Impact of Glycemic Control on the Progression of Aortic Stenosis: a Common Data Model Cohort Study

In-Chang Hwang (✉ inchang.hwang@gmail.com)

Seoul National University Bundang Hospital <https://orcid.org/0000-0003-4966-3924>

Seok Kim

Seoul National University Bundang Hospital

Dachung Boo

Seoul National University Bundang Hospital

Changhyun Park

Seoul National University Bundang Hospital

Sooyoung Yoo

Seoul National University Bundang Hospital

Yeonyee E Yoon

Seoul National University Bundang Hospital

Goo-Yeong Cho

Seoul National University Bundang Hospital

Research Article

Keywords: aortic stenosis, progression, diabetes mellitus, glycemic control

Posted Date: March 2nd, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1173479/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: The presence of diabetes mellitus (DM) is a well-established risk factor for the progression of degenerative aortic stenosis (AS). However, no study has investigated the impact of glycemic control on the rate of AS progression. We aimed to assess the association between the degree of glycemic control and the AS progression, using an electronic health record-based common data model (CDM).

Methods: We identified 1420 patients with mild to moderate AS (defined as an aortic valve [AV] maximal velocity [Vpeak] of 2.0–4.0 m/sec) at baseline, and follow-up echocardiography performed at an interval of ≥ 6 months. Patients were divided into 3 groups: no DM (n=1037), well-controlled DM (mean glycated hemoglobin [HbA1c] $< 7.0\%$ during the study period; n=186), and poorly controlled DM (mean HbA1c $\geq 7.0\%$ during the study period; n=143). The primary outcome was the AS progression rate, calculated as the annualized change in the Vpeak (Δ Vpeak/year).

Results: During follow-up (median 18.4 months), the total study population showed a gradual progression in AS severity. The mean HbA1c level during follow-up was proportionally associated with a higher AS progression rate ($\beta=0.024$; 95% confidence interval [CI] 0.006–0.043; $p=0.011$); a 1% increase in HbA1c was associated with a 27% higher risk of accelerated AS progression, and HbA1c $\geq 7.0\%$ was significantly associated with an accelerated AS progression (adjusted odds ratio=1.524; 95% CI 1.010–2.285; $p=0.043$). This association between the degree of glycemic control and AS progression rate was observed regardless of the baseline AS severity.

Conclusion: In patients with mild to moderate AS, the degree of glycemic control was significantly associated with AS progression. More intensive glycemic control might be beneficial for the prevention of AS progression in patients with DM and mild to moderate AS.

Background

Degenerative aortic stenosis (AS) is a progressive disease, in which the main pathophysiology is atherosclerosis with inflammation, fibrosis, and calcification of the aortic valve (AV) (1, 2). The presence of diabetes mellitus (DM) contributes to the development and progression of AS, through the augmentation of proinflammatory processes, enhanced lipid accumulation, and accelerated calcification of valvular endothelial and interstitial cells (3). These pathophysiologic links have been confirmed in clinical studies, which showed a significant association between the presence of DM and the risk of developing AS, as well as the progression of AS (4–7).

Although the association between the presence of DM and accelerated AS progression is well-established, no study has investigated the association between the degree of glycemic control and the rate of AS progression. Based on the underlying pathophysiology of AS progression, it could be expected that patients with poorly-controlled DM have more rapid AS progression. In a recent study of AV specimens from patients undergoing AV replacement, increased expression of valvular advanced glycation end products (AGEs) was associated with AS severity, suggesting that the level of glycemic

control might be associated with AS progression rate (8). This association would have clinical significance, given the lack of effective medical therapy to prevent AS progression (9).

In the present study, we aimed to assess the association between the degree of glycemic control and AS progression rate in patients with mild or moderate AS, using an electronic health record (EHR)-based common data model (CDM).

Methods

Data sources

This study utilized Observational Health Data Sciences and Informatics (OHDSI) open source software and the Observational Medical Outcomes Partnership (OMOP)-CDM version 5.3. The CDM comprised de-identified patient-level EHR data from outpatients and inpatients was obtained between April 2003 and July 2019, routinely collected during medical services at Seoul National University Bundang Hospital. The study protocol was approved by our institutional review board (B-1812-510-111), which waived the requirement of informed consent. All aspects of the study were conducted in accordance with the Declaration of Helsinki.

Study population

Patients with mild to moderate AS (defined as an AV maximal velocity [V_{peak}] of 2.0 – 4.0 m/sec) at baseline and follow-up echocardiography, performed at an interval of ≥ 6 months, were included. Considering the intermittent changes in the antidiabetic medications and the fluctuations of HbA1c levels, we selected the first 2 echocardiograms (baseline showing mild to moderate AS, and follow-up at an interval of ≥ 6 months), even in patients who underwent three or more echocardiographic examinations. The exclusion criteria were as follows: (1) age <19 years; (2) open heart surgery or transcatheter valve implantation before or during follow-up; (3) longest interval between the paired echocardiogram evaluations was less than 6 months; and (4) unavailable glycated hemoglobin (HbA1c) data (Figure 1).

Patients with DM were designated by Systematized Nomenclature of Medicine Clinical Terms (SNOMED-CT), current use of antidiabetic medication, and a fasting glucose ≥ 126 mg/dL or HbA1c $\geq 6.5\%$. “Well-controlled DM” was defined as a mean HbA1c level <7.0% during the study period, and “poorly-controlled DM” was defined as a mean HbA1c level $\geq 7.0\%$ during the study period.

Patients meeting the above eligibility criteria and definitions were identified using ATLAS version 2.8.0 and Structured Query Language (SQL) codes; outliers, as determined by R programming version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria), were excluded. The overall attrition diagram and a detailed list of concept ID and International Classification of Disease (ICD) codes used for constructing target definitions and exclusion criteria are provided in **Supplementary Table S1**.

Echocardiography

All echocardiographic images were obtained using a standard ultrasound machine with a 2.5-MHz probe. Standard techniques were used to obtain M-mode, 2-dimensional, and Doppler measurements, in accordance with the American Society of Echocardiography's guidelines (10, 11). The Vpeak was recorded using the apical, right parasternal, or suprasternal window yielding the highest velocity signal. The mean pressure gradient across the AV (meanPG) was calculated using a modified Bernoulli equation, and the AV area (AVA) was estimated from the continuity equation using the left ventricular outflow tract diameter and flow velocity.

Study outcomes

The primary outcome was the AS progression rate, calculated as the annualized change in the Vpeak ($\Delta V_{\text{peak}}/\text{year}$). Annualized changes in the meanPG ($\Delta \text{meanPG}/\text{year}$) and AVA ($\Delta \text{AVA}/\text{year}$) were also considered; however, due to missing AVA values in the dataset, the change in AVA was not assessed as a study outcome.

In order to evaluate the impact of the presence of DM and the degree of glycemic control on the AS progression rate, the study population was divided into three groups: patients without DM (no DM; n = 1037), patients with well-controlled DM (HbA1c <7.0%; n = 186), and patients with poorly-controlled DM (HbA1c $\geq$ 7.0%; n = 143).

Statistical analysis

Continuous variables are presented as the median with interquartile range (IQR), and categorical variables as frequencies. Differences between groups were evaluated using the Kruskal-Wallis test or one-way analysis of variance (ANOVA) with Bonferroni correction for multiple comparisons for continuous variables and the χ^2 test for categorical variables.

Trends in the AS progression rate ($\Delta V_{\text{peak}}/\text{year}$) according to the presence of DM and degree of glycemic control, as well as the baseline Vpeak, were assessed using the penalized smoothing spline methods. The association between the degree of glycemic control and AS progression rate ($\Delta V_{\text{peak}}/\text{year}$) was assessed using linear regression modeling. Variables with a P-value of <0.1 on univariable analysis were entered into the multivariable regression analysis, using the stepwise backward elimination method. Additionally, as the highest $\Delta V_{\text{peak}}/\text{year}$ tertile among patients with DM in the present study was 0.2 m/sec/year, patients with $\Delta V_{\text{peak}}/\text{year}$ values >0.2 m/sec/year were considered to indicate accelerated AS progression. The association between the degree of glycemic control and accelerated AS progression was assessed using logistic regression modeling, and variables with a P-value of <0.1 on univariable analysis were entered into the multivariable regression analysis, using the stepwise backward elimination method.

Data were analyzed using R programming version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria). A two-sided p-value of <0.05 was considered statistically significant.

Results

Baseline characteristics

Baseline characteristics, laboratory findings, and echocardiography data of the total study population are summarized in Table 1. The median age was 74 (IQR 65–80) years and 47% were male. Compared to those without DM (n = 1037), the patients with DM had higher frequencies of comorbidities, which were more frequent in those with poorly-controlled DM than in those with well-controlled DM.

Table 1
Baseline characteristics and the rates of AS progression

	Total study population (n = 1420)	Group 1 No DM (n = 1037)	Group 2 DM, well- controlled (n = 186)	Group 3 DM, poorly- controlled (n = 143)	Overall P
Age (years)	74 (65 – 80)	73 (63 – 79)	76 (70 – 81)	75 (70 – 80)	<0.001
Male sex	667 (47.0%)	470 (45.8%)	108 (56.0%)	67 (46.5%)	0.033
Body-mass index (kg/m ²)	24.2 (22.2 – 26.7)	24.0 (22.1 – 26.3)	24.5 (22.3 – 27.5)	24.9 (23.0 – 27.9)	<0.001
Body-surface area (m ²)	1.6 (1.5 – 1.8)	1.6 (1.5 – 1.8)	1.7 (1.6 – 1.8)	1.7 (1.6 – 1.8)	0.002
Systolic blood pressure (mmHg)	129 (116 – 143)	128 (116 – 141)	129 (118 – 146)	134 (118 – 149)	0.015
Diastolic blood pressure (mmHg)	70 (63 – 79)	71 (64 – 79)	68 (62 – 75)	68 (60 – 77)	0.006
Heart rate (bpm)	72 (64 – 84)	72 (64 – 85)	73 (64 – 83)	72 (65 – 82)	0.798
Hypertension	394 (27.8%)	247 (17.4%)	85 (6.0%)	47 (3.3%)	<0.001
Dyslipidemia	259 (18.2%)	0 (0.0%)	186 (100.0%)	143 (100.0%)	<0.001
Coronary artery disease	276 (19.4%)	177 (12.5%)	52 (3.7%)	40 (2.8%)	<0.001
Heart failure	129 (9.1%)	82 (5.8%)	25 (1.8%)	17 (1.2%)	0.043
Atrial fibrillation	161 (11.3%)	109 (7.7%)	25 (1.8%)	19 (1.3%)	0.466
Laboratory findings					
Hemoglobin (g/dL)	12.4 (10.8 – 13.7)	12.6 (11.2 – 13.9)	11.4 (10.3 – 13.2)	11.5 910.1 – 13.1)	<0.001
Creatinine (mg/dL)	0.9 (0.7 – 1.2)	0.9 (0.7 – 1.1)	1.1 (0.8 – 1.6)	1.0 (0.8 – 1.5)	<0.001
GFR (mL/min/1.73m ²)	75.3 (50.9 – 95.9)	82.5 (58.8 – 97.1)	60.2 (35.8 – 85.0)	64.8 (36.3 – 88.0)	<0.001
Values are given as the mean with standard deviation or as a number (percentage).					
Abbreviations: AS, aortic stenosis; DM, diabetes mellitus; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LAVI, left atrial volume index; Vpeak, aortic valve maximal velocity; meanPG, mean pressure gradients across the aortic valve; AVA, aortic valve area; RAS, renin-angiotensin system; DOAC, direct oral anticoagulants; DPP4, dipeptidyl peptidase-4; SGLT2, sodium-glucose cotransporter 2.					

	Total study population (n = 1420)	Group 1 No DM (n = 1037)	Group 2 DM, well- controlled (n = 186)	Group 3 DM, poorly- controlled (n = 143)	Overall P
Fasting glucose (mg/dL)	105 (93 – 129)	101 (92 – 114)	118 (100 – 144)	141 (113.5 – 173)	<0.001
HbA1c (%)	6.1 (5.6 – 6.9)	5.8 (5.4 – 6.1)	6.4 (5.9 – 6.8)	7.6 (7.0 – 8.6)	<0.001
Total cholesterol (mg/dL)	158 (133 – 186)	164 (139 – 193)	143 (122 – 168.5)	141 (127 – 164)	<0.001
Triglyceride (mg/dL)	104 (77 – 144)	99 (74 – 142)	112.5 (76 – 146.5)	113 (84.8 – 173)	0.007
HDL cholesterol (mg/dL)	47 (38 – 56)	49 (41 – 60)	42 (36 – 53)	41 (35 – 49)	<0.001
LDL cholesterol (mg/dL)	89 (71 – 109)	95 (75 – 116)	83 (65 – 100)	79 (63 – 97)	<0.001
Echocardiographic parameters					
LVEF (%)	62.5 (57.0 – 67.2)	62.7 (57.4 – 67.2)	62.3 (55.7 – 67.2)	62.3 (55.7 – 67.2)	0.381
LVMI (g/m ²)	108.9 (91.9 – 130.4)	108.1 (90.7 – 130.6)	113.6 (94.5 – 133.1)	106.6 (95.5 – 125.3)	0.311
LAVI (mL/m ²)	43.2 (32.8 – 60.2)	42.7 (32.3 – 60.5)	44.1 (34.4 – 60.8)	44 (32.3 – 57.8)	0.981
Vpeak (m/sec)	2.5 (2.2 – 2.9)	2.5 (2.2 – 3.0)	2.4 (2.2 – 2.8)	2.4 (2.2 – 2.9)	0.017
meanPG (mmHg)	13.1 (10.2 – 19.4)	13.3 (10.4 – 20.0)	12.5 (10.0 – 17.1)	12.9 (10.0 – 18.5)	0.075
AVA (cm ²)	1.3 (1.1 – 1.6)	1.3 (1.1 – 1.6)	1.3 (1.2 – 1.6)	1.3 (1.1 – 1.4)	0.293
Medication					
RAS blocker	478 (33.7%)	309 (30.1%)	96 (49.7%)	57 (39.6%)	<0.001

Values are given as the mean with standard deviation or as a number (percentage).

Abbreviations: AS, aortic stenosis; DM, diabetes mellitus; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LAVI, left atrial volume index; Vpeak, aortic valve maximal velocity; meanPG, mean pressure gradients across the aortic valve; AVA, aortic valve area; RAS, renin-angiotensin system; DOAC, direct oral anticoagulants; DPP4, dipeptidyl peptidase-4; SGLT2, sodium-glucose cotransporter 2.

	Total study population (n = 1420)	Group 1 No DM (n = 1037)	Group 2 DM, well- controlled (n = 186)	Group 3 DM, poorly- controlled (n = 143)	Overall P
Beta blocker	302 (21.3%)	194 (18.9%)	56 (29.0%)	44 (30.6%)	<0.001
Calcium channel blocker	333 (23.5%)	203 (19.8%)	76 (39.4%)	46 (31.9%)	<0.001
Spirolactone	72 (5.1%)	53 (5.2%)	10 (5.2%)	7 (4.9%)	0.988
Statins	468 (33.0%)	291 (28.3%)	84 (43.5%)	83 (57.6%)	<0.001
Warfarin	149 (10.5%)	116 (11.3%)	16 (8.3%)	7 (4.9%)	0.037
DOAC	38 (2.7%)	24 (2.3%)	8 (4.2%)	5 (3.5%)	0.307
Antiplatelet agents	458 (32.3%)	284 (27.7%)	89 (46.1%)	75 (52.1%)	<0.001
Metformin	105 (7.4%)	0 (0.0%)	60 (31.2%)	45 (31.3%)	<0.001
DPP4 inhibitors	65 (4.6%)	0 (0.0%)	31 (16.1%)	34 (23.6%)	<0.001
SGLT2 inhibitors	1 (0.1%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0.048
Sulfonylurea	78 (5.5%)	0 (0.0%)	41 (21.2%)	37 (25.7%)	<0.001
Thiazolidinedione	6 (0.4%)	0 (0.0%)	2 (1.0%)	4 (2.8%)	<0.001
Alpha glucosidase inhibitor	12 (0.8%)	0 (0.0%)	7 (3.6%)	5 (3.5%)	<0.001
AS progression rate					
Follow-up interval (months)	18.4 (12.3 – 31.4)	18.6 (12.4 – 31.8)	18.6 (12.3 – 27.8)	16.7 (11.6 – 29.0)	0.199
Δ Vpeak/year (m/sec/year)	0.065 (-0.036 – 0.223)	0.057 (-0.042 – 0.225)	0.071 (0.000 – 0.205)	0.092 (-0.002 – 0.273)	0.015
Δ meanPG/year (mmHg/year)	0.709 (-0.548 – 2.910)	0.585 (-0.624 – 2.812)	0.991 (-0.229 – 2.638)	1.178 (-0.156 – 3.259)	0.059
Values are given as the mean with standard deviation or as a number (percentage).					
Abbreviations: AS, aortic stenosis; DM, diabetes mellitus; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LAVI, left atrial volume index; Vpeak, aortic valve maximal velocity; meanPG, mean pressure gradients across the aortic valve; AVA, aortic valve area; RAS, renin-angiotensin system; DOAC, direct oral anticoagulants; DPP4, dipeptidyl peptidase-4; SGLT2, sodium-glucose cotransporter 2.					

The median HbA1c levels were 5.8% (IQR 5.4–6.1) in patients without DM, 6.4% (IQR 5.9–6.8) in patients with well-controlled DM, and 7.6% (IQR 7.0–8.6) in patients with poorly-controlled DM. At baseline, the median Vpeak, meanPG, and AVA were 2.5 m/sec (IQR 2.2–2.9), 13.1 mmHg (IQR 10.2–19.4), and 1.3 cm² (IQR 1.1–1.6) in total study population, and the severity of AS was similar between the 3 groups.

Association between glycemic control and AS progression

The rate of AS progression was different between the groups: the Δ Vpeak/year was 0.06 m/sec/year (IQR -0.04–0.23) in patients without DM, 0.07 m/sec/year (IQR 0.00–0.21) in patients with well-controlled DM, and 0.09 m/sec/year (IQR 0.00–0.27) in those with poorly-controlled DM (overall p=0.015) (Table 1). The rate of AS progression assessed by the changes in the meanPG and AVA showed similar trends of a lower AS progression rate in patients without DM, and a higher AS progression rate in patients with DM, especially in those with poorly-controlled DM.

In order to evaluate the overall impact of glycemic control on the rate of AS progression, the Δ Vpeak/year and Δ meanPG/year were plotted according to the mean HbA1c levels in Figure 2. The AS progression rate was proportional to the degree of glycemic control, showing a more rapid progression in those with a higher HbA1c level. The association between the degree of glycemic control and the rate of AS progression (Δ Vpeak/year) was further assessed in linear regression analyses (Table 2 and Supplementary Table S2). In the multivariable regression model, the higher mean HbA1c level during follow-up (β = 0.024; 95% CI 0.006–0.043; p=0.011), higher Vpeak at baseline (β = 0.056; 95% CI 0.014–0.098; p=0.010), higher total cholesterol level at baseline (β = 0.001; 95% CI 0.000–0.001; p=0.022), and the presence of coronary artery disease (β = 0.066; 95% CI 0.012–0.120; p=0.016) were significantly associated with the higher rate of AS progression; whereas the presence of heart failure was negatively associated with the rate of AS progression (Table 2).

Table 2
Multivariable linear regression models for the predictors of AS progression rate

	β	95% CI	P value
CAD	0.066	0.012 – 0.120	0.016
Heart failure	-0.109	-0.188 – -0.031	0.006
Total cholesterol (per +1 mg/dL)	0.001	0.000 – 0.001	0.022
HbA1 (per +1%)	0.024	0.006 – 0.043	0.011
Vpeak (per +1 m/sec)	0.056	0.014 – 0.098	0.010
Univariable factors with P-values <0.1 were entered into the multivariable linear regression analysis, using the stepwise backward elimination method. Variables with significant association with AS progression (Δ Vpeak/year) are shown.			
Abbreviations: CI, confidence interval; CAD, coronary artery disease; HbA1c, glycated hemoglobin; Vpeak, aortic valve maximal velocity.			

Considering that the baseline Vpeak was significantly associated with the rate of AS progression, we compared the rate of AS progression between the patients without DM, those with well-controlled DM, and those with poorly-controlled DM, across the range of baseline Vpeak (Figure 3). As the baseline Vpeak increases, the rate of AS progression rate showed a tendency to gradually increase (Figure 3A). Of note, compared to those without DM, the increase in the AS progression rate according to the baseline Vpeak value showed a steeper pattern in patients with DM, and the slope was the steepest in those with poorly-controlled DM. The same trend was observed, when the AS progression rate was assessed using the changes in the meanPG (Figure 3B).

Using the $\Delta V_{\text{peak}}/\text{year}$ value of >0.2 m/sec/year as the cutoff for accelerated AS progression, we performed logistic regression analyses to investigate the association between the glycemic control and the accelerated AS progression (Table 3 and Supplementary Table S3). In the multivariable logistic regression analysis, the mean HbA1c level was significantly associated with the accelerated AS progression (adjusted OR=1.267; 95% CI 1.106–1.453; $p < 0.001$). This association maintained its statistical significance when the glycemic control level was used as a categorical variable (mean HbA1c $\geq 7.0\%$) (adjusted OR=1.524; 95% CI 1.010–2.285; $p=0.043$).

Table 3
Multivariable logistic regression models for the predictors of accelerated AS progression

	Assessed as continuous variables			Assessed as categorical variables		
	Adjusted OR	95% CI	P value	Adjusted OR	95% CI	P value
Male sex	1.539	1.092 – 2.177	0.014	-	-	-
Total cholesterol (per +1 mg/dL)	1.007	1.002 – 1.011	0.002	1.006	1.002 – 1.010	0.005
HbA1c (per +1%)	1.267	1.106 – 1.453	<0.001	-	-	-
HbA1c $\geq 7.0\%$	-	-	-	1.524	1.010 – 2.285	0.043
Vpeak (per +1 m/sec)	1.659	1.233 – 2.231	<0.001	-	-	-
Vpeak ≥ 3 m/sec	-	-	-	1.696	1.151 – 2.487	0.007
RAS blocker	0.657	0.454 – 0.943	0.024	0.654	0.453 – 0.935	0.021
Spironolactone	-	-	-	0.293	0.068 – 0.865	0.050
Univariable factors with P-values <0.1 were entered into the multivariable logistic regression analysis, using the stepwise backward elimination method. Variables with significant association with accelerated AS progression (Δ Vpeak/year >0.2 m/sec/year) are shown.						
Abbreviations: OR, odds ratio; CI, confidence interval; HbA1c, glycated hemoglobin; Vpeak, aortic valve maximal velocity; RAS, renin-angiotensin system.						

Discussion

In the present study, we assessed the AS progression rate according to the presence of DM and degree of glycemic control among 1420 patients with mild to moderate AS, using an EHR-based CDM model. The presence of DM, as well as the glycemic control level, was significantly associated with accelerated AS progression. To our knowledge, this is the first study to demonstrate an association between the degree of glycemic control and the AS progression rates. Our findings highlight the importance of glycemic control in patients with DM and mild to moderate AS.

The presence of DM is a well-established risk factor for AS development and progression. A study of 6780 participants from the Multi-Ethnic Study of Atherosclerosis (MESA) showed that patients with DM have a 1.7–2.1 fold higher risk of AV calcification, as detected on computed tomography (4).

Furthermore, *Kamalesh et al* evaluated the change in AVA in 166 patients with AS, and found that among

those with moderate AS at baseline, patients with DM had a larger reduction in AVA than patients without DM (5). More recently, large-scale population studies have confirmed the significant impact of DM on AS progression. For example, the Cardiovascular Health in Ambulatory Care Research Team (CANHEART) study assessed the risk of incident severe AS in 1.12 million individuals during a median of 13 years, and reported that the presence of DM increased the risk of developing severe AS by 50% (7). Similarly, a study by *Larsson et al* assessed the association of DM with seven cardiovascular diseases among more than 70,000 adults, and demonstrated that the presence of type 2 DM increased the risk of incident AS by 34% (6).

The robust association between the presence of DM and accelerated AS progression can be explained by various pathophysiologic mechanisms. Patients with DM have a higher expression of proinflammatory C-reactive protein (CRP) in AV tissue, and higher levels of CRP and tissue factor in plasma, than patients without DM, suggesting that increased proinflammatory processes lead to accelerated AS progression (12, 13). In addition, transient hyperglycemia has been shown to lead to excessive proinflammatory phospholipid synthesis and coagulation activation in valvular interstitial cells, supporting the impact of proinflammatory signals on accelerated AS progression in patients with DM (14).

Although the impact of the presence of DM on AS progression has been well-established, the impact of the degree of glycemic control on AS progression was largely unknown prior to the present study. In a recent study by *Kopytek et al*, patients with DM showed increased expression of AGEs and AGE receptors in AV tissue, which was correlated with the HbA1c level (8). Although this finding suggests that patients with poorly-controlled DM have accelerated AS progression, the AS progression rate was not assessed in this previous study. Considering the beneficial effects of strict glycemic control on the prevention of major cardiovascular adverse events, and the underlying pathophysiology, we thought it reasonable to hypothesize that the degree of glycemic control is associated with the AS progression rate.

In the present study, we compared the AS progression rate based on echocardiographic parameters between patients without DM, with well-controlled DM, and with poorly-controlled DM. The mean HbA1c level during the study period was used as the indicator of glycemic control, which enabled the direct assessment of the association between the degree of glycemic control and the AS progression rate. Compared to that in patients without DM, AS progression was accelerated in patients with DM, and the progression was accelerated to a greater degree in those with poor glycemic control than in those with well-controlled DM (representative cases shown in Figure 4). These findings emphasize the importance of strict glycemic control in patients with mild to moderate AS, in order to prevent the development of severe AS and the resultant invasive procedures, as well as a poor prognosis. Additionally, these findings suggest that the benefits of strict glycemic control in patients with DM are not limited to the prevention of coronary events, but also include the attenuation of AS progression.

Furthermore, the potential benefit of strict glycemic control was consistently observed across the entire range of baseline AS severity in our study population. The present study results confirm previous studies that showed a more rapid progression rate in those with higher baseline Vpeak. Additionally, we newly

showed that the degree of glycemic control affected the AS progression rates regardless of the baseline AS severity, suggesting that strict glycemic control would have consistent benefits in patients with mild to moderate AS.

The present study has several limitations. First, it was a retrospective cohort study, and thus, the causal relationship between glycemic control and AS progression requires further confirmation in a clinical trial. Second, we could not assess differences in AS progression rate according to the class or dosage of antidiabetic drugs, because the antidiabetic drugs prescribed in the study population were frequently adjusted during follow-up. Given the potential effects of the antidiabetic drug class on the AS progression rate (15), further studies with larger sample size or clinical trials are warranted. Third, our study focused on the changes in echocardiographic parameters, but not AV calcification as assessed by computed tomography, or AV inflammation as assessed by nuclear imaging. Finally, we included patients with mild or moderate AS, and therefore, our findings may not be applicable to those with AV calcification without stenosis, or those with advanced severe AS. However, considering the pathophysiology of AS progression, strict diabetic control might be beneficial in those with degenerative AV changes, even before the development of overt AS. In patients with severe AS, the benefits of strict glycemic control might not include the prevention of AS progression; however, the benefit in terms the prevention of other cardiovascular diseases is still valid.

Conclusion

In patients with mild or moderate AS, the degree of glycemic control is significantly associated with the AS progression rate. Accordingly, more intensive glycemic control might be beneficial for the prevention of AS progression in patients with DM and mild to moderate AS. Future clinical trials are warranted to confirm the causal relationship between the glycemic control and AS progression.

Abbreviations

AS, aortic stenosis; AGEs, advanced glycation end products; AV, aortic valve; AVA, aortic valve area; CDM, common data model; CI, confidence interval; DM, diabetes mellitus; HER, electronic health record; HbA1c, glycated hemoglobin; IQR, interquartile range; OR, odds ratio; Vpeak, aortic valve maximal velocity; meanPG, mean pressure gradient across the aortic valve.

Declarations

Ethics approval and consent to participate: The study protocol was approved by the institutional review board of Seoul National University Bundang Hospital; given the retrospective nature of the study, the need for informed consent was waived.

Consent for publication: Not applicable

Availability of data and materials: The de-identified data that support the findings of this study are available from the corresponding author upon reasonable request and appropriate permission from the institutional review board.

Competing interests: There are no conflicts of interest or competing interests to report.

Funding: This research was supported by the Seoul National University Bundang Hospital Research Fund (No. 18-2018-0036). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Authors' contributions: ICH: conceptualization, study design, data interpretation, writing – original draft, review and editing; SK: data analysis and interpretation, writing – review and editing; DB: data analysis and interpretation, writing – review and editing; CP: data analysis and interpretation, writing – review and editing; SY: study design, data interpretation, writing – review and editing; YYY: writing – review and editing; GYC: writing – review and editing. All authors have read and approved the manuscript

Acknowledgements: None

References

1. Pawade TA, Newby DE, Dweck MR. Calcification in Aortic Stenosis: The Skeleton Key. *J Am Coll Cardiol*. 2015;66(5):561-77.
2. Peeters F, Meex SJR, Dweck MR, Aikawa E, Crijns H, Schurgers LJ, et al. Calcific aortic valve stenosis: hard disease in the heart: A biomolecular approach towards diagnosis and treatment. *Eur Heart J*. 2018;39(28):2618-24.
3. Banovic M, Athithan L, McCann GP. Aortic stenosis and diabetes mellitus: An ominous combination. *Diab Vasc Dis Res*. 2019;16(4):310-23.
4. Katz R, Wong ND, Kronmal R, Takasu J, Shavelle DM, Probstfield JL, et al. Features of the metabolic syndrome and diabetes mellitus as predictors of aortic valve calcification in the Multi-Ethnic Study of Atherosclerosis. *Circulation*. 2006;113(17):2113-9.
5. Kamalesh M, Ng C, El Masry H, Eckert G, Sawada S. Does diabetes accelerate progression of calcific aortic stenosis? *Eur J Echocardiogr*. 2009;10(6):723-5.
6. Larsson SC, Wallin A, Hakansson N, Stackelberg O, Back M, Wolk A. Type 1 and type 2 diabetes mellitus and incidence of seven cardiovascular diseases. *Int J Cardiol*. 2018;262:66-70.
7. Yan AT, Koh M, Chan KK, Guo H, Alter DA, Austin PC, et al. Association Between Cardiovascular Risk Factors and Aortic Stenosis: The CANHEART Aortic Stenosis Study. *J Am Coll Cardiol*. 2017;69(12):1523-32.
8. Kopytek M, Zabczyk M, Mazur P, Undas A, Natarska J. Accumulation of advanced glycation end products (AGEs) is associated with the severity of aortic stenosis in patients with concomitant type 2 diabetes. *Cardiovasc Diabetol*. 2020;19(1):92.

9. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, 3rd, Gentile F, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021;143(5):e72-e227.
10. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28(1):1-39 e14.
11. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29(4):277-314.
12. Natorska J, Wypasek E, Grudzien G, Sobczyk D, Marek G, Filip G, et al. Does diabetes accelerate the progression of aortic stenosis through enhanced inflammatory response within aortic valves? *Inflammation*. 2012;35(3):834-40.
13. Galante A, Pietroiusti A, Vellini M, Piccolo P, Possati G, De Bonis M, et al. C-reactive protein is increased in patients with degenerative aortic valvular stenosis. *J Am Coll Cardiol*. 2001;38(4):1078-82.
14. Ciortan L, Macarie RD, Cecoltan S, Vadana M, Tucureanu MM, Mihaila AC, et al. Chronic High Glucose Concentration Induces Inflammatory and Remodeling Changes in Valvular Endothelial Cells and Valvular Interstitial Cells in a Gelatin Methacrylate 3D Model of the Human Aortic Valve. *Polymers (Basel)*. 2020;12(12).
15. Choi B, Lee S, Kim SM, Lee EJ, Lee SR, Kim DH, et al. Dipeptidyl Peptidase-4 Induces Aortic Valve Calcification by Inhibiting Insulin-Like Growth Factor-1 Signaling in Valvular Interstitial Cells. *Circulation*. 2017;135(20):1935-50.

Figures

Figure 1

Figure 1

Study attrition diagram

Abbreviations: AS, aortic stenosis; DM, diabetes mellitus.

Figure 2

Figure 2

Trends in AS progression according to the degree of glycemic control

The association between the mean HbA1c levels and the AS progression rate, as assessed by the change in **(A)** Vpeak and **(B)** meanPG, is shown.

Abbreviations: AS, aortic stenosis; Vpeak, aortic valve maximal velocity; meanPG, mean pressure gradients across the aortic valve.

Figure 3

Figure 3

Differences in AS progression according to the presence of diabetes mellitus and degree of glycemic control

The AS progression rates, as assessed by the change in **(A)** Vpeak and **(B)** meanPG, is shown across the range of baseline AS severity in patients without DM, with well-controlled DM, and with poorly-controlled DM.

Abbreviations: AS, aortic stenosis; DM, diabetic mellitus; Vpeak, aortic valve maximal velocity; meanPG, mean pressure gradients across the aortic valve.

Figure 4

Representative cases

(A) *Patient A*, without diabetes, had low HbA1c levels during follow-up (mean HbA1c, 5.7%) and showed a slow progression of AS ($\Delta V_{\text{peak}}/\text{year}$, 0.2 m/sec/year; ΔmeanPG , 2.2 mmHg/year; ΔAVA , -0.09 cm²/year). **(B)** *Patient B* was diagnosed as having diabetes, and maintained a tight glycemic control (mean HbA1c, 6.1%). During follow-up, the progression of AS was modest ($\Delta V_{\text{peak}}/\text{year}$, 0.3 m/sec/year; ΔmeanPG , 5.1 mmHg/year; ΔAVA , -0.11 cm²/year). **(C)** *Patient C*, in whom the glycemic control was poor (mean HbA1c, 8.9%), showed an accelerated AS progression during follow-up ($\Delta V_{\text{peak}}/\text{year}$, 0.7 m/sec/year; ΔmeanPG , 10.5 mmHg/year; ΔAVA , -0.36 cm²/year).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [GlycemiccontrolASprogressionCDMSupplement.docx](#)