.0001*)*
No diabetes	1323 (90.4)	1431 (86.1)	1553 (80.3)	1235 (81.4)	*<0.0001*)*	3390 (83.7)	2153 (85.1)	*0.189**	1811 (85.3)	3731 (81.4)	*<0.0001*)*
New/Diet treatment	30 (2.0)	32 (1.9)	42 (2.2)	19 (1.3)		23 (0.6)	9 (0.4)		29 (1.4)	94 (2.1)	
Tablet treatment	59 (4.0)	106 (6.4)	181 (9.4)	133 (8.8)		168 (4.2)	100 (4.0)		74 (3.5)	194 (4.2)	
Insulin treatment	48 (3.3)	70 (4.2)	83 (4.3)	67 (4.4)		300 (7.4)	179 (7.1)		113 (5.3)	366 (8.0)	
Underweight (< 18.5)	34 (3.0)	22 (1.3)	29 (1.5)	16 (1.1)	*<0.0001*)*	29 (0.8)	72 (3.1)	*<0.0001*)*	20 (0.9)	81 (1.8)	*0.0002*)*
Normal Weight (18.5-24.9)	454 (40.6)	584 (35.5)	609 (32.3)	478 (32.5)		1197 (31.8)	928 (39.4)		626 (29.5)	1499 (32.7)	
Overweight (25.0-34.9)	578 (51.7)	944 (57.4)	1126 (59.8)	868 (59.0)		2343 (62.2)	1174 (49.9)		1042 (49.1)	2474 (54.0)	
Heavy overweight (>35)	53 (4.7)	94 (5.7)	120 (6.4)	108 (7.3)		195 (5.2)	180 (7.7)		149 (7.0)	226 (4.9)	
Mechanical valve	817 (53.0)	563 (32.8)	431 (22.3)	312 (20.6)	*<0.0001*)*	1496 (36.2)	627 (24.4)	*<0.0001*)*			
Bioprosthetic valve	724 (47.0)	1152 (67.2)	1504 (77.7)	1205 (79.4)		2639 (63.8)	1946 (75.6)				

Table 2: Postoperative events divided on valve type and gender. VT/VF=ventricular tachycardia/fibrillation; RBC=red blood cells; Mech=mechanical; Biopro=bioprosthetic; SAVR=surgical aortic valve replacement. All statistics χ2-test.

Postoperative event	Mechanical			Bioprosthetic			All SAVR					
	Male	Female	*p-value*	Male	Female	*p-value*	Mech	Biopro	*p-value*	Male	Female	*p-value*
Re-exploration	1,87	2,55	*0.316*	1,48	1,54	*0.859*	2,07	1,51	*0.093*	1,62	1,79	*0.603*
Stroke	1,40	0,96	*0.402*	1,67	1,80	*0.734*	1,27	1,72	*0.168*	1,57	1,59	*0.944*
AMI	2,81	2,55	*0.742*	1,97	2,47	*0.255*	2,73	2,18	*0.167*	2,27	2,49	*0.572*
New Dialysis	1,07	1,75	*0.199*	2,01	2,72	*0.111*	1,27	2,31	*0.045*	1,67	2,49	*0.019*
VT/VF	0,80	0,48	*0.415*	0,61	0,41	*0.368*	0,71	0,52	*0.358*	0,68	0,43	*0.192*
RBC ≥ 8 units	1,07	2,07	*0.069*	1,93	2,01	*0.861*	1,37	1,96	*0.085*	1,62	2,02	*0.226*
Inotropes	14,30	12,12	*0.187*	19,29	15,84	*0.025*	13,66	17,82	*<0.0001*	17,48	14,93	*0.006*
Total events	13,44	10,37	*0.051*	14,13	13,78	*0.738*	12,53	13,98	*0.105*	13,88	12,95	*0.277*

Events incl Inotropes	24,06	18,98	*0.011*	28,12	24,63	*0.008*	22,56	26,64	*0.0004*	26,65	23,25	*0.002*
Re-SAVR	1,87	2,55	*0.316*	1,48	1,54	*0.859*	2,07	1,51	*0.093*	1,62	1,79	*0.603*
In-hospital/30-day mortality	1,00	2,23	*0.026*	2,80	3,70	*0.088*	1,37	3,18	*<0.0001*	2,15	3,34	*0.003*
1-year mortality	3,07	3,83	*0.376*	6,18	6,22	*0.995*	3,30	6,20	*<0.0001*	5,05	5,64	*0.3*
5-year mortality	9,37	11,47	*0.264*	22,13	22,60	*0.98*	10,01	22,34	*<0.0001*	17,17	19,80	*0.015*

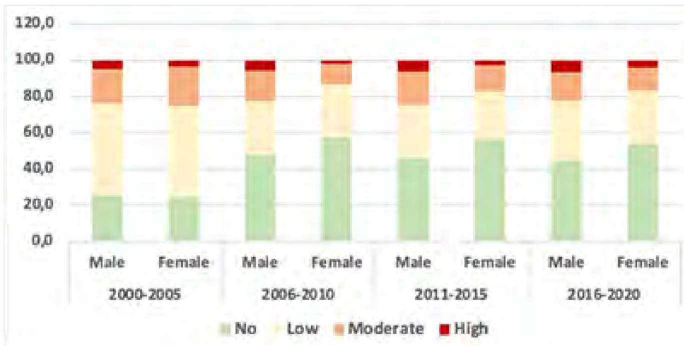


Figure 2: The comorbidity-scores including diabetes factor divided on periods and gender.

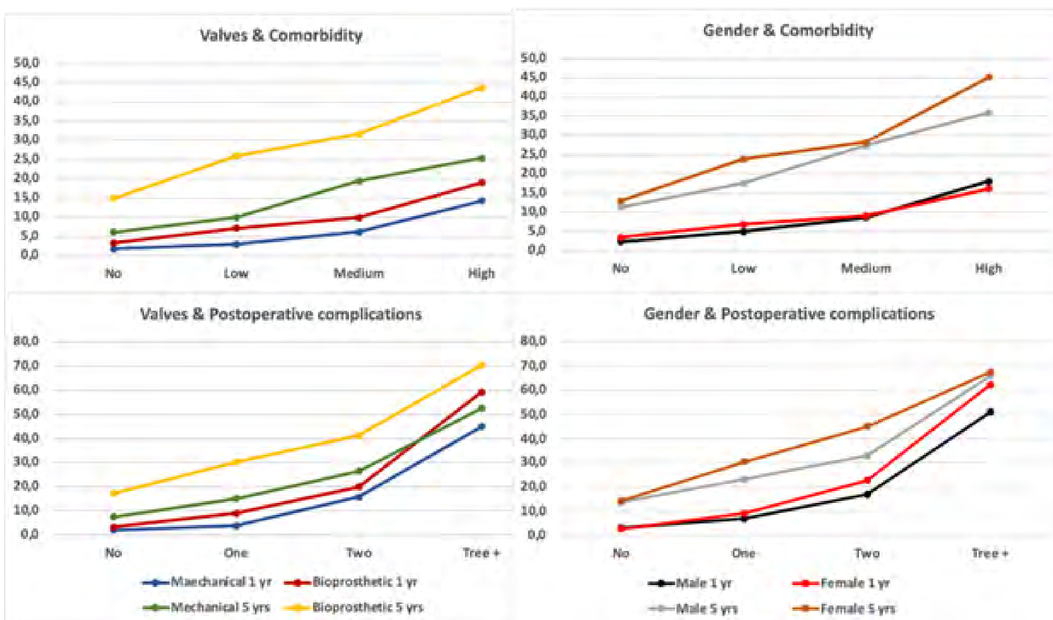


Figure 3: 1- and 5- year mortality divided comorbidity (upper panels), postoperative complications (lower panels), valve types (left panels) and gender (right panels). Significant differences in 1- and 5-year mortality between both comorbidity groups (P<0.001) and postoperative complications (P<0.001). Significant differences in 1- and 5-year mortality in valve types, both comorbidity (P<0.001) and postoperative complications (P<0.001). No difference between genders regarding comorbidity in 1-yr mortality (P=0.707). Significant difference in comorbidity in 5-year mortality (P=0.002). Significant differences in gender and postoperative complications both 1-yr (P<0.001) and 5-years (P=0.037), all 2-way ANOVA

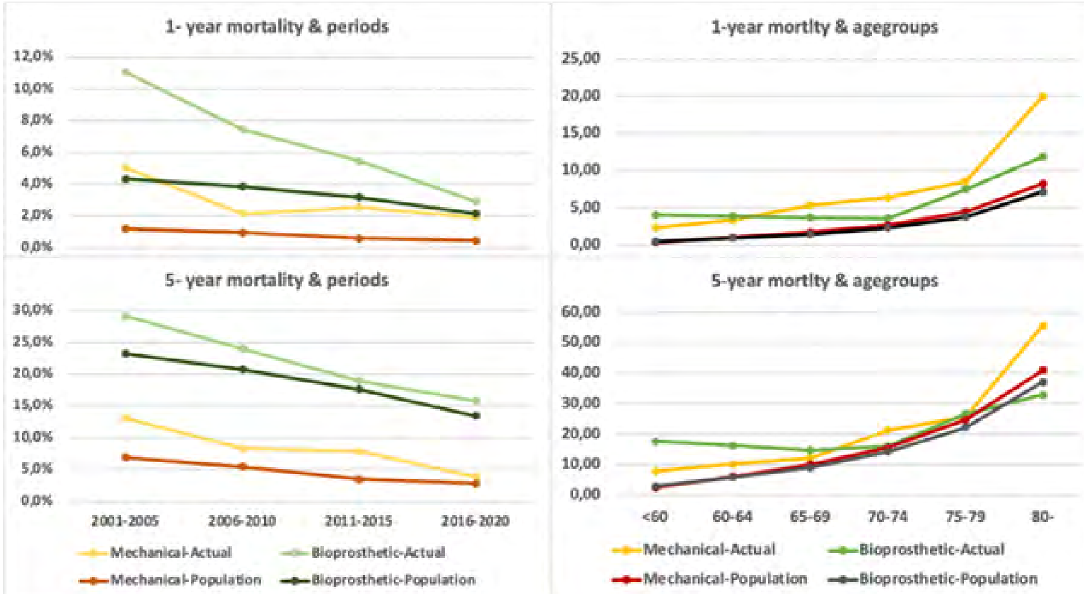


Figure 4: 1- and 5- year actual and population background mortality divided on valve types and periods (left panel) and age-groups (right panel). Periods: Both periods and valve types significantly different in 1- and 5-year actual mortality (P<0.001). Age-groups: No difference between valve-types in 1-year (P=0.094) and 5-year (P=0.552) while differences in age-groups 1-year (P=0.004) and 5-year (P<0.001). Background mortality different all curves (P<0.001), All 2-way ANOVA

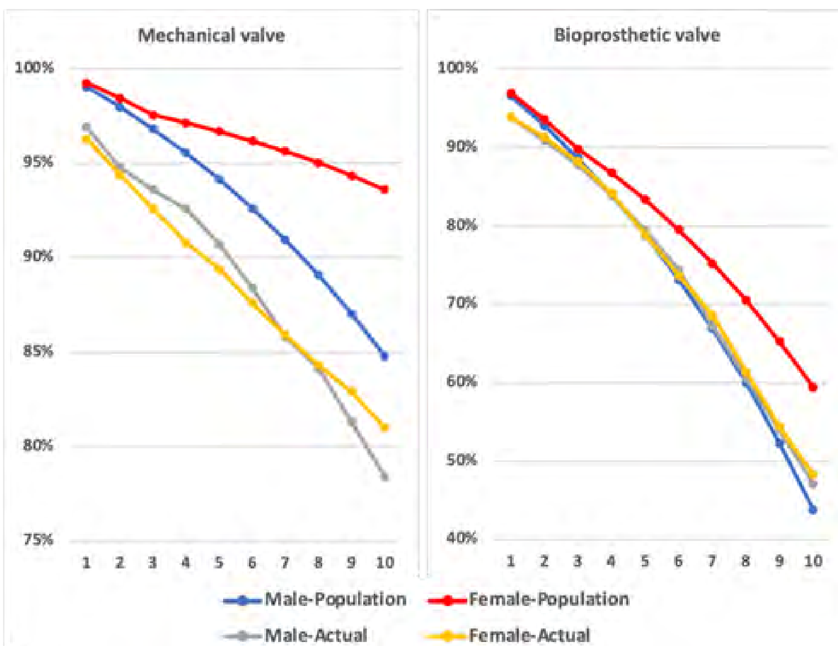


Figure 5: Actual and population 10-year survival. Neither men nor women actual survival approached the population survival in the 10 years period. Kaplan-Meier survival plot showed no mortality differences in gender in Mechanical valve (P=0.493) or Bioprosthetic (P=0.759). The difference in population mortality is due to women's longer living time and the age differences at surgery procedure.

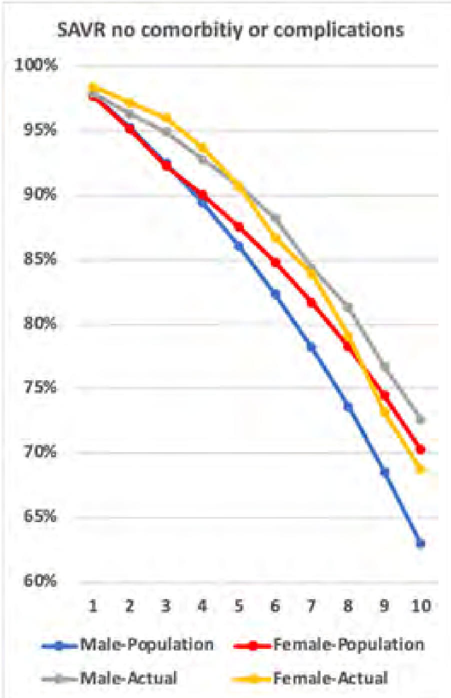


Figure 6: Actual and population 10-year survival of SAVR procedures in patient with no comorbidity and no postoperative complications. Kaplan-Meier survival plot showed no mortality differences in gender (P=0.140). Initially both men and women had better survival than the population survival. Men continued a better survival after 10 years, while women after 8 years had lower survival than population.

5. Discussion

The primary finding was decreasing fraction of females subjected to SAVR. Females were older, had significant higher portion with either underweight or heavy overweight, but with lower comorbidities including diabetes compared to men. Regarding outcomes, females more often required treatment with inotropes and dialysis, and additionally had a higher in-hospital, as well as 5-year mortality compared to men. The valve choice changed with less mechanical valve implantations - 53.0% in first period to 20.6% in the last.

Although inconclusive, publications have shown equal prevalence of AS in men and women [10, 12, 18] the utilization of SAVR is mostly consistently higher in men compared to women [12-14], though higher ratios in females are also seen [19]. Several plausible explanations are postulated in the existing literature. Disparity in the incidence of aortic valve disease has been explained by 2-fold higher risk of development of AS in men than in women [20], but although the general higher male representation, a nationwide American study of 113,847 hospitalized patients admitted with aortic valve disorder, showed a less pronounced disparity with a male ratio of 55.1% [21]. A Swedish study was nearer to parity as men constituted 52% of all newly diagnosed patients with aortic stenosis [22] and further to higher female representation in a smaller Canadian study with 52% females [19] to a large Scottish registry of 19,733 patients with 53.2% females [23].

In contrast, the female fraction for SAVR from our well-defined uptake area (with all treatments registered), declined from 42.9% in the first period to 31.8% in 2016-2020. The decline, combined with overall constant female fraction in AVR is likely governed by preference to TAVR in an attempt to reduce the female higher risk of mortality and complications observed in SAVR [11, 14]. Additionally, the risk of patient prosthesis mismatch is higher in females, which could favour TAVR [24]. Regarding disparity in referral for testing, it was revealed in previous studies that, women with AS were less likely to be seen by a specialist and less likely to be referred for testing [13], which hardly should be the case in our health care system with free and uniform health surveillance and treatment. However, analysis of basic data from our registry showed that, of all 269,164 first entries of any cardiovascular procedures 59.5% were men, and regarding referral to any invasive or surgical cardiovascular procedure 51.4% of men compared to only 29.6% of women were submitted, giving the big overall lower female fraction for SAVR. This observation may thus support some barriers in both pre- and in-hospital handling.

The discrepancy can further be underlined by the fact, that the mortality due to cardiovascular causes is almost identical in Denmark. Women hold average 49.7% of deaths during the last 15 years (2007-2021), with men 228 and women 223 deaths of cardiovascular reasons per 100,000 inhabitants per year [17].

The speculation of underrepresentation of females for SAVR has been previously substantiated by observations of higher age and comorbidity i.e., diabetes, hypertension, atrial fibrillation, and anaemia but lower prevalence of i.e., ischaemic heart disease (IHD), peripheral arterial disease as well as renal disease [8, 10]. Females in our study were older and had less IHD, based on lower previous acute myocardial infarction and less often preoperatively dialysed, but contrary to some of the findings, females caried less registered possible risk factors and comorbidity (Table 2).

The findings of higher proportion of females receiving a bioprosthetic valve in our study can mostly be explained by the higher age. The recommendations of valve types in AVR have changed since the guidelines in 2014 [3] to 2020 [6] allowing higher proportion of bioprosthetic valves compared to mechanical. The last guidelines suggest that patients less than 50 years of age should receive a mechanical valve, both options are considered valuable for those between 50 and 65 years and for patients beyond 65 years a bioprosthetic valve is recommended [6]. In our uptake area the shift seems to have been a little earlier. In the early period, 97.8% of patients received a mechanical valve which decreased to 85.6% in the last period, which further great difference as higher fraction of males received mechanical (87.3% vs 78.3). In patients above 65 years, there is a more uniform handling as more than 99 % in both males and females received a bioprosthetic valve.

The change in handling might be challenged if just following the raw mortality as this seem considerable higher than mechanical

(Table 2) but analysing periods with compensation for age and the higher female fraction of bioprosthetic valves, there is no difference in mortality between mechanical and bioprosthetic valves (Figure 4).

The analysis further revealed that, females had higher postoperative complications and higher in-hospital mortality. The females in our analysis received higher proportion of bioprosthetic valves which have higher inherent risk of severe patient prosthesis mismatch (PPM). Through previous studies, it has been observed that, PPM after bioprosthetic SAVR resulting in residual left ventricular outflow tract obstruction and persistent transvalvular gradients [25] is followed by longer intensive care unit and hospital lengths of stay [26] and significantly higher early and late mortality. However, although intensive care time in our cohort was higher in mechanical valves (39.6 vs 37.1 hours) and females (39.8 vs 36,7 hours), an association between mortality and possible PPM cannot be denied. On the same grounds, the prosthesis mismatch may offer challenges in the immediate postoperative period with episodes of hemodynamic disturbances. Higher need of inotropes and increased incidence of need of dialysis in the postoperative period in women can be attributed to the altered anatomy secondary to prosthesis mismatch. Further, higher proportion of women in our study had extremes of weights, which may contribute to the negative outcome after SAVR in women compared to men [27], as extremes of body weight and following altered cardiac structures, offer significant challenges with technically more demanding procedures.

Further, it is interesting to observe that, the overall EuroSCORE in our study (females 6.05 vs males 5.77) is relatively high compared to other studies, although the marginal difference is in line with other studies [28] and thus the different nature of the aortic valve disease in men and women is likely the cause of the higher postoperative mortality in females.

One confounding factor which can have etiological significance for the higher mortality amongst women seem to be the specific clinical and pathophysiological features in myocardial adaptation following SAVR, resulting in more hypertrophic hearts [29], which further can be enhanced by the modulating impact of oestrogens [30]. However, higher mortality in females in the presence of similar comorbidities in both genders in our study opens hunt to explore further confounding factors apart from type of valve, age, and extremes of weights.

One of the important factors which decide outcome of cardiac surgery is post operative cardiac rehabilitation (CR) which has significant impact on restitution and survival [31]. The benefits from rehabilitation programs usually accomplish within weeks and thus, all cardiac patients might be selected for enrollment in CR programs adapted to physical and psychological conditions. However, through a nationwide survey it was found that, women were less likely than men to enroll in CR following myocardial infarction or CABG [32]. Further, patients older than the age of 65, and particular women were generally less likely to enroll in CR programs [33] underlined by a systematic review revealing that, women reported multilevel barriers for non-participation and dropouts from CR programs [34]. This may also be actual in our cohort despite the uniform health and social care system in Denmark with probably less logistic and personal barriers, which could speculate the difference in short- and long-term mortality.

Several studies claim the result of SAVR is good or excellent, but relatively few compare the survival with a matched or background population. A large cohort study of isolated AVR claimed that the long-term survival after open AVR was excellent, with a survival in patients older than 70 years matching a similarly aged US population [35] and another study showed up to 8 years comparable to a matched general population [36]. However, especially in younger patients, the conclusion was a suboptimal survival compared to age and gender matched population [37], which agrees with our younger patients receiving a mechanical valve, who never catch up with the population survival (Figure 5). In the older patients receiving a bioprosthetic valve men showed 5-6 years after surgery a better survival than the population, while females never catch up. These findings agree with similar pattern of gender differences in our study of CABG patients [38], but promising, low risk patients without postoperative complication has a survival in men continuously better and for females the first 7-8 years compared to background population.

5.1. Strengths and Limitations

The authors had full access to all procedure data registered in the WDHR and declare accountability for the data integrity and analysis.

The primary strengths of this study are the use of data from well-established reporting and database system founded on mandatory and obligatory prospectively reported data from all institution in a fixed uptake area. The large cohort with detailed data and complete follow-up on all patients undergoing cardiac surgery during more than 2 decades allows robust estimations of results and adverse events in patients scheduled for SAVR.

However, the retrospective evaluation has intrinsic bias and conveys possible confounders, but since registrations are mandatory and outcomes can be accounted for in all included patients, the possible effect is attenuated. Nevertheless, our study has inherent limitations, as we cannot discard the non-randomized nature and possible effects of missing covariates, which potentially increase the risk of confounding.

Both preoperative evaluation, indication together with surgical and anaesthesiological policies and practice have changed over the observation time, but the treatment in Denmark is generally very uniform, and due to the education system, all doctors are trained in more than one centre.

6. Conclusion

The number of females referred for SAVR is still far less than men, and both the short- and long-term mortality is still higher in females. Although the mortality seems higher after bioprosthetic the correlation with age groups diminish the difference to none.

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