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Temporal trends and socioeconomic differences in treatment and mortality following a diagnosis of aortic stenosis

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ABSTRACT

Aims: This study aims at determining the temporal trends and the socioeconomic differences in treatment and mortality following a diagnosis of aortic stenosis.

Methods and results: A total of 45,026 patients with a first-time diagnosis of aortic stenosis were identified in the Danish National Patient Registry in the period 2000–17. The risk of AVR within the first year after diagnosis decreased (OR = 1.84 in 2000–02 compared to 2015–16) and the risk was lower in the low-level educational group (OR = 0.85) and in the medium-level group (OR = 0.94) compared to high-level education. The risk of death after AVR within the first year decreased (OR = 2.25 in 2000–02 compared to 2015–16) and the risk was higher in the low-level educational group (OR = 1.32) and in the medium-level group (OR = 1.28) compared to high-level education. The risk of death within the first year after diagnosis, for those patients who did not get an AVR during the follow-up, decreased (OR = 3.08 in 2000–02 compared to 2015–16) and the risk was higher in the low-level educational group (OR = 1.21) and in the medium-level group (OR = 1.10) compared to high-level education.

Conclusion: Since 2000 there has been a decrease in both AVR treatment rate, mortality rate after AVR and mortality rate in patients not receiving AVR. For patients with lower-level education there is lower AVR treatment rate, higher mortality rate after AVR and higher mortality rate in patients not receiving AVR.

1. Introduction

Aortic stenosis is the most common valvular heart disease and it is primarily a disease of the elderly [1–3]. The prevalence is estimated to be 2% in people over 65 years [4]. With the ageing of the western populations, the burden of aortic stenosis is expected to increase [4–9]. The majority of aortic stenosis is degenerative and shares risk factors with those of atherosclerosis [7,10–15], e.g. hypertension, advanced age, smoking, metabolic syndrome, hyperlipidemia, obesity, diabetes and being male. Aortic stenosis is often characterized by a long, asymptomatic phase in which the mortality is rather low [16,17] followed by a significantly higher mortality after symptom onset. For patients with severe aortic stenosis or patients with onset of symptoms, conservative management is not an option and the only treatment is aortic valve replacement (AVR) [17]. Surgical aortic valve replacement (SAVR) has been the standard procedure for many years. With the emergence of transcatheter aortic valve replacement (TAVR) in the last two decades, treatment options for the elderly and more frail patients have improved distinctly [3,18,19]. AVR is associated with postoperative morbidity and mortality, and the timing of treatment is therefore essential in the management of aortic stenosis [18,20,21].

The increasing incidence and prevalence of aortic stenosis leads to more patients potentially eligible for AVR [5,22,23]. During the last two decades there has been a decline in mortality rates after AVR, and patient comorbidity and risk factor profiles have improved [24–27]. The annual number of AVR has increased [8,24,28] but the temporal trends in AVR treatment rates are not known on a population-level.

It is well established that there is an accumulation of lifestyle-related risk factors resulting in higher incidence, morbidity and mortality among people with lower socioeconomic status (SES) [29–32]. Since aortic stenosis shares risk factors with those of other non-communicable diseases such as atherosclerosis, one could assume that the association is also present in the treatment and mortality of aortic stenosis. The results are conflicting, with several studies finding no SES differences in treatment or mortality rates [33–35], while other studies have found a small negative effect of low SES on risk of

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[1] All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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treatment [36] and long-term survival [37,38]. Common for all the mentioned studies is the lack of data on individual SES, since all information on SES is area-based.

Despite the increase in the burden of disease from aortic stenosis, it is not well-established if there are socioeconomic differences in treatment rate and mortality rate of aortic stenosis [39]. Furthermore, studies based on surgical registries exclude the patients that are diagnosed with aortic stenosis but die without AVR [40]. We therefore undertook a registry-based study on the entire Danish population between 30 and 79 years of age. The aim of the study is to examine temporal trends from 2000 to 17 and socioeconomic differences in

1. Time from diagnosis to AVR
2. Time from AVR to death
3. Time from diagnosis to death without AVR

2. Methods

2.1. Registries

In Denmark, every person has a unique social security number, making it possible to link nationwide registries. The Danish National Patient Registry (NPR) is a nationwide registry that covers all hospital-based contacts in the public as well as private Danish healthcare sector [41]. Since 1978, the NPR has covered all admissions, and since 1995, the NPR has also covered all outpatient and emergency room contacts. From the NPR we have obtained information on patients with an aortic stenosis diagnosis as well as their comorbidities using each person's unique personal registration number. Information on surgeries and other procedures were also found in the NPR.

Information on vital status was obtained from the Central Population Register [42].

From Statistics Denmark we have obtained information on the highest attained education [43], because we used education as a proxy for socioeconomic status. We have almost complete information on the highest attained education for the entire study period up to the age of 79.

2.2. Study population

The study population was defined as all Danish citizens, aged 30 to 79 at the time of diagnosis in the 2000 to 2017 period, with one of the following ICD10-codes I35.0, I35.2 or I35.8 as the primary or secondary diagnosis. We included both inpatient and outpatient first-time contacts. Exclusion criteria were patients diagnosed with aortic stenosis in the period between 1995 and 1999. In Denmark, surgeries are classified in a Danish version of the NOMESCO Classification of Surgical Procedures [44]. All procedures with a KFM code (surgery on the aortic valve) were included. We included detailed information on the type of procedure to ensure that we could distinguish between SAVR (surgical aortic valve replacement) and TAVR (transcatheter aortic valve replacement). The Charlson comorbidity index was calculated to enable confounder control and to control for the patients' pre-existing comorbidity at time of diagnosis and treatment.

The periods were divided into categories of 3-year periods: 2000–2002, 2003–2005, 2006–2008, 2009–2011, 2012–2014 and 2015–2017. Age was divided into three age groups: 30–59, 60–69 and 70–79. The Charlson comorbidity index was grouped into three groups: 0 points, 1 to 2 points and 3+ points. The highest attained education was also divided into three groups: low-level (primary education), medium-level (upper secondary school and vocational training) and high-level (higher education e.g. Bachelor, Master, PhD).

2.3. Statistical analysis

We followed each patient from the time of diagnosis until death or December 31, 2017, whichever came first. AVR was defined as either SAVR or TAVR. We analyzed the following three transitions: 1) from diagnosis to AVR; 2) from AVR until death; 3) from diagnosis until death, censoring patients with AVR at time of AVR. We analyzed 1-year risk using logistic regression and 5-year risk using Cox proportional hazards models. The excess risk for each period and educational group was calculated controlling for sex, Charlson comorbidity index and age. We used 5% as level of significance. All analysis was performed using SAS 9.4 (SAS Institute, Cary, North Carolina, USA).

2.4. Ethics

The study is approved by The Danish Data Protection Agency, journal number 2015-57-0008.

3. Results

We identified 45,026 patients between the age of 30 and 79 years with a first-time diagnosis of aortic stenosis in the period 2000–17 (Table 1). We observed most patients in the oldest age groups, more men than women, and an increase in number of patients over time. Most patients were from the lowest educational group and most patients had a low Charlson score.

The crude proportion of patients treated with AVR within the first year from diagnosis declined over time (Table 1). We observed more frequent AVR within the first year for the younger age groups and for men. The crude proportion of patients treated with AVR within the first year from diagnosis increased with increasing educational level and decreased with increasing Charlson score.

For the crude proportion of death within the first year of diagnosis, we observed the highest rates at the beginning of the period, the oldest age groups, men, low and medium-level education and medium and high Charlson score (Table 1).

We identified 13,861 patients, who received AVR at some point during the study period (Table 1). The crude number of AVR procedures increased over time and AVR was more frequent for the oldest age groups, men, lower educational levels, and lower Charlson scores. Over 90% of all procedures were SAVR, and less than 10% were TAVR. Since 2000, the crude proportion of deaths within the first year after AVR decreased. There were no differences between men and women. The death proportion within the first year was higher among the oldest age groups, the lower-level educational groups and the higher Charlson groups. The death proportion within the first year was a little higher for TAVR than for SAVR.

The risk of treatment with AVR decreased over the study period, both within one and 5 years after diagnosis (Table 2). The risk of AVR declined steadily over the periods. The risk of AVR within the first year from diagnosis declined from OR = 1.84 in the first period to OR = 1 in the last period. The risk of AVR within 5 years from diagnosis showed a similar pattern with HR = 1.79 in the first period and HR = 1 in the last period. The risk of treatment with AVR within the first year was lower in the low-level educational group (OR = 0.85) and in the medium-level group (OR = 0.94) compared to high-level education (Table 2). The hazard ratio of AVR within 5 years from diagnosis showed the same educational pattern. The effects of period and educational level were highly significant. The estimates of the confounders (sex, age group, and Charlson) can be found in the Supplementary Table A.

The risk of death following AVR decreased over the study period, both within 1 and 5 years after AVR (Table 3). The risk of dying following AVR declined steadily over the periods. The mortality risk within the first year from AVR declined from OR = 2.25 in the first period to OR = 1 in the last period. The mortality risk within 5 years from AVR showed the same pattern with HR = 1.65 in the first period and HR = 1 in the last period. The risk of death within 1 year after AVR (Table 3) were higher in the low-level educational group (OR = 1.32) and in the medium-level group (OR = 1.28). The effect of education was significant. The hazard ratio of dying within the first 5 years after AVR showed

Table 1
Baseline characteristics of the study population.

		First-time AS diagnosis ($N = 45{,}026$)	AVR within 1 year from diagnosis ($N = 9578$)	Death within 1 year from diagnosis ($N = 3785$)	AVR[b] ($N = 13{,}861$)	Death within 1 year after AVR ($N = 1065$)
		N	%	%	N	%
Period	2000–2002	4553	25.8	12.9	1133	11.2
	2003–2005	6151	26.4	10.1	2012	9.5
	2006–2008	6822	24.7	9.6	2233	8.3
	2009–2011	7971	22.1	8.2	2547	8.0
	2012–2014	9521	19.4	7.4	3001	6.5
	2015–2017[a]	10,008	16.3	6.3	2935	6.2
Age (years)	30–59	6517	25.8	3.9	2103	4.2
	60–69	12,800	24.3	6.4	4229	6.1
	70–79	25,709	19.9	11.2	7529	10.1
Sex	Women	18,208	17.6	8.1	4552	7.7
	Men	26,818	25.1	9.2	9309	8.1
Education	Low-level	20,277	20.3	10.2	5782	9.0
	Medium-level	16,380	23.2	8.1	5238	7.7
	High-level	7296	24.5	6.3	2500	5.8
	missing	1073	22.5	8.1	341	8.5
Treatment type	SAVR	n/a	n/a	n/a	12,546	7.7
	TAVR	n/a	n/a	n/a	1315	11.0
Charlson score	0 points	28,735	23.9	4.4	7729	4.4
	1–2 point(s)	11,699	20.3	13.1	4359	9.9
	3+ points	4592	15.0	24.3	1773	18.4

[a] Due to lack of follow-up time for patients diagnosed in 2017, the period is 2015–2016 for 1-year surgery and death proportion.
[b] AVR population consists of all patients that receive an AVR at some point during the study period.

the same pattern; however, the effects were smaller and not significant. The estimates of the confounders (sex, age group, and Charlson) can be found in the Supplementary Table B.

For those patients who did not get an AVR during the follow-up, the risk of dying after being diagnosed decreased over the study period, both within 1 and 5 years after a first-time diagnosis (Table 4). The risk of dying declined steadily over the periods. The mortality risk within the first year declined from OR = 3.08 in the first period to OR = 1 in the last period. The mortality risk within 5 years showed the same pattern with HR = 1.86 in the first period and HR = 1 in the last period. For those patients who did not get an AVR (Table 4), the risk of dying within 1 year after being diagnosed was higher in the low-level educational group (OR = 1.21) and in the medium-level group (OR = 1.10). The hazard ratio of dying within 5 years after diagnosis, without receiving an AVR, were higher in the low-level educational group (HR = 1.38) and medium-level group (HR = 1.18). The estimates of the confounders (sex, age group, and Charlson) can be found in the Supplementary Table C.

Supplementary Fig. A in the supplementary materials summarizes the findings regarding educational effects within 1 year from diagnosis or AVR, while Supplementary Fig. B summarizes the temporal trends.

4. Discussion

Our study presents nationwide register-based data regarding treatment and mortality in patients with a first-time diagnosis of aortic stenosis in the period 2000–17. The temporal trends showed a decrease in both the treatment rate and the mortality rate. The analysis also demonstrated a socioeconomic disparity in the treatment rate as well as in the mortality rate.

4.1. Temporal trends in treatment and mortality

The risk of treatment with AVR within 1 and 5 year from diagnosis showed a significant decrease over the 18 years from 2000 to 2017. A Scottish study [2] based on data from 1997 to 2005 found that the risk of AVR increased slightly during the study period. This is the opposite of ours; however, the Scottish study is based only on inpatients. A Swedish study [26] found a relatively constant treatment rate in the period 1989–2009. When including outpatients in their analysis, they found the treatment rate decreased slightly towards the end of the period. The proportion of outpatients is increasing [23] and it is likely that outpatients have more asymptomatic or less severe aortic stenosis at the time of diagnosis. The incidence rate of aortic stenosis almost doubled

Table 2
Risk of AVR following an AS diagnosis. Logistic regression analysis (1 year) and Cox survival analysis (5 years).

		Logistic regression: AVR within 1 year after first diagnosis				Cox: risk of AVR up to 5 years after first diagnosis			
		OR	95% CI		*P*-value	HR	95% CI		*P*-value
Period	2000–2002	1.84	1.67	2.03	<0.0001	1.79	1.66	1.92	<0.0001
	2003–2005	1.89	1.73	2.07		1.72	1.61	1.84	
	2006–2008	1.72	1.58	1.87		1.59	1.49	1.70	
	2009–2011	1.47	1.35	1.60		1.49	1.40	1.59	
	2012–2014	1.24	1.14	1.35		1.27	1.20	1.36	
	2015–2017[a]	1				1			
Education	Low-level	0.85	0.80	0.92	<0.0001	0.88	0.84	0.93	<0.0001
	Medium-level	0.94	0.88	1.01		0.94	0.89	0.98	
	High-level	1				1			

OR, odds ratio; HR, hazard ratio.
[a] Due to lack of follow-up time for patients diagnosed in 2017, the period is 2015–2016 for logistic regression analysis.

Table 3
Death following AVR. Logistic regression analysis (1 year) and Cox survival analysis (5 years).

		Logistic regression: death within 1 year after AVR				Cox: risk of death within 5 years after AVR			
		OR	95% CI		*P*-value	HR	95% CI		*P*-value
Period	2000–2002	2.25	1.72	2.95	<0.0001	1.65	1.37	1.98	<0.0001
	2003–2005	1.79	1.40	2.28		1.57	1.33	1.85	
	2006–2008	1.47	1.15	1.87		1.43	1.21	1.68	
	2009–2011	1.30	1.03	1.66		1.26	1.07	1.48	
	2012–2014	1.00	0.79	1.27		1.16	0.99	1.36	
	2015–2017[a]	1				1			
Education	Low-level	1.32	1.07	1.61	0.026	1.14	1.01	1.28	0.087
	Medium-level	1.28	1.04	1.58		1.10	0.98	1.24	
	High-level	1				1			

OR, odds ratio; HR, hazard ratio.
[a] Due to lack of follow-up time for patients with AVR in 2017, the period is 2015–2016 for logistic regression analysis.

between 2000 and 2017 [23]. However, it is unknown if the increase is due to earlier detection of less severe aortic stenosis. Since the annual number of AVRs also increases over time [24,28], the explanation for the decreasing treatment rate might be that patients are less sick at the time of diagnosis, leading to more patients following a watchful waiting regimen instead of referral to AVR.

The risk of dying after AVR decreases over time, both within 1 and 5 years after AVR. Especially mortality within the first year after AVR has dropped distinctly. This is in line with the finding of others [2,24,26,27,45]. The decreasing mortality after AVR might be related to a combination of fewer postoperative complications due to better surgical techniques, implementation of guidelines and increasingly better adherence to guidelines, simplification of the TAVR procedure, and accumulation of clinical experience [25]. Earlier detection of aortic stenosis, earlier referral, and presence of less severe cardiovascular health problems at time of diagnosis are also mentioned as explanations [2,27]. However, some studies find that patient risk profiles have improved [2,27], while others find no differences in patient risk profiles [45]. A study comparing the characteristics of patients undergoing AVR in 1997 and 2006, showed that patients in 2006 were older and had more frequent comorbidities like diabetes, hypertension, COPD and cerebrovascular disease than patients in 1997 [46].

The risk of dying after an aortic stenosis diagnosis without receiving an AVR declined rapidly during the study period. This is in line with the Swedish study that found a decreasing mortality rate both within 1 and 3 years from diagnosis for patients not receiving AVR [26]. Improved risk factor control over time and improved treatment for common comorbidities like heart failure and AMI might contribute to lowering the mortality rate. After the widespread dissemination of TAVR, primarily during the last half of the period, many patients prior deemed inoperable will now be treated with TAVR. As a result, there will be fewer inoperable patients with an inherently very high mortality rate. Furthermore, earlier diagnosis might lead to more patients being eligible for AVR because of the better possibility of correct timing of treatment.

4.2. Socioeconomic differences in treatment and mortality

Our study indicates that patients with lower education do not receive treatment with AVR to the same degree as patients with higher levels of education. A study from the US found that higher area-based income was associated with a higher likelihood of receiving TAVR in patients with severe aortic stenosis [36]. There were no differences in comorbidity level for those receiving TAVR versus those treated conservatively. However, in Japan, a country with universal health care coverage, there was no area-based social disparity in the treatment rate of aortic stenosis [33].

An explanation for the social disparity in the treatment rate in our study might be that patients with lower-level education are diagnosed at a more advanced stage of the disease, resulting in more patients being inoperable at time of diagnosis. Furthermore, it is expected that patients with lower SES at time of diagnosis have an accumulation of risk factors (e.g. smoking, physical inactivity, obesity) which can be contributing factors in the decision making. We would also expect that patients with lower-level education have a higher burden of associated comorbidities [34] and concomitant procedures, but this confounder should be somewhat eliminated, since we have controlled for the Charlson comorbidity index at time of diagnosis.

Since we expect patients with lower-level education to have an accumulation of risk factors and higher comorbidity, we would expect some SES disadvantage in the survival after AVR. Our study finds that a higher mortality following AVR is related to a lower level of education, primarily within the first year after the procedure. In line with our results, other studies have found minor social disparities in mortality

Table 4
Death after first AS diagnosis without AVR. Logistic regression analysis (1 year) and Cox survival analysis (5 years).

		Logistic regression: Death within 1 year after first diagnosis				Cox survival analysis: Risk of death up to 5 years after first diagnosis			
		OR	95% CI		*P*-value	HR	95% CI		*P*-value
Period	2000–2002	3.08	2.63	3.60	<0.0001	1.86	1.68	2.07	<0.0001
	2003–2005	2.18	1.87	2.53		1.57	1.42	1.73	
	2006–2008	2.10	1.81	2.44		1.43	1.29	1.57	
	2009–2011	1.68	1.45	1.95		1.19	1.08	1.32	
	2012–2014	1.38	1.20	1.59		1.15	1.05	1.27	
	2015–2017[a]	1				1			
Education	Low-level	1.21	1.07	1.38	0.006	1.38	1.27	1.49	<0.0001
	Medium-level	1.10	0.96	1.25		1.18	1.08	1.28	
	High-level	1				1			

OR, odds ratio; HR, hazard ratio.
[a] Due to lack of follow-up time for patients diagnosed in 2017, the period is 2015–2016 for logistic regression analysis.

after AVR [2,37,38,47]; however, other studies have found no differences in mortality [33,34]. Common for all the studies are the lack of individual-level information on SES. Among the explanations for the higher mortality for low SES are lower rates of exercise, higher lipid levels, more obesity, diabetes, hypertension, smoking, and concurrent diseases [37]. A Scottish study found that predictors of death from aortic stenosis were diabetes, cancer, respiratory diseases, concurrent heart failure and MI, renal diseases, age, earlier time period, being male, and lower SES [2].

For those patients who die without AVR, there were also a disadvantage of low SES. The difference between educational groups increased with time from diagnosis. To our knowledge, this is the first study to examine mortality and SES differences in a nation-wide cohort of patients with aortic stenosis not receiving AVR.

If patients from higher-level SES are diagnosed at an earlier stage, fewer of those will be treated conservatively. Likewise, if patients from lower-level SES are diagnosed at a more advanced stage, there is a substantial risk of heart failure, leading to lower AVR treatment rate and higher mortality without AVR.

4.3. Strengths and limitations

The Danish healthcare system is based on free access to health care, regardless of employment status and without the need for private health insurance. This equal access to high-quality treatment in Denmark may help prevent some of the socioeconomic health disparities, which minimizes the risk of selection bias in our study. With the unique Danish personal registration number, it is possible to link nationwide registries. The NPR is of very high quality since it serves as the hospitals' reimbursement system, and reporting to the NPR is mandatory. Validation studies shows very high positive predictive value for AS diagnosis [48] and surgery [49]. The information on education is also of high quality with only few data missing. However, due to the incomplete data on education for patients aged 80 or more, we do not know if our findings are also present among the oldest part of the population, where AS is most frequent. On the other hand, we are able to provide information on education on an individual level for most of the patients aged 30–79. To our knowledge, this is the first study linking information on individual level SES with treatment and mortality from aortic stenosis. Furthermore, a strength of our study is that we have information on outpatients and not simply hospitalized patients.

There is a risk of unmeasured confounding related to a possible accumulation of risk factors in patients with lower-level SES, resulting in lower treatment rate. Since we do not have any information on the patients' risk factor status and health-related lifestyles, we cannot control for this in the analysis. We do not have information regarding the severity of the disease, e.g. data from echocardiography, and consequently, we are unable to verify our hypothesis that patients from lower SES are diagnosed at a more advanced stage of the disease. The lack of echocardiographic data, specific symptoms details, or the class of indication for AVR means that it is not possible to investigate if the diagnostic approach has changed over the study period.

5. Conclusion and clinical implications

Our study presents nationwide register-based data regarding treatment and mortality on patients with a first-time diagnosis of aortic stenosis in the period between 2000 and 2017. This is the first study linking individual-level SES with treatment and mortality following an aortic stenosis diagnosis.

The main results are i) since 2000, there has been a decrease in both AVR treatment rate, mortality rate following AVR and mortality rate in patients not receiving AVR; ii) for patients with lower-level education there is lower AVR treatment rate, higher mortality rate after AVR and higher mortality rate in patients not receiving AVR.

Our study can contribute with knowledge that highlights the potential importance of reducing disparities in the allocation of healthcare resources, access to AVR, and postoperative care across SES groups.

Data availability

The data underlying this article cannot be shared due to the Danish legislation on data protection.

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Declaration of competing interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2021.05.039.

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