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CLINICAL RESEARCH
Valvular heart disease

Severe aortic stenosis: secular trends of incidence and outcomes

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Abstract

Background and Aims Severe aortic stenosis (AS) is the guideline-based indication for aortic valve replacement (AVR), which has markedly increased with transcatheter approaches, suggesting possible increasing AS incidence. However, reported secular trends of AS incidence remain contradictory and lack quantitative Doppler echocardiographic ascertainment.

Methods All adults residents in Olmsted County (MN, USA) diagnosed over 20 years (1997–2016) with incident severe AS (first diagnosis) based on quantitatively defined measures (aortic valve area ≤ 1 cm^2, aortic valve area index ≤ 0.6 cm^2/m^2, mean gradient ≥ 40 mmHg, peak velocity ≥ 4 m/s, Doppler velocity index ≤ 0.25) were counted to define trends in incidence, presentation, treatment, and outcome.

Results Incident severe AS was diagnosed in 1069 community residents. The incidence rate was 52.5 [49.4–55.8] per 100 000 patient-year, slightly higher in males vs. females and was almost unchanged after age and sex adjustment for the US population 53.8 [50.6–57.0] per 100 000 residents/year. Over 20 years, severe AS incidence remained stable (P = .2) but absolute burden of incident cases markedly increased (P = .0004) due to population growth. Incidence trend differed by sex, stable in men (incidence rate ratio 0.99, P = .7) but declining in women (incidence rate ratio 0.93, P = .02). Over the study, AS clinical characteristics remained remarkably stable and AVR performance grew and was more prompt (from 1.3 [0.1–3.3] years in 1997–2000 to 0.5 [0.2–2.1] years in 2013–16, P = .001) but undertreatment remained prominent (>40%). Early AVR was associated with survival benefit (adjusted hazard ratio 0.55 [0.42–0.71], P < .0001). Despite these improvements, overall mortality (3-month 8% and 3-year 36%), was swift, considerable and unabated (all P ≥ .4) throughout the study.

Conclusions Over 20 years, the population incidence of severe AS remained stable with increased absolute case burden related to population growth. Despite stable severe AS presentation, AVR performance grew notably, but while declining, undertreatment remained substantial and disease lethality did not yet decline. These population-based findings have important implications for improving AS management pathways.

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Structured Graphical Abstract

Key Question

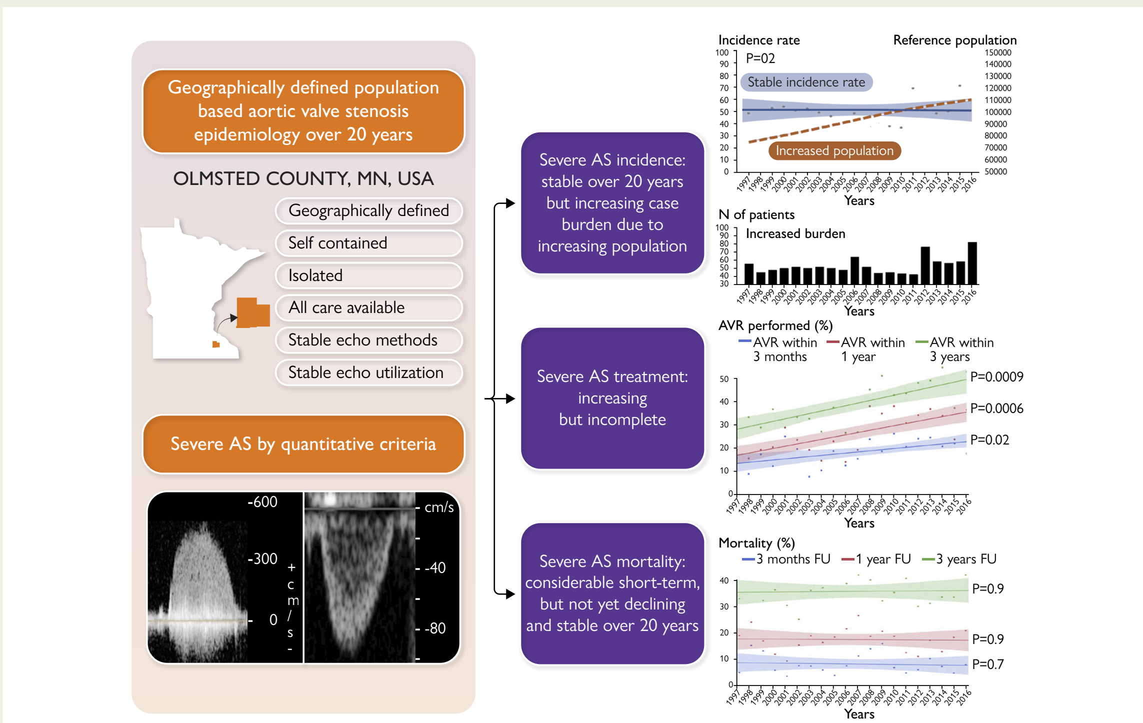
Did incidence, clinical presentation, treatment, and outcome for quantitatively defined severe aortic stenosis (AS) change over the last 20 years in a population-based community?

Key Finding

Over 20 years, severe AS incidence remained overall stable, although women showed a slight trend towards declining incidence. While the clinical/echocardiographic presentation remained stable, severe AS was treated more and earlier, but undertreatment remained sizable. Overall mortality stayed swift, considerable, and unabated.

Take Home Message

The population incidence of severe AS remains stable with increased absolute case-burden related to population-growth. Despite stable severe AS presentation, AVR performance grows notably. While declining, undertreatment remains substantial, and disease-lethality has not declined. These population-based findings have important implications for improving AS management pathways.



Secular trends of incidence, management, and outcome of severe aortic valve stenosis identified by quantitative echocardiographic criteria in the Olmsted County population. AS, aortic stenosis; AVR, aortic valve replacement.

Keywords Community based study • General population • Aortic valve stenosis • Incidence • Outcome • Aortic valve replacement

Introduction

Aortic stenosis (AS) is prevalent,[1] due to calcific valvular degeneration with ageing in developed countries[2,3] and the most frequent indication for valve interventions in Europe[4] and the USA.[5,6] While recommended criteria for AS diagnosis and management remained stable,[7,8] combined transcatheter and surgical aortic valve replacement (AVR) volumes grew markedly in the USA[5,6] and Europe.[9,10] This secular trend is welcome for patients affected by a disease without effective medical treatment,[11] but raises many unresolved questions. Increased AVR volumes may reflect efforts at addressing AS undertreatment,[12] by earlier or more extensive indications,[13,14] linked to therapeutic benefits of transcatheter intervention,[15] or alternatively simply mirror growing population and/or AS incidence. Resolving this conundrum is essential, since recent clinical trials demonstrated survival benefits of AVR over medical treatment,[15] and sustained good results of transcatheter aortic valve implantation (TAVI) in the long-term.[16] Hence, assessing AS incidence, potential secular trends and implications, has considerable importance for deploying healthcare resources for high-cost procedures.[17]

In that regard, available information is contradictory, methodologically disputed, and confusing. On the one hand, data from the entire nation of Sweden suggested a significant decline of AS incidence,[18] but the pan-European cardiovascular statistics observed an explosion of AS prevalence, multiplied 15-fold between 1990 and 2019.[19] Similarly, increasing AS incidence in Quebec[20] contradicts analysis by the Global Burden of Disease initiative suggesting increased cases but stable incidence.[21] These analyses are all questionable, affected by dependence on clinical ICD coding based on unknown criteria[18–21] and/or complex algorithms yielding tenuous estimates.[21,22] Case ascertainment by Doppler echocardiography remained mostly undefined and when obtained in population screening studies, yielded minimal case numbers.[23] Uncertainties regarding completeness of case detection, veracity of truly new diagnoses, and changes in echocardiographic utilization all leave considerable doubts on validity of incidence estimates/trends.[18–21] Thus, these incidence estimates diverge and are inconclusive. Furthermore, population-based secular trends in AS presentation, undertreatment, and outcomes remain unknown. To define secular trends in epidemiology, clinical presentation, management and outcomes of severe AS using objective echocardiographic diagnostic criteria, we gathered all incident cases diagnosed among the population-based residents of Olmsted County, MN, USA, over 20 years (1997–2016) taking advantage of the stable and consistent diagnostic methodology in the community.

Methods

Subjects

We detected all consecutive incident cases of severe AS diagnosed by Doppler echocardiography affecting residents ≥ 18 years of Olmsted County, MN, USA, between 1997 and 2016. This involved identifying severe valvular (not sub- or supra-valvular) AS diagnosed by Doppler echocardiography using guideline-based criteria from laboratories serving the county. We retained incident cases, without previous severe AS diagnosis by prior echocardiograms. Then, Olmsted County residency (not moved in for medical care) prior to AS diagnosis was ascertained using the Rochester Epidemiology Project, a validated epidemiological and research infrastructure.[24] Inclusion/exclusion did not consider outpatient or inpatient diagnosis, therapy received, conditions associated or birth location. Patients with severe AS younger than 18 years or with exclusive non-valvular obstruction were not included.

Clinical characteristics

Patients' history, symptoms, comorbidity and clinical characteristics were retrieved unaltered from electronic medical records and integrated into EuroSCORE II calculation; vital signs were measured at echocardiography. Atrial fibrillation was diagnosed by electrocardiogram. Biological data (haemoglobin, creatinine) within 3 months of diagnosis were retrieved electronically from their repository and glomerular filtration rate (GFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

Doppler echocardiography was performed in routine practice at Mayo Clinic (1997–2016) and Olmsted Medical Center (2010–16) in Rochester, MN by Mayo-trained physicians/technicians using standard protocol and similar repositories, ensuring complete procedural uniformity.

For AS diagnosis,[25] highest velocity from all echocardiographic windows (systematic right parasternal) yielded peak/mean transvalvular gradient and Doppler velocity index (DVI), averaging multiple beats. Left ventricular (LV) outflow tract measurements using zoomed parasternal long-axis view determined aortic valve area (AVA) by continuity equation and aortic stroke volume, absolute and indexed for body surface area. Severe AS was defined by at least one of the following: AVA ≤ 1 cm^2, AVA index ≤ 0.6 cm^2/m^2, mean gradient ≥ 40 mmHg, peak velocity ≥ 4 m/s, or DVI ≤ 0.25.

Valvular regurgitations were graded and LV dimensions, ejection fraction, mass measured by guideline-based approaches. Using tricuspid regurgitant signal and estimated right atrial pressure, pulmonary artery pressure was derived. All echocardiographic data (qualitative/quantitative) were retrieved unaltered via electronic transfer from original reports comprehensively validated/signed by cardiologists. To define trends in echocardiography utilization, yearly individual Olmsted County adult residents undergoing ≥ 1 examination during the study period were retrieved.

Follow-up and interventions were gathered from institutional repositories, medical notes, and local/state/national databases to determine occurrence and date of AVR (surgical/TAVI), death, and/or heart failure and latest follow-up.

Statistical analysis

Continuous variables are presented as means ± standard deviation or median [interquartile range, IQR] and categorical variables as percentages. Secular trends for baseline clinical and echocardiographic characteristics are displayed in five 4-year periods for ease of presentation and were tested for yearly trend based on general linearized models across the 20-year study.

Severe AS crude incidence [95% confidence interval] was calculated as ratio of yearly incident cases to Olmsted County adult population defined by US census bureau, overall and by sex, and trends over time tested by Poisson regression (validity of Poisson model evaluated by distribution of deviance using goodness-of-fit χ^2 test). Adjusted incidence (to US population age/sex) and trends were also examined. Incidence changes were assessed by incidence rate ratio (IRR), the linearized ratio of incidences later/earlier periods and Jonckheere-Terpstra tests used to test trends over time. Aortic stenosis prevalence on 31 December 2016 was calculated as ratio of patients/(population alive) overall and by age/sex.

The primary outcome measure was all-cause mortality and secondary endpoints were AVR (surgical/TAVI) performance, and combined endpoints of death/AVR and death/heart failure, over all follow-up, under medical management (censoring at AVR), and post-AVR presented at specific time intervals and all times. Survival was displayed using Kaplan–Meier method and compared using log-rank test. Landmark analysis was performed to account for impact of early AVR (within 3 months of AS diagnosis) on outcome, excluding patients medically deceased or censored within that phase. Cox proportional-hazards models calculated hazards for endpoints overall and per study years. Regression analysis estimated odds of AVR trends by study-year increment. $P < .05$ was considered statistically significant. All analyses were performed using JMP 16 and SAS software.

Results

Incident severe aortic stenosis

Overall incidence

A total of 1069 community-dwelling adult patients were first diagnosed with severe AS 1997–2016, at age 77 ± 14 years (median 77 [71–86], 10%–90% range [59–92]), 519 (49%) in women. Overall crude incidence (per 100 000 residents/year) of newly diagnosed severe AS in the adult community was 52.5 [49.4–55.8], slightly higher in male (56.0 [51.4–60.9]) than in female (49.3 [45.1–53.6]) ($P < .05$). Age- and sex-adjusted (for adult US population) severe AS incidence was almost unaffected (53.8 [50.6–57.0] per 100 000 residents/year).

Secular trends of severe aortic stenosis incidence

Absolute burden of incident severe AS is indicated per 4-year period (*Table 1*) and per year (*Figure 1*, lower cartouche), fluctuating year-over-year but increasing overall from 57 total cases in 1997 (203 for the 4-year period 1997–2000) to 85 in 2016 (254 for 2013–16), $P < .001$. *Figure 1* (upper cartouche) shows progressive increase in Olmsted County adult population 1997–2016 and the calculated incidence of severe AS per year, demonstrating year-to-year fluctuations but secular trend remaining stable ($P = .23$ in Poisson regression with good residual deviance for the model). Adjusted severe AS incidence (to US adult population age/sex—see Supplementary data online, *Figure S1*), showed also no change ($P = .73$) over 20 years. Thus, severe

Table 1 Clinical characteristics at diagnosis and secular trends

	All incident severe AS (*N* = 1069)	Secular trends					*P* for trend
		1997–2000 (*N* = 203)	2001–04 (*N* = 251)	2005–08 (*N* = 158)	2009–12 (*N* = 203)	2013–16 (*N* = 254)	
Age, years	77 ± 14	76 ± 16	78 ± 13	76 ± 16	76 ± 14	78 ± 12	.3
Female sex	519 (49)	136 (54)	136 (54)	74 (47)	91 (45)	110 (43)	.02
Height, m	1.66 ± 11	1.65 ± 0.13	1.66 ± 0.10	1.66 ± 0.11	1.67 ± 0.10	1.66 ± 0.11	.4
Weight, kg	79 ± 21	75 ± 20	77 ± 19	79 ± 20	84 ± 22	81 ± 21	<.0001
BSA, m^2	1.84 ± 0.55	1.74 ± 0.54	1.78 ± 0.51	1.84 ± 0.55	1.97 ± 0.57	1.89 ± 0.56	.0004
BMI, kg/m	28 ± 7	27.7 ± 9.8	27.6 ± 5.6	28.1 ± 5.6	29.7 ± 7.0	29.2 ± 6.3	.001
Heart rate, b.p.m.	71 ± 15	72 ± 14	72 ± 15	71 ± 17	71 ± 15	70 ± 14	.5
Systolic BP, mmHg	131 ± 25	139 ± 23	125 ± 30	126 ± 23	126 ± 22	129 ± 22	<.0001
Diastolic BP, mmHg	69 ± 13	73 ± 12	71 ± 13	66 ± 13	70 ± 13	68 ± 13	<.0001
Dyspnoea, *n* (%)	58	59	66	72	66	57	.6
Angina, *n* (%)	37	38	43	53	41	32	.05
Syncope, *n* (%)	13	9	15	16	15	15	.1
Any symptom, *n* (%)	713 (74)	117 (69)	187 (77)	115 (78)	139 (75)	165 (71)	.5
Haemoglobin, g/L	12.9 ± 1.42	12.8 ± 1.4	12.9 ± 1.4	12.8 ± 1.6	12.9 ± 1.1	12.9 ± 1.6	.5
Creatinine, mg/dL	1.32 ± 0.88	1.40 ± 0.99	1.32 ± 0.90	1.34 ± 0.89	1.23 ± 0.74	1.31 ± 0.89	.2
EuroSCORE II, %	5.45 ± 6.78	4.5 ± 4.5	5.2 ± 5.9	7.5 ± 9.8	4.7 ± 5.8	5.4 ± 5.5	.5
Atrial fibrillation, *n* (%)	298 (27)	50 (24)	65 (26)	54 (34)	54 (26)	75 (29)	.1
Diabetes, *n* (%)	317 (30)	36 (17)	60 (24)	45 (28)	73 (36)	103 (41)	<.0001
Dyslipidaemia, *n* (%)	661 (62)	75 (37)	123 (49)	106 (67)	157 (77)	200 (78)	<.0001
Hypertension, *n* (%)	762 (71)	110 (54)	179 (71)	113 (72)	158 (78)	202 (80)	<.0001
Pacemaker, *n* (%)	74 (7)	7 (3)	16 (6)	18 (11)	14 (7)	19 (7)	.08
CABG history, *n* (%)	128 (12)	23 (11)	27 (11)	27 (17)	22 (11)	29 (11)	.9

BMI, body mass index; BSA, body surface area; CABG, coronary artery bypass grafting.

AS case burden growth in adult community is exclusively due to population growth without change in incidence rate.

To verify imaging utilization trends, utilization of echocardiography per 100 000 persons-year among adults in Olmsted County was plotted (see Supplementary data online, *Figure S2*), displaying no demonstrable change (*P* for trend = .41).

Secular trend of severe aortic stenosis incidence by sex

Analysis of severe AS incidence was stratified by sex, showing case burden increasing in men, from 29 in 1997 (95 for 1997–2000) to 39 in 2016 (136 for 2013–16) and statistically stable in women, 28 in 1997 (108 for 1997–2000) and 43 in 2016 (110 for 2013–16) (*Figure 2* lower cartouches). With adult population increasing markedly in men and women; thus, AS incidence remained stable in men (IRR: 0.99, *P* = .72) and slightly but significantly declined over 20 years in women: (IRR: 0.93, *P* = .024) (*Figure 2* upper cartouches).

Estimated severe AS prevalence on 31 December 2016 was overall 419.3 [390.8–448.2] per 100 000 adults in Olmsted County, lower for women 342.1 [304.4–381.5] per 100 000 than for men, 501.8 [459.8–543.7] (*P* < .0001) and exponentially increased with age (see Supplementary data online, *Figure S3*), from 0.06% at <45 years to 2.5% ≥ 75 years, in both sexes. Among prevalent cases 31 December 2016, 53% were still untreated.

Severe aortic stenosis presentation in the community and secular trends

Incident severe AS diagnosis was associated with advanced age and comorbidity burden (mean EuroSCORE II 5.5%) as shown in *Table 1*. Symptoms were frequent and echocardiography generally demonstrated normal left ventricular size and ejection fraction (*Table 1*). Secular trends analysis throughout the 20-year study period showed that age at diagnosis and burden of comorbidity/risk (EuroSCORE II) remained stable (*Table 1*). Similarly, history of coronary bypass, pacemaker implantation, atrial fibrillation were unchanged while creatinine/haemoglobin levels were stable. Overall, GFR showed modest increase, notable in women but not in men (see Supplementary data online, *Table S1*). Conversely, we observed trends non-specific of AS, such as increasing weight, body mass index and diabetes; trends for

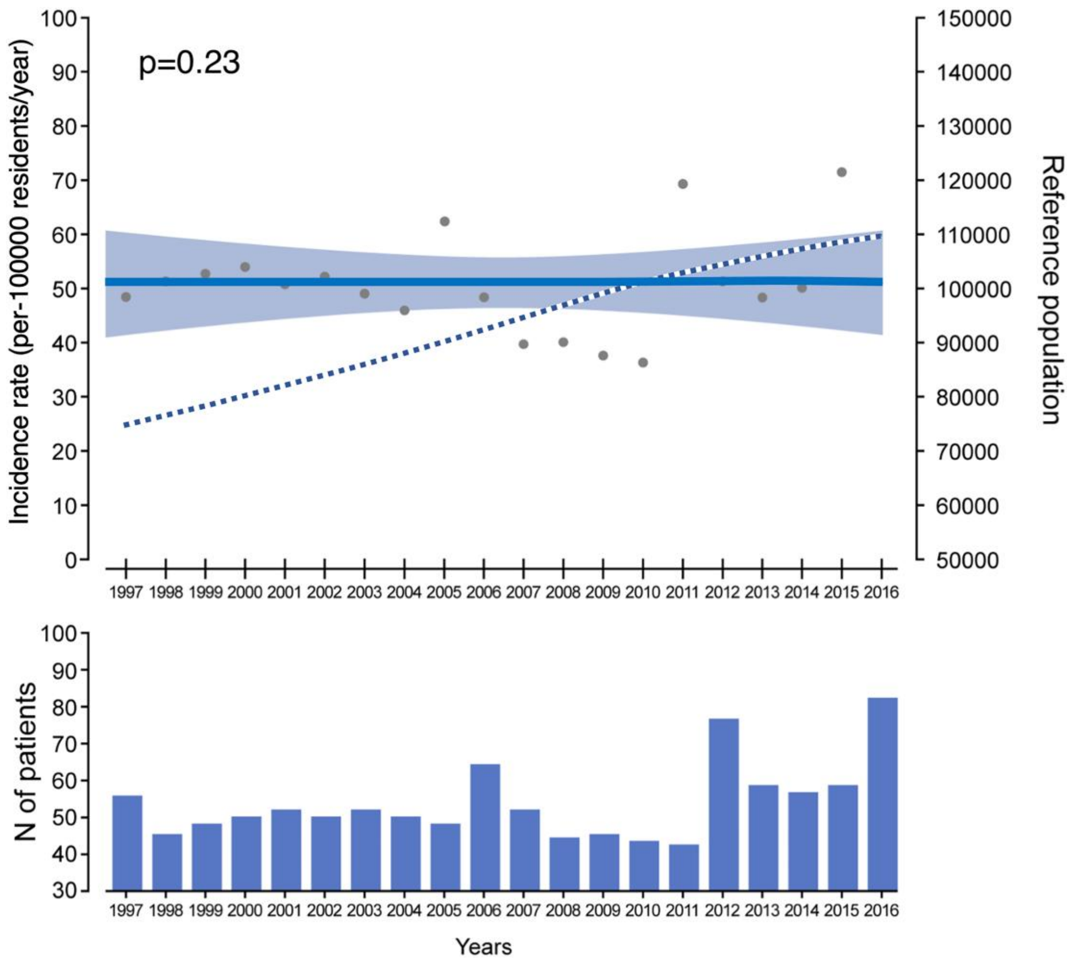


Figure 1 Secular trends of incidence and burden of severe AS in the community: the progressive increase in Olmsted County adult population between 1997 and 2016 is shown in the upper cartouche (dashed line); the calculated incidence rate of severe AS is shown by the dots and linearizes (continuous line with shaded 95% CI), indicating stable incidence over the study years. The bar graph represents the number of incident cases per year

increasing hypertension diagnoses, while systolic/diastolic blood pressures declined, were probably linked to guideline changes.

Proportion of women among incident severe AS (*Table 1*) declined from 54% in 1997–2000 to 43% in 2013–16 ($P = .024$) linked to their declining incidence. Severe AS presentation was generally stable, with most patients symptomatic (74%) throughout the 20 years, although angina tended to decrease as specific symptom ($P = .051$).

Echocardiographic characteristics (*Table 2*) at diagnosis were mostly unchanged. Left ventricular size and ejection fraction remained stable ($P > .6$) and reduced ejection fraction (<50%), noted in 18% of patients, remained a stable proportion (20% in 1997 and 18% in 2016, *P* for trend = .30). Accordingly, stroke volume index and the proportion of low-flow severe AS (stroke volume index < 35 mL/m^2) remained stable. Haemodynamics showed little change (slightly higher mean gradient and peak velocity, slightly larger AVA, and lower DVI) with AVA index remaining stable. Thus, functionally, severe AS and haemodynamic/LV consequences showed little changes over 20 years.

Treatment and outcomes secular trends

During follow-up (mean: 5.7 ± 5.2, median [IQR]: 4.2 [1.7–8.3] years) 521 community members with severe AS underwent AVR (surgical in 433 and TAVI in 88) and 739 died (485 under medical management, i.e. without AVR).

Aortic valve replacement was performed in 209 (40%) women and 312 (60%) men, 1.75 ± 2.52 years after severe AS diagnosis (18% within 3 months post-diagnosis, 26% within 1 year, and 39% within 3 years). Ultimately, 51% of patients with severe AS did not receive AVR during follow-up.

Secular trends over 20 years demonstrated increasing AVR proportion at any time interval (*Figure 3*). From 1997–2000 to 2013–16, AVR performance within 3 months post-diagnosis rose from 14% to 21% (*P* for trend .023), within 1 year from 19% to 33% ($P < .001$), within 3 years from 31% to 49% ($P < .001$), and at any time-point from 42% to 56% ($P < .001$). Furthermore, the median [IQR] time to AVR fell from 1.3 [0.1–3.3] years in 1997–2000 to 0.48 [0.15–2.11] years in 2013–16 ($P = .001$). Odds ratio per year of AVR within 3 months was 1.032 [1.005–1.060], $P = .01$ unadjusted and 1.039 [1.015–1.070], $P = .001$ adjusted for age, sex, and peak aortic velocity; within 3 years, it was 1.051 [1.029–1.075], $P = .005$ and 1.059 [1.034–1.085], $P < .001$ adjusted. There were no significant interaction sex-AVR secular trends at 3 months, 1 year, or 3 years or anytime (all $P > .14$). Thus, secular trends in community patients with severe AS demonstrate increased performance of AVR, earlier after diagnosis.

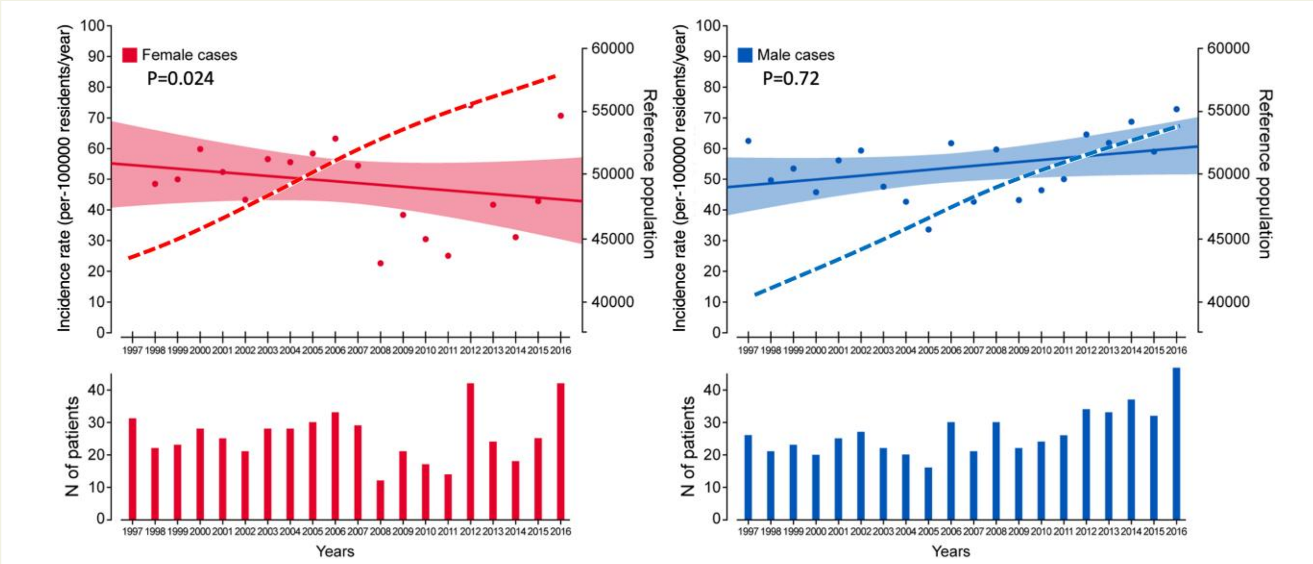


Figure 2 Secular trends of incidence and burden of severe AS by sex: the progressive increase in Olmsted County adult population between 1997 and 2016 is shown in the upper cartouche for female (left, dashed line) and male (right, dashed line); the calculated incidence rate of severe AS is shown by the dots and linearizes (continuous blue line with shaded 95% CI), indicating modest decrease in incidence over the study years for female and stable incidence for male. The bar graph represents the number of incident cases per year

Nevertheless, undertreatment of severe AS remains considerable (>40%) related to surgical risk and age: EuroSCORE II was considerably higher in patients never referred to AVR: 7.27 [IQR: 6.61–7.93] vs. 3.05 [IQR: 2.50–3-59] in patients referred early (within 3 months) and 2.97 [IQR: 2.56–3.38] in patients referred later to AVR, and adjusted odds ratio for age ≥ 65 years was 0.53 [0.37–0.75], $P < .001$ for AVR at 1 year.

Mortality [95% confidence interval] post-diagnosis was considerable, 8.3% [6.8–10.1] within 3 months, 17.8% [15.6–20.2] within 1 year, 36% [33–39] within 3 years, and 49 ± 2% at 5 years. Mortality under medical management was even more considerable, 3 months: 9.6% [7.8–11.7], 1 year: 21.7% [19.0–24.7], and 3 years: 51% [47–55]. Secular trends over 20 years demonstrated no change in overall mortality (*Figure 4*); from 1997–2000 to 2013–16, 9.9% to 7.9% within 3 months (P for trend .44), 18.2% to 18.1% within 1 year (P for trend = .39), 36.5% to 36.2% within 3 years (P for trend = .72), and at 5 years 49 ± 4% to 52 ± 4% (P for trend = .65). Odds ratios of mortality within 3 months were 0.99 [0.96–1.03] per year, $P = .79$ unadjusted and 0.99 [0.95–1.02], $P = .42$ adjusted for age, sex, and EuroSCORE II and 1.03 [0.98–1.07], $P = .26$ adjusted additionally for ejection fraction and peak aortic velocity. Mortality throughout follow-up in Cox proportional-hazards models showed no change with hazard ratio 1.00 [0.99–1.02], $P = .65$ per 1 study year unadjusted and 1.01 [0.99–1.03], $P = .10$, adjusted for age, sex, EuroSCORE II, ejection fraction, and peak aortic velocity. Overall, 202 suffered heart failure episodes and the endpoint of death or heart failure was noted in 11 ± 1% at 3 months, 24 ± 1% at 1 year, and 41 ± 2% at 3 years post-diagnosis. There was no trend for improvement of this endpoint over 20 years, univariably ($P = .80$) or after full adjustment ($P = 1.00$).

Early AVR (within 3 months post-diagnosis) was associated with subsequent lower mortality in landmark analysis (5-year survival 77 ± 3% vs. 50 ± 2%, $P < .0001$; hazard ratio 0.57 [0.44–0.76], $P < .001$, adjusted for age, sex, EuroSCORE II, ejection fraction, symptoms, and peak aortic velocity). Study year, added to the model, was not associated with mortality ($P = .22$) and showed no interaction with early AVR ($P = .76$). Early AVR was also associated with lower combined endpoint of mortality or heart failure in landmark analysis (adjusted hazard ratio 0.65 [0.50–0.83], $P < .001$).

Post-AVR mortality remained relatively high (28 ± 2% at 5 years post-AVR) most strongly influenced by age ($P < .001$) and EuroSCORE II ($P < .001$) and was slightly lower after early AVR (adjusted hazard ratio 0.64 [0.47–0.88], $P = .005$). Of note, early AVR survival benefit was strong with EuroSCORE II < 12% (adjusted hazard ratio 0.55 [0.42–0.71], $P < .001$), but undiscernible in the small subset (8%—$n = 79$) with EuroSCORE II ≥ 12% (adjusted hazard ratio 0.97 [0.29–3.29], $P = .96$). Finally, only 63 patients (6%) were alive and unoperated at follow-up end with mortality or AVR rates of 26% at 3 months, 42% at 1 year, and 84% at 5 years underscoring profound limitations of conservative management after severe AS diagnosis.

Discussion

This is the first large population-based community study analysing long-term secular trends in incidence, presentation, outcome and treatment of severe AS, based on quantitative Doppler echocardiography performed by a consistent physicians/sonographers team. Severe AS incidence is ∼52/100 000 adults per year, slightly higher in men vs. women. Secular trends show over 20 years, overall stable incidence of severe AS with increasing case burden purely due to population growth; by sex incidence remained stable in men while slightly but significantly decreasing in women. Secular trends also showed AS presentation features (age, symptoms, comorbidity, valvular and ventricular characteristics) changing little over time. Conversely, severe AS management changed with increasing/earlier AVR performance, but pervasive undertreatment persists, with >40% of community patients never enjoying AVR benefits during their lifetime. While early AVR (within 3 months) is associated with higher survival, overall mortality following severe AS diagnosis remained considerable and unchanged

Table 2 Echocardiographic characteristics at diagnosis and secular trends

	All incident severe AS (*N* = 1069)	1997–2000 (*N* = 203)	2001–04 (*N* = 251)	2005–08 (*N* = 158)	2009–12 (*N* = 203)	2013–16 (*N* = 254)	*P* for trend
LV septal thickness, mm	12 ± 2	12 ± 2	12 ± 3	12 ± 3	12 ± 2	12 ± 2	.9
LV diastolic diameter, mm	49 ± 7	50 ± 7	48 ± 7	49 ± 7	49 ± 6	49 ± 6	.7
LV systolic diameter, mm	32 ± 8	32 ± 8	31 ± 9	32 ± 9	31 ± 7	32 ± 7	.7
LV mass index, g/m^2	116 ± 34	130 ± 46	112 ± 34	117 ± 35	113 ± 28	116 ± 33	.05
LV ejection fraction, %	59 ± 13	59 ± 14	59 ± 15	59 ± 12	61 ± 12	58 ± 13	.80
LV ejection fraction < 0.50, %	18	20	19	19	13	20	.30
Peak velocity, m/s	3.89 ± 0.74	3.84 ± 0.87	3.84 ± 0.83	3.89 ± 0.71	3.99 ± 0.61	3.93 ± 0.64	.02
Mean gradient, mmHg	38 ± 15	36 ± 17	36 ± 17	37 ± 13	39 ± 12	38 ± 13	.006
AVA, cm^2	0.90 ± 0.21	0.87 ± 0.21	0.89 ± 0.19	0.93 ± 0.21	0.92 ± 0.18	0.91 ± 0.21	.03
Doppler velocity index	0.24 ± 0.10	0.25 ± 0.06	0.25 ± 0.05	0.24 ± 0.05	0.24 ± 0.05	0.23 ± 0.05	<.001
AVA index, cm^2/m^2	0.49 ± 0.10	0.50 ± 0.11	0.49 ± 0.09	0.50 ± 0.09	0.49 ± 0.10	0.50 ± 0.10	.90
SVi, mL/m^2	48 ± 15	49 ± 16	47 ± 14	49 ± 15	47 ± 14	47 ± 15	.54
SVi < 35 mL/m^2, %	19	18	20	17	15	22	.45
Systolic PA pressure, mmHg	42 ± 14	43 ± 13	42 ± 14	44 ± 17	39 ± 13	41 ± 15	.02

AS, aortic stenosis; AVA, aortic valve area; LV, left ventricle; PA, pulmonary artery; SVi, stroke volume index.

over 20 years (*Structured Graphical Abstract*). Thus, evidence-based and guideline-recommended advances in management have not yet translated into improved outcomes, suggesting that population-efficient management of severe AS warrants profound and continued improvements.

Incidence of severe aortic stenosis

Clarifying severe AS incidence is crucial because the disease is frequent and the predominant indication for valve interventions in developed countries.[4–6] Previous estimates remained in doubt since associated studies were rarely population-based,[18,20] or used ICD codes with uncertain substantiation by quantitative Doppler echocardiographic criteria. Studies with Doppler echocardiographic ascertainment enrolled only few population-based cases based on systematic screening[23,26] or could not define rigorous population base.[27,28] Various studies attempted estimating burden/incidence trends of AS with complex algorithms incorporating limited existing data.[19,21,29] Hence, rigorously defined population-based severe AS incidence has remained elusive with contradictory estimates for secular trends,[18,20] leaving considerable doubts on appropriate public health approaches. Conversely, exponential growth of AVR for AS that followed transcatheter approaches advent, strongly raised questions of increasing AS prevalence. Because clinical trials demonstrated that AVR for severe AS, surgical[30] or TAVI,[15] yields improved clinical outcomes, severe AS trends in incidence and management are crucial gaps of knowledge to resolve. We, therefore, focused on Olmsted County, MN, USA, an isolated population with contained medical care by few providing centres linked by the Rochester Epidemiology Project, allowing complete population-based case counts, by consistent quantitative AS assessment. This unique stable epidemiological/clinical environment allows reporting that severe AS incidence is ∼52/100 000 adults, slightly higher in men, predominant in older subjects, yielding exponentially increasing prevalence with age, similar to that measured by systematic screening.[23,26] Crucially, over 20 years, there is no secular trends for change in incidence of severe AS, even after adjustment for age and sex of the US adult population. Conversely, county population and yearly case burden grew considerably, similarly to clinical observations.[19] However, severe AS incidence slightly declined in women, consistent with declining proportion of women nationwide among patients treated by AVR.[5] Sex-related differences in AS pathophysiology have been described,[31,32] whereby women progress to severe AS with less calcification density than men, possibly due to different valve fibrosis.[33] This observation warrants more basic research into AS initiation/progression mechanisms,[34,35] and large epidemiological projects to continuously monitor trends in men and women.

Presentation, management, and outcome in severe aortic stenosis

Patients affected by AS are often elderly with age-related comorbidity,[11,12] and clinical and Doppler echocardiographic characteristics remaining stable over 20 years, most noticeably with high but stable frequency of symptomatic patients. While symptomatic status underpins guideline recommendations for AVR in severe AS,[7,8] many patients are not referred,[4] since symptoms are often difficult to interpret,[12] particularly in high-risk patients of advanced age.[15,16] This systematic undertreatment of severe AS[36] has been recognized retrospectively since the advent of TAVI,[5,9] but its scale remained undefined. Our population-based study demonstrated that AVR performance increased markedly[5] but undertreatment remains pervasive, because unless AVR is undertaken promptly after diagnosis, it is unlikely to be ever performed.[18] Indeed, mortality associated with severe AS remains stubbornly high (∼18% at 1 year),[20] with no trend for improvement, yet. This troubling lack of outcome improvement[20] may recognize various causes. Severe AS affects elderly patients with comorbidity that may hinder survival

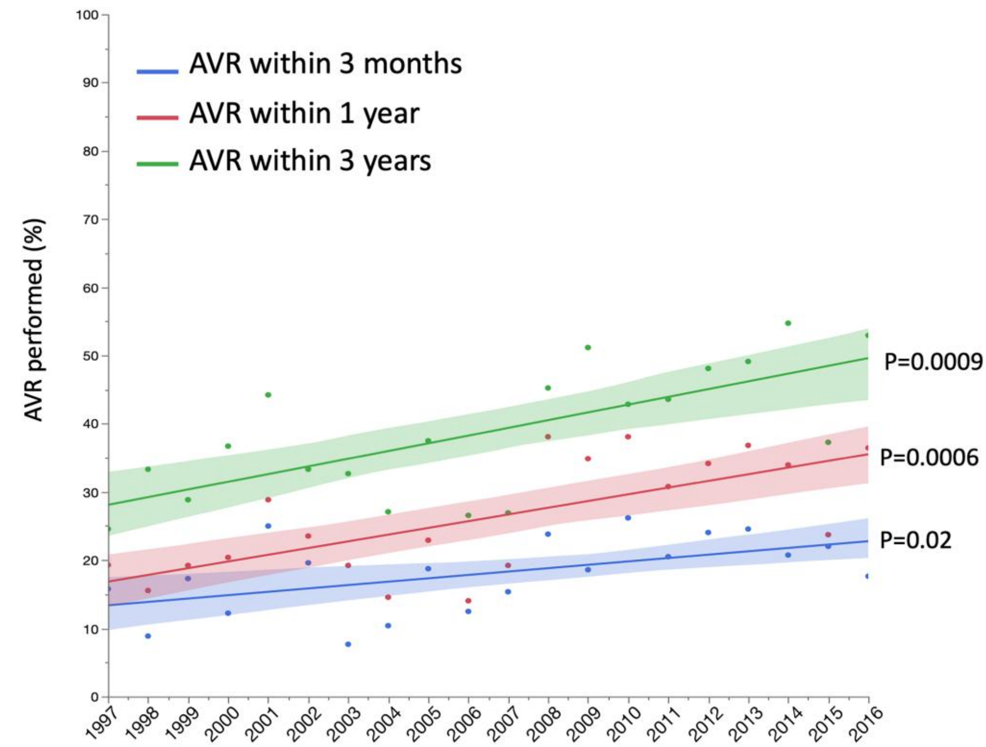


Figure 3 Performance of aortic valve replacement after diagnosis of severe aortic stenosis in the community: the proportion of patients undergoing AVR for each year of the study (1997–2016) is represented by a dot within 3 months (blue), within 1 year (red), and within 3 years (green) with the growing trends indicated by the regression line and correspondingly coloured zone

improvement with aortic valve interventions. Conversely, valve interventions effectiveness in improving mortality at whole population level is stalled by persistent undertreatment, as suggested by the risk reduction linked to early AVR, consistent throughout 20 years and only attenuated in the small subset (8% of all AS) with major comorbidity (EuroSCORE II ≥ 12%). This is further supported by clinical trials demonstrating AVR outcome benefits, by early surgery[30] or even with prohibitive risk.[15] While clinical trials of early TAVI are ongoing, undertreatment exceeding 40% of severe AS is unacceptable and prompt treatment after initial diagnosis of severe AS is an important goal.[18] The 'watchful-waiting' delaying AVR performance, with clinical guidelines emphasizing symptoms importance, may underestimate their difficult assessment and attribution to AS in elderly patients,[36] at notable procedural risks. However, the considerable and swift mortality, >8% within 3 months of diagnosis, ∼18% within 1 year,[20] with by 5 years almost all unoperated patients deceased, shows that time is critical after AS diagnosis, warranting prompt clinical action. While not all patients may ultimately be suitable for AVR, it is desirable that most are promptly referred to a multidisciplinary heart valve clinic for detailed evaluation to determine the potential opportunity for prompt AVR, surgical or transcatheter.

Strengths and limitations

Incidence secular trends preferably comprise national or provincial populations but would lack Doppler echocardiographic objective incident (not follow-up) case ascertainment. Precise counts of population at risk (denominator) and incident cases (numerator), strict case definitions, and quantitative and consistent case ascertainment are available in the stable imaging environment at county level. Furthermore, this approach provides large case counts with narrow uncertainty margins vs. sample screening of general population.[23] Severe AS incidence estimates may be affected by increased availability of Doppler echocardiography, resulting in spurious increments, while stable county utilization rules out this pitfall. Olmsted County dwellers are mostly from northern European heritage and generalizability could be questioned. However, while treatment access may be different by race/ethnicity,[37] no rationale exists for different racial/ethnic AS prevalence/natural history, and valve disease population-based trends in our community closely match national data in USA[1] and Europe[4] making this issue moot. Severe AS often presents with gradients lower than guideline-based thresholds,[12] associated with complex physiologic mechanisms;[38] however, secular trends for severe AS incidence based on multiple criteria (≥2) or on PARTNER trial criteria[15] were stable over 20 years (both $P > .39$) demonstrating stability of our results irrespective of definitions. Detailed clinical and Doppler echocardiographic data demonstrate baseline characteristics stability, implying that increased AVR indications do not stem from increased disease severity but from increased recognition of early AVR benefits. After 2016, nationwide volume of transcatheter AVR continued to increase, but compounded slight decline of surgical AVR vs. large growth of population, of transcatheter intervening centres and of valve-in-valve procedures.[5] Thus, AS case-per-centre growth is much less impressive and encompasses encroachment on younger patients at lower risk, suggesting

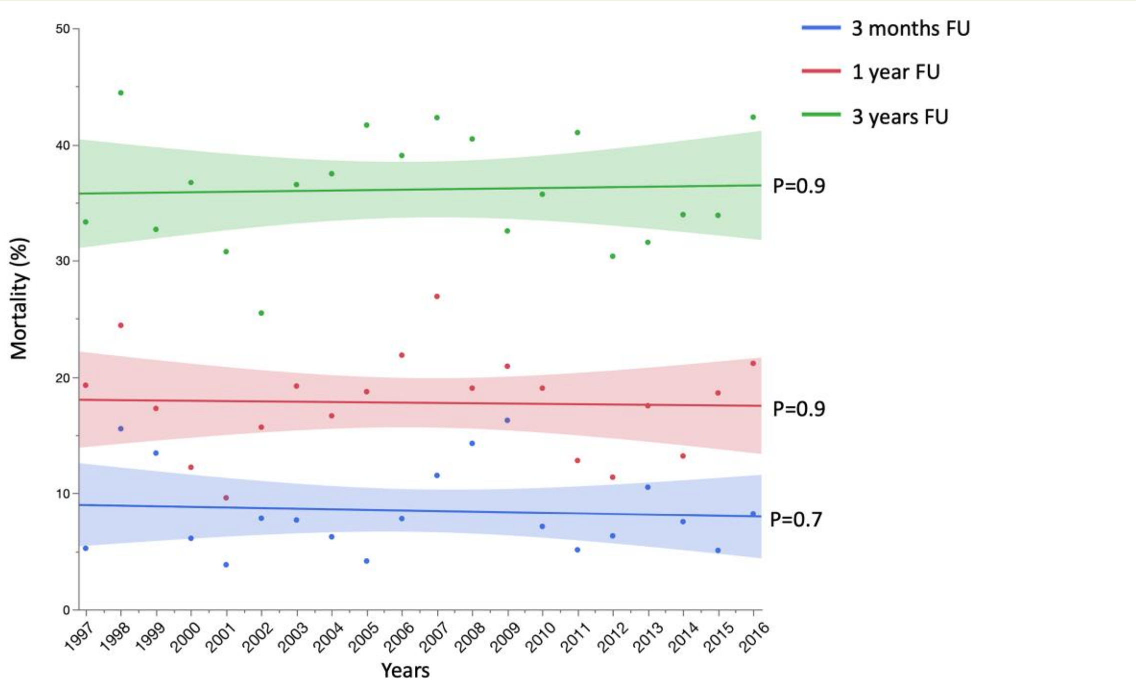


Figure 4 Overall mortality following the diagnosis of severe aortic stenosis in the community: the proportion of patients with severe AS deceased within each specific time interval is indicated by a dot for each year of the study (1997–2016) within 3 months (blue), within 1 year (red), and within 3 years (green) with the stable trends indicated by the regression line and correspondingly coloured zone. Note the very high and swift mortality observed after the diagnosis of severe aortic stenosis

indication-creep towards less severe AS.[5,10] Hence, presuming that increased AVR volume reflects collapsed undertreatment would be presumptuous. Furthermore, because evaluation of AS treatment and outcome requires years of follow-up, obtaining current-year evaluation of undertreatment/survival while desirable is unrealistic. Thus, future studies extending our findings are warranted.

Conclusion

In this large population-based community study—the first of its kind—severe AS incidence was ∼52/100 000 adults per year and slightly higher in men than women. Secular trends over a 20-year study period demonstrated that severe AS incidence remained unchanged with case burden growth linked to population growth. While incidence remained stable in men, it slightly but significantly decreased in women. While clinical and echocardiographic AS presentation remained stable, secular trends identified marked increase in AVR volumes and reduced time to treatment. Nevertheless, >40% of patients were never offered AVR during their lifetime and the challenge of persistent undertreatment of severe AS remains considerable. While early AVR is associated with substantial survival improvement, mortality following AS diagnosis remained high and unabated. Thus, sustained efforts to improve access, prompt diagnosis, early specialist assessment, and timely interventions are urgently required for the entire community.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

M.E.-S. reported consulting fees from Edwards, Corcym, and Artivion. J.C. reported to be in Medtronic surgery advisory board.

Data Availability

Data cannot be made available a priori for institutional policy but can be provided upon reasonable request.

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Ethical Approval

Institutional IRB approved the study.

Pre-registered Clinical Trial Number

None supplied.

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