




# BMJ Open Associations between aortic regurgitation severity and risk of incident myocardial infarction and stroke among patients with degenerative aortic valve disease: insights from a large Chinese population-based cohort study

Guangxiao Li <sup>1,2</sup> Tan Li,<sup>3</sup> Yanli Chen,<sup>1</sup> Xiaofan Guo,<sup>1</sup> Zhao Li,<sup>1</sup> Ying Zhou,<sup>1</sup> Hongmei Yang,<sup>1</sup> Shasha Yu,<sup>1</sup> Guozhe Sun,<sup>1</sup> Liqiang Zheng <sup>4</sup>, Yingxian Sun <sup>1</sup>

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For numbered affiliations see end of article.

**Correspondence to**  
Dr Yingxian Sun;  
[yxsun@cmu.edu.cn](mailto:yxsun@cmu.edu.cn)

## ABSTRACT

**Objectives** Few studies have explored whether the risk of myocardial infarction (MI) or stroke varies among patients with degenerative aortic valve disease (DAVD) with different severity of aortic regurgitation (AR) or not. Thus, a prospective study was conducted to elucidate the causal relationship between AR severity and risk of incident MI and stroke among patients with DAVD recruited from a general population in Northeast China.

**Design** Prospective cohort study.

**Setting** Community-based study carried out in rural areas of Northeast China.

**Methods** There were 3675 patients with DAVD aged ≥45 years eligible for the prospective study. During a median follow-up time of 4.64 years, 99 participants lost to follow-up. Cox regression analyses were used to investigate the association between baseline AR severity and the risk of incident MI or stroke.

**Results** In the final cohort of 3576 patients with DAVD, there were 3153 patients without AR (88.2%), 386 patients with mild AR (10.8%) and 37 patients with moderate or severe AR (1.0%). Multivariate analyses showed that, compared with participants without AR, those with moderate/severe AR were associated with 8.33 and 6.22-fold increased risk of MI and MI mortality, respectively. However, no significant associations between AR and the risk of stroke or stroke mortality were observed.

**Conclusions** As compared with no AR, moderate/severe AR but not mild AR was an independent predictor for the risk of MI and MI mortality. AR was not significantly associated with stroke or stroke mortality, irrespective of AR severity. Secondary prevention strategies should be taken to delay the progression of DAVD and thus reduce the incidence of MI.

## INTRODUCTION

Over the past decades, the predominant cause of valvular heart diseases (VHDs) gradually

## Strengths and limitations of this study

- Whether the risk of myocardial infarction (MI) or stroke varies across patients with degenerative aortic valve disease (DAVD) with different severity of aortic regurgitation (AR) remains unclear.
- A cohort study was conducted to elucidate the association between AR severity and risk of MI and stroke.
- The study participants were recruited using a multi-stage, randomly stratified cluster-sampling strategy.
- The diagnoses of MI were made by the local cardiologists, and not all patients with MI underwent coronary angiography.
- The relatively small number of patients with DAVD with moderate/severe AR limited the statistical power.

transits from rheumatic to age-related degenerative aetiology.<sup>1 2</sup> Degenerative VHDs have become an important public health problem that results in high morbidity and mortality in the ageing population.<sup>3</sup> Of them, degenerative aortic valve disease (DAVD) is the most commonly observed. It was reported that the prevalence of aortic valve sclerosis, calcification or thickening was approximately 21%–31% in subjects ≥65 years of age.<sup>4 5</sup> According to the Framingham Study, the prevalence of overall aortic regurgitation (AR) was estimated at 4.9%, while the prevalence of moderate and severe AR was 0.5%.<sup>6</sup> The incidence and severity of AR increase with age, reaching a peak between 40 and 60 years of age.<sup>6</sup>

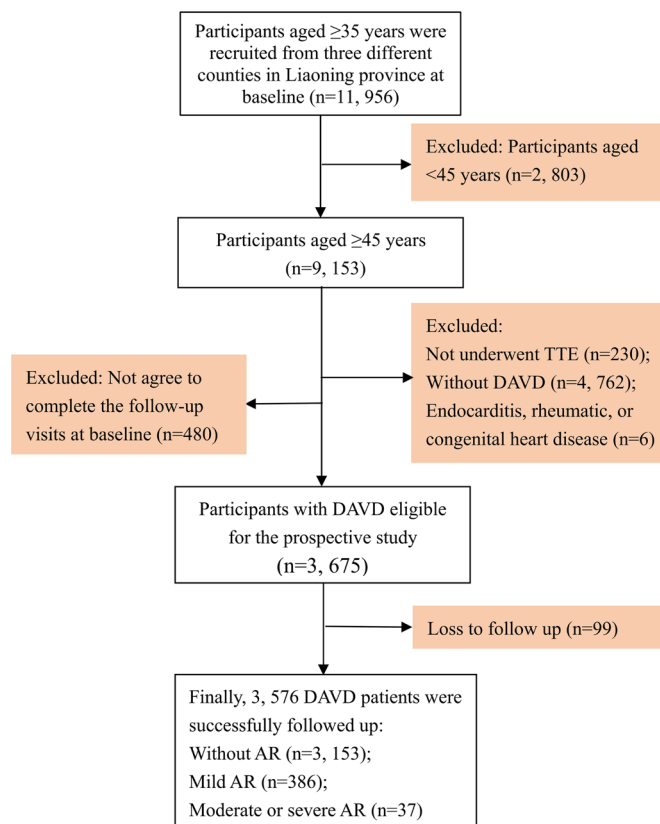
Accumulated evidence showed that aortic valve sclerosis and vascular atherosclerosis might share a common pathological background. The risk factors involved in the development of aortic valve sclerosis were similar to that in the development of vascular atherosclerosis, including ageing, gender, hypertension, smoking, hyperlipidaemia, diabetes.<sup>7–9</sup> Though many studies had reported a significant association between DAVD and risk of concomitant coronary artery disease,<sup>9–10</sup> most of them were cross-sectional or retrospective studies, which limited their ability to infer the possible causal relationship. Moreover, some previous studies were hospital-based and only enrolled patients undergoing valve replacement treatment for severe VHDs.<sup>11–13</sup> Few studies have explored whether the risk of coexisting myocardial infarction (MI) varies among patients with DAVD with different severity of AR or not. Additionally, less is known about whether there is any significant association between AR severity and concomitant stroke among patients with DAVD. Thus, we conducted a large and prospective study to elucidate the causal relationship between AR severity and risk of MI as well as stroke among patients with DAVD (aged  $\geq 45$  years) recruited from a general Chinese population.

## METHODS

### Study subjects

The Northeast China Rural Cardiovascular Health Study is a community-based prospective cohort study that is carried out in rural areas of Northeast China. A full description of the study design can refer to the previous articles by our study group.<sup>14–16</sup> In brief, a total of 11 956 participants aged  $\geq 35$  years were enrolled from three counties (Dawa, Zhangwu and Liaoyang) in Liaoning province during 2012–2013, using a multistage, randomly stratified cluster-sampling strategy. Detailed information was collected at baseline for all participants. They were invited to attend a follow-up study in 2015 and 2017, respectively. Cardiovascular events were then collected and evaluated. Participants who completed at least one follow-up visit were considered successfully followed up.

As shown in [figure 1](#), the participants were further screened depending on the purpose of the current study. Of the 11 956 participants, 2803 participants were excluded because they were aged  $< 45$  years. Furthermore, participants who did not undergo transthoracic echocardiogram (TTE) or had not DAVD were excluded ( $n=230$  and  $n=4762$ , respectively). Participants with endocarditis, rheumatic or congenital heart disease were also excluded ( $n=6$ ). Participants who did not agree to complete the follow-up visits at baseline were excluded as well ( $n=480$ ). Finally, there were 3675 patients with DAVD eligible for the prospective study. During the follow-up period, 99 of them lost to follow-up, and 3576 of them finished the follow-up visits, with a median follow-up time of 4.64 (IQR: 4.36–4.92) years.



**Figure 1** The flowchart for the selection of study subjects. AR, aortic regurgitation; DAVD, degenerative aortic valve disease; TTE, transthoracic echocardiogram.

### Data collection

At baseline, all research subjects were interviewed face-to-face by cardiologists and nurses using a standardised questionnaire. Detailed information on demographic characteristics, cardiovascular risk factors and medical records was obtained. History of MI, atrial fibrillation (AF), heart failure and stroke was self-reported and further confirmed by medical records. Usage of anti-hypertensive and antidiabetic drugs within 2 weeks at baseline was self-reported as well. Blood pressure was measured three times in a resting state with an interval of at least 5 min using a standardised automatic electronic sphygmomanometer (HEM-907; Omron, Tokyo, Japan). The average value was used for statistical analysis. To accurately measure height and weight, all study subjects should take off their shoes and wear light clothes. Fasting blood samples were collected by trained nurses after fasting for at least 12 hours. Fasting plasma glucose (FPG), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), serum creatinine, calcium and phosphorus were measured automatically (Olympus AU 640, Tokyo, Japan).

Hypertension was defined as systolic blood pressure (SBP)  $\geq 140$  mm Hg or diastolic blood pressure (DBP)  $\geq 90$  mm Hg. Participants who were taking antihypertensive drugs were also diagnosed as hypertension. Diabetes was defined as FPG  $\geq 7.0$  mmol/L,<sup>17</sup> with known

diabetes, or current use of antidiabetic drugs. The lipid profiles that met at least one the following criteria would be diagnosed as dyslipidaemia<sup>18</sup>: TC  $\geq 6.21$  mmol/L, TG  $\geq 2.26$  mmol/L, LDL-C  $\geq 4.16$  mmol/L or HDL-C  $< 1.03$  mmol/L. The estimated glomerular filtration rate (eGFR) was calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation.<sup>19</sup>

### Electrocardiographic evaluation

As previously described, baseline echocardiogram was conducted by using the commercially available Doppler echocardiographic machine (Vivid, GE Healthcare, Chicago, USA), with 3.0-MHz transducer.<sup>20</sup> The TTE included M-mode, two-dimensional, spectral and colour Doppler. All participants were examined in the lateral position. The echocardiograms were analysed and read by three experienced sonographers specialised in echocardiography. Any discrepancy would be resolved by discussion.

DAVD was defined as an abnormal irregular thickening or a focal or diffuse increase of the echogenicity of the leaflets with or without reduced systolic opening.<sup>4</sup> The colour flow Doppler enables the visualisation of the actual regurgitant jet.<sup>21</sup> The severity of AR was estimated by the ratio of the regurgitant jet width to the LV outflow tract in the centrally directed jet.<sup>22</sup> A ratio of  $< 25\%$ ,  $25\%–64\%$  and  $\geq 65\%$  indicate mild, moderate and severe AR, respectively.<sup>22</sup> Similarly, tricuspid and mitral valve regurgitation was judged by the existence of the regurgitant jet or not. The assessment of valve stenosis (including tricuspid stenosis, mitral stenosis and aortic stenosis) was conducted according to the European Association of Echocardiography (EAE)/American Society of Echocardiography (ASE) recommendations for clinical practice.<sup>23</sup>

The measurements of aortic annular diameter (AOD), interventricular septal thickness (IVSd), LV end-diastolic internal dimension (LVIDd), LV end-systolic internal dimension (LVIDs) and posterior wall thickness were performed following the guideline of the ASE.<sup>24</sup> Left ventricular mass (LVM) was calculated using a corrected formula derived from the ASE-cube LV mass formula.<sup>25</sup>  $LVM = 0.8 \times (1.04 \times (IVSd + LVIDd + PWTd)^3 - LVIDd^3) + 0.6$  g. The LVM index (LVMI) was estimated as a ratio of LVM to body surface area. The LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) were calculated using the equation developed by Teichholz *et al.*<sup>26</sup> Stroke volume (SV) was equal to LVEDV–LVESV. LV ejection fraction (LVEF) was calculated as  $((LVEDV - LVESV) / LVEDV) \times 100\%$ .

### Definition of endpoints

The clinical outcome of the current study was the presence of new-onset MI or stroke during the follow-up period, irrespective of the prior history. MI and stroke specific mortality was also recorded. MI was diagnosed following the third universal definition of MI.<sup>27</sup> According to the WHO Multinational Monitoring of Trends and Determinants in Cardiovascular Disease criteria,<sup>28</sup> stroke

was defined as the rapid development of focal or global cerebral function disturbance lasting  $> 24$  hour (unless interrupted by surgery or mortality), without apparent non-vascular causes. Haemorrhagic stroke was defined as the bursting of the blood vessel, consisted of intracerebral haemorrhage and subarachnoid haemorrhage. Ischaemic stroke was defined as a stroke with thrombosis or embolism. Transient ischaemic attack and chronic cerebral vascular disease were not included.

For all study subjects reporting possible diagnoses or mortality, all available clinical information was gathered, including medical records and death certificates. The diagnoses of any cardiovascular events should be made in a secondary hospital or upper grade of hospital by patients' attending physicians. All materials were further reviewed and judged by the endpoint assessment committee.<sup>16</sup>

### Patient and public involvement statement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

### Statistical analysis

Continuous data were summarised as means $\pm$ SD and the linear trend across different AR severity groups was examined using the linear term of analysis of variance (ANOVA) test. Categorical data were expressed as counts (%) and the linear trend across different AR severity groups was estimated using the linear-by-linear association of  $\chi^2$  test or Fisher's exact test, as appropriate. Cumulative incidences of MI, MI mortality, stroke and stroke mortality were depicted using the Kaplan-Meier curves. The differences in cumulative incidences across different AR severity groups were examined using the log-rank test. The HRs and their corresponding 95% CIs of AR severity on risk of clinical outcomes were calculated using Cox proportional hazard models, adjusting for age, sex, BMI, smoking, drinking, hypertension, diabetes, history of MI, history of AF, history of heart failure, history of stroke, dyslipidaemia, eGFR, calcium, phosphorus, aortic peak velocity, LVMI and LVEF, as appropriate. Sensitivity analysis was conducted by excluding participants with a history of MI or stroke at baseline to further confirm the causal relationship.

All statistical analyses were performed using SPSS V.22.0 software (IBM Corporation, Chicago, Illinois, USA). Missing data were handled using the multiple imputation method. Kaplan-Meier curves were drawn using GraphPad Prism V.8.0 for Windows (GraphPad Software, La Jolla, California, USA). The forest plot was depicted using R software V.3.6.3 (R Core Team, 2020). All tests were two-tailed and p value  $< 0.05$  was considered statistically significant.

**Table 1** Baseline clinical characteristics for patients with DAVD stratified by AR severity

Variables	AR severity			P <sub>trend</sub>
	No AR (n=3153)	Mild AR (n=386)	Moderate or severe AR (n=37)	
Age, y	61.59±8.13	64.36±9.55	65.98±8.83	<0.01
Sex (male), n (%)	1305 (41.4)	238 (61.7)	18 (48.6)	<0.001
BSA, m <sup>2</sup> *	1.61±0.17	1.62±0.17	1.59±0.19	0.52
BMI, kg/m <sup>2</sup> *	24.65±3.79	24.23±3.54	23.84±3.08	0.20
Smoking, n (%)	1113 (35.3)	148 (38.3)	13 (35.1)	0.33
Drinking, n (%)	600 (19.0)	99 (25.6)	6 (16.2)	0.02
SBP, mm Hg*	148.97±24.43	154.00±32.20	146.58±21.11	0.69
DBP, mm Hg*	83.05±12.02	82.42±12.12	76.80±9.62	<0.01
Pulse pressure, mm Hg	65.92±18.91	71.58±21.43	69.78±17.60	0.18
Heart rate, bmp*	79.13±14.09	76.89±14.15	78.83±11.37	0.96
Hypertension, n (%)	2028 (64.3)	277 (71.8)	25 (67.6)	<0.01
Antihypertensive drugs, n (%)	689 (21.9)	92 (23.8)	11 (29.7)	0.18
Diabetes, n (%)	433 (13.7)	49 (12.7)	8 (21.6)	0.79
Antidiabetic drugs, n (%)	157 (5.0)	23 (6.0)	3 (8.1)	0.26
History of MI	49 (1.6)	13 (3.4)	1 (2.7)	0.02
History of AF	44 (1.4)	8 (2.1)	3 (8.1)	0.01
History of heart failure	47 (1.5)	9 (2.3)	1 (2.7)	0.18
History of stroke	197 (6.2)	24 (6.2)	2 (5.4)	0.90
TC, mmol/L*	5.43±1.11	5.29±1.16	5.22±0.95	0.25
TG, mmol/L*	1.63±1.32	1.52±1.05	1.28±0.62	0.10
LDL-C, mmol/L*	3.09±0.85	3.02±0.93	2.94±0.73	0.29
HDL-C, mmol/L*	1.44±0.40	1.46±0.41	1.50±0.36	0.31
Dyslipidaemia, n (%)	1235 (39.2)	138 (35.8)	8 (21.6)	0.03
eGFR, mL/min.1.73 m <sup>2</sup>	87.22±14.44	86.26±14.42	79.68±15.04	<0.01
FPG, mmol/L*	6.08±1.85	5.99±1.71	6.17±1.33	0.75
Calcium, mmol/L*	2.33±0.13	2.32±0.12	2.30±0.13	0.14
Phosphorus, mmol/L*	1.14±0.18	1.09±0.17	1.11±0.17	0.43

\*Missing values: BSA or BMI 30 cases; SBP, DBP or heart rate, 31 cases; TC, TG, LDL-C or HDL-C, 29 cases; eGFR, 29 cases; FPG, 29 cases; calcium, 29 cases; phosphorus, 30 cases. Missing values were filled using multiple imputation method.

AF, atrial fibrillation; AR, aortic regurgitation; BMI, body mass index; BSA, body surface area; DAVD, degenerative aortic valve disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

## RESULTS

### Baseline clinical and echocardiographic characteristics of patients with DAVD with different AR severity

Baseline clinical characteristics of the participants diagnosed with patients with DAVD were grouped according to the AR severity in table 1. Of the final cohort of 3576 patients with DAVD, there were 3153 patients without AR (88.2%), 386 patients with mild AR (10.8%) and 37 patients with moderate or severe AR (1.0%). As shown in table 1, patients with DAVD with mild AR or moderate/severe AR were older and more likely to be men, as compared with patients with DAVD without AR (P<sub>trend</sub> <0.01 and P<sub>trend</sub> <0.001, respectively). The DBP level declined gradually with increasing severity of

AR (P<sub>trend</sub> <0.01). In contrast, the prevalence of hypertension increased across different AR severity groups (P<sub>trend</sub> <0.01). Significant trends were not observed for BMI, smoking, drinking, SBP, heart rate, antihypertensive drugs, diabetes and antidiabetic drugs across different AR severity groups (all with P<sub>trend</sub> >0.05). The history of heart failure and stroke across the three groups was comparable, but not for the history of MI or AF (P<sub>trend</sub>=0.02 and 0.01, respectively). There were no linear trends in the levels of TC, TG, LDL-C, HDL-C, FPG, calcium and phosphorus (all with P<sub>trend</sub> >0.05), while the proportion of dyslipidaemia and the level of eGFR decreased with the worsening of AR (P<sub>trend</sub>=0.03 and P<sub>trend</sub> <0.01, respectively).

**Table 2** Baseline echocardiographic characteristics for patients with DAVD stratified by AR severity

Variables	AR severity			P <sub>trend</sub>
	No AR (n=3153)	Mild AR (n=386)	Moderate or severe AR (n=37)	
<b>Echocardiographic data</b>				
AOD, cm*	2.26±0.28	2.35±0.30	2.39±0.43	<0.01
Aortic peak velocity, cm/s*	120.41±24.44	124.77±23.48	144.16±50.74	<0.001
IVSd, cm	0.90±0.12	0.93±0.14	0.98±0.16	<0.001
LVIDd, cm	4.70±0.42	4.85±0.46	5.23±0.88	<0.001
LVIDs, cm	3.11±0.43	3.21±0.47	3.50±0.63	<0.001
PWTd, cm*	0.87±0.11	0.90±0.12	0.94±0.16	<0.001
LVM, g	141.58±36.70	156.71±43.77	192.38±77.75	<0.001
LVMI, g/m <sup>2</sup> *	87.95±20.21	96.08±23.70	118.26±41.03	<0.001
LVEDV, mL	103.53±21.91	111.71±25.68	136.55±63.18	<0.001
LVESV, mL	39.30±13.22	42.55±15.97	53.20±25.29	<0.001
SV, mL	64.23±17.55	69.17±19.45	83.35±43.11	<0.001
LVEF, %	61.94±10.05	61.92±10.29	60.47±10.26	0.38
<b>Other concomitant VHD</b>				
Tricuspid stenosis, n (%)	0 (0)	0 (0)	0 (0)	–
Tricuspid regurgitation, n (%)	82 (2.6)	23 (6.0)	3 (8.1)	<0.001
Mitral stenosis, n (%)	0 (0)	0 (0)	3 (8.1)	<0.001
Mitral regurgitation, n (%)	108 (3.4)	35 (9.1)	7 (18.9)	<0.001
Aortic stenosis, n (%)	4 (0.1)	2 (0.5)	3 (8.1)	<0.001

\*Missing values: AOD, 5 cases; aortic peak velocity, 3 cases; PWTd, 4 cases; LVM, 4 cases; LVMI, 34 cases. Missing values were filled using multiple imputation method.

AOD, aortic annular diameter; AR, aortic regurgitation; DAVD, degenerative aortic valve disease; IVSd, interventricular septal thickness; LVEDV, LV end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, LV end-systolic volume; LVIDd, LV end-diastolic internal dimension; LVIDs, LV end-systolic internal dimension; LVM, left ventricular mass; LVMI, left ventricular mass index; PWTd, posterior wall thickness; SV, stroke volume; VHD, valvular heart disease.

At baseline, patients with DAVD with more severe AR were more likely to have elevated AOD, aortic peak velocity, IVSd, LVIDd, LVIDs, PWTd, LVM, LVMI, LVEDV, LVESV and SV (table 2). In addition to AR, the most common concomitant VHD was the mitral regurgitation (150/3576, 4.2%), followed by the tricuspid regurgitation (108/3576, 3.0%). Whereas, only a few patients with DAVD had concomitant mitral stenosis (3/3576, 0.1%) and aortic stenosis (9/3576, 0.3%). None of the patients with DAVD had concomitant tricuspid stenosis. Furthermore, the prevalence of concomitant VHDs increased with the worsening degree of AR (all with P<sub>trend</sub> <0.001).

#### Crude incidence of clinical outcomes among patients with DAVD with different AR severity

Table 3 lists the crude incidences of MI, MI mortality, stroke and stroke mortality. A significant stepwise increase in MI (1.2% vs 2.3% vs 16.2%, P<sub>trend</sub> <0.001) and MI mortality (0.8% vs 1.8% vs 13.5%, P<sub>trend</sub> <0.001) was observed in the transition from no AR to moderate/severe AR. However, our results failed to show any significant trend in the stroke or stroke mortality incidence across different AR

severity groups (both with P<sub>trend</sub> >0.05). Stratified analyses by stroke types showed similar findings as well.

#### Kaplan-Meier curves for the cumulative incidence of clinical outcomes with different AR severity

The Kaplan-Meier curves for each endpoint in patients with DAVD with different AR severity are shown in figure 2. Higher cumulative incidences of MI and MI mortality were observed among patients with DAVD with moderate or severe AR, as compared with those without AR or mild AR (both with log-rank test p<0.001). However, the differences in the incidences of stroke or stroke mortality for the three AR severity groups were not statistically significant (log-rank p=0.22 and p=0.30, respectively).

#### Cox regression analyses for the prognostic significance of AR severity among patients with DAVD

Figure 3 shows the multivariate-adjusted HRs and their corresponding 95% CIs for the MI, MI mortality, stroke and stroke mortality, respectively. Moderate/severe AR was independently associated with a 8.33 and 6.22-fold increased risk of MI and MI mortality as compared with

**Table 3** Crude incidence of clinical outcomes among patients with DAVD with different AR severity

Outcomes	Incidence			P <sub>trend</sub>
	No AR (n=3153)	Mild AR (n=386)	Moderate or severe AR (n=37)	
MI, n (%)	39 (1.2)	9 (2.3)	6 (16.2)	<0.001
MI mortality, n (%)	25 (0.8)	7 (1.8)	5 (13.5)	<0.001
Stroke, n (%)*	192 (6.1)	20 (5.2)	4 (10.8)	1.00
Ischaemic stroke, n (%)	145 (4.6)	14 (3.6)	3 (8.1)	0.91
Haemorrhagic stroke, n (%)	38 (1.2)	5 (1.3)	1 (2.7)	0.68
Stroke mortality, n (%)*	76 (2.4)	9 (2.3)	2 (5.4)	0.65
Ischaemic stroke, n (%)	34 (1.1)	5 (1.3)	1 (2.7)	0.51
Haemorrhagic stroke, n (%)	33 (1.0)	3 (0.8)	1 (2.7)	1.00

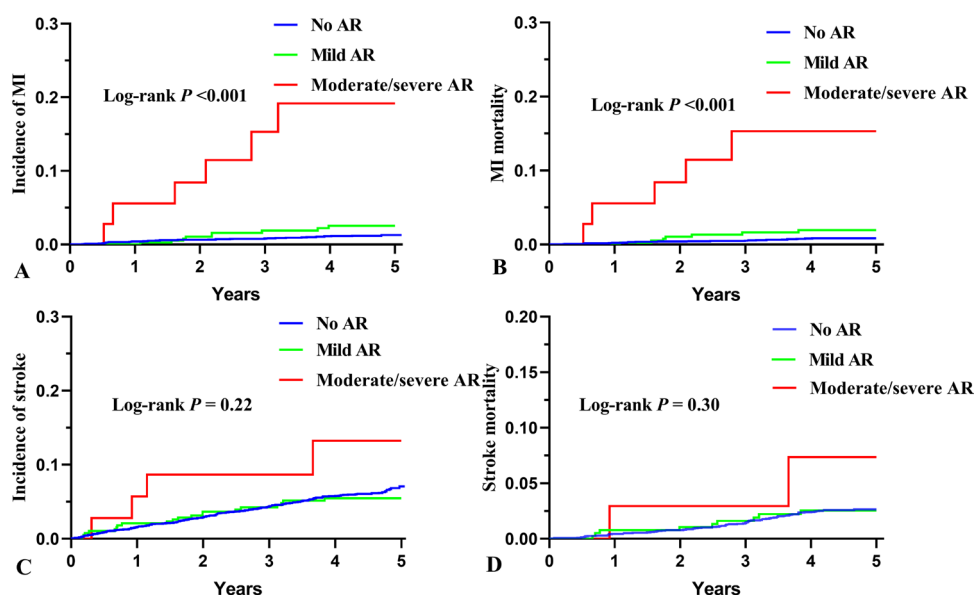
\*10 cases had unknown stroke type.

AR, aortic regurgitation; DAVD, degenerative aortic valve disease; MI, myocardial infarction.

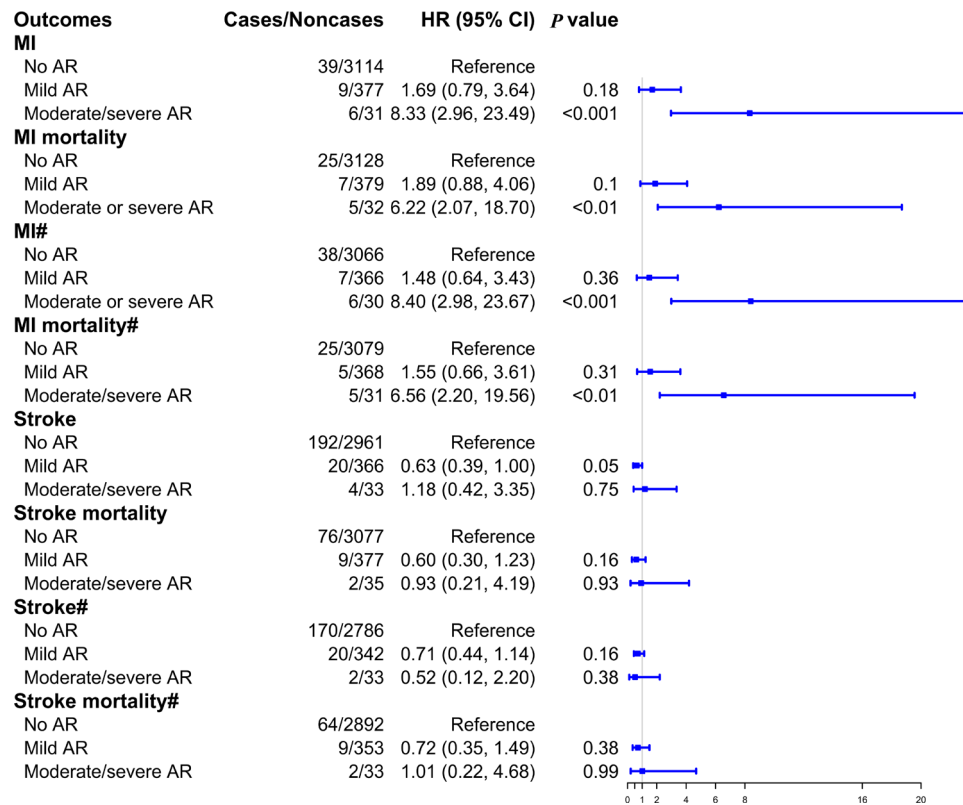
no AR (MI, HR=8.33, 95% CI: 2.96 to 23.49,  $p<0.001$ ; MI mortality, HR=6.22, 95% CI: 2.07 to 18.70,  $p<0.01$ ). However, the associations between mild AR and the risk of MI and MI mortality were not statistically significant when compared with no AR ( $p=0.25$  and  $p=0.08$ , respectively). Neither mild AR nor moderate/severe AR was associated with an elevated risk of stroke or stroke mortality, compared with no AR. Furthermore, to establish the causal relationship, Cox regression analyses investigating the AR severity on risk of different clinical outcomes were further conducted by excluding patients with DAVD with prior history of MI or stroke at baseline. The associations between moderate/severe AR and risk of MI and MI mortality remained statistically significant (MI, HR=8.40, 95% CI: 2.98 to 23.67,  $p<0.01$ ; MI mortality, HR=6.56, 95% CI: 2.20 to 19.56,  $p<0.01$ ).

## DISCUSSION

Of the 3576 patients with DAVD recruited from a general Chinese population, 423 patients (11.8%) had concomitant AR. The linear trends were significant for age, sex proportion, DBP, hypertension, prior MI, AF, dyslipidaemia and eGFR across different AR groups. All echocardiographic parameters and prevalence of other coexisting VHDs significantly increased with the worsening degree of AR except for the level of LVEF. Multivariate Cox regression analyses showed that, compared with participants without AR, those with moderate/severe AR were associated with 8.33 and 6.22-fold increased risk of MI and MI mortality, respectively. However, the associations between moderate/severe AR and the risk of stroke or stroke mortality were not significant ( $p=0.75$  and  $0.93$ ,



**Figure 2** The Kaplan-Meier curves for the associations between AR severity and risk of different clinical outcomes among patients with DAVD. (A) MI, (B) MI mortality, (C) stroke and (D) stroke mortality. AR, aortic regurgitation; DAVD, degenerative aortic valve disease; MI, myocardial infarction.



**Figure 3** The adjusted HRs and the corresponding 95% CIs for the associations between AR severity and risk of different clinical outcomes among patients with DAVD. Adjusted for age, sex, BMI, smoking, drinking, hypertension, diabetes, history of MI, history of AF, history of heart failure, history of stroke, dyslipidaemia, eGFR, calcium, phosphorus, AOD, aortic peak velocity, LVMI and LVEF as appropriate. AF, atrial fibrillation; AR, aortic regurgitation; AOD, aortic annular diameter; BMI, body mass index; DAVD, degenerative aortic valve disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MI, myocardial infarction. #Participants with history of MI or stroke at baseline were excluded as appropriate.

respectively). Meanwhile, the risk of all clinical outcomes in the mild AR group was similar to that in the no AR group (all with  $p > 0.05$ ).

Interestingly, we found that the most prevalent concomitant VHD was AR rather than AS in our study population (11.8% vs 0.25%), which was greatly different from that in the Western population.<sup>1</sup> Our findings were consistent with the conclusion of a previous population-based study from China.<sup>29</sup> In that study, the detection rates of moderate or severe AR were much higher than those of AS in two different age groups (65–64 years: 2.12% vs 0.75%;  $\geq 75$  years: 2.85% vs 0.89%), involving 49 995 cases and 34 671 cases, respectively.<sup>29</sup> In our study, the prevalence of moderate or severe AR among 3576 patients with DAVD aging  $\geq 45$  years was 1.03%, which was far higher when compared with that of AS (0.25%). Similarly, another Chinese study based on the elderly population indicated that the most frequent VHD was AR, followed by tricuspid regurgitation and mitral regurgitation.<sup>30</sup> The discrepancies in prevalence rates of VHDs might partly be attributable to the differences in diagnostic criteria, data sources (population-based or hospital-based), clinical characteristics and year of data collection.<sup>30</sup> Nevertheless, our results did suggest that the spectrum of VHDs was different between the Western and Chinese populations

to some extent. Thus, more attention should be paid to this characteristic in future transcatheter aortic valve replacement (TAVR) device designs for the treatment of AR.<sup>29</sup>

The severity of DAVD progresses with age. Degenerative AR was more common in men than women, which was in accordance with finding from a previous study.<sup>31</sup> According to the haemodynamics of AR,<sup>21 32</sup> severe AR reveals a widened pulse pressure from increased SV and elevated SBP but a rapid decline in DBP. In our study, SV and DBP showed a significant linear trend as the AR deteriorates. However, the linear trend was not found for SBP across different AR groups. As reported in published literature, VHDs such as aortic stenosis and mitral regurgitation were predictors of AF.<sup>33</sup> Our results indicated that moderate/severe AR was significantly associated with a high prevalence of AF (8.2%). The eGFR gradually declined with the increasing severity of AR. Previous studies suggested that the presence of chronic kidney disease might accelerate and amplify the process of aortic valve calcification via multiple mechanisms, such as inflammation, anaemia, oxidative stress, haemodynamic overload and abnormal calcium/phosphate metabolism even if serum calcium/phosphate levels are within normal ranges.<sup>34–36</sup>



AR can not only result from malfunction of the aortic leaflets themselves, but also from the dilatation of the aortic root and annulus, or both.<sup>6-37</sup> Thus, increased AOD was observed in patients with DAVD with worsening AR. Furthermore, as the degree of AR became more severe, the SV increased, which would cause a rise in aortic peak velocity.<sup>38</sup> Additionally, the chronic volume overload due to AR allows for a compensatory remodelling of the left ventricle (LV) characterised as eccentric hypertrophy of the cardiac myocytes and chamber dilation.<sup>21-39</sup> This allows for the balance of LV systolic function and prevents sudden elevation in end-diastolic pressure.<sup>21</sup> As AR worsens, the LV remodelling worsens, resulting in increased interstitial fibrosis and decreased LV compliance, elevated end-systolic volume, elevated end-diastolic pressure, further cardiac enlargement and impaired systolic function.<sup>21</sup> The above haemodynamic and anatomical changes were supported by the echocardiographic parameters in [table 2](#).

As compared with no AR, moderate/severe AR but not mild AR was an independent predictor of the risk of MI and MI mortality. AR was not significantly associated with stroke or stroke mortality. Previous evidence suggested that DAVD was an atherosclerosis-like process involving the aortic valve,<sup>40</sup> in which DAVD and atherosclerosis shared a common pathogenic mechanism. Therefore, predictive factors of aortic sclerosis were risk factors of atherosclerosis as well.<sup>7-9</sup> The severity of aortic valve lesions was positively correlated with the burden of atherosclerotic lesions, accounting for the linear trend of MI risk among patients with DAVD across different AR severity. The myocardial hypertrophy resulted from AR can lead to an imbalance between myocardial oxygen supply and demand.<sup>41</sup> Furthermore, the elevated LV end-diastolic pressure and shortened diastole from tachycardia change the coronary flow dynamics, decreasing the coronary perfusion, and thus aggravating coronary artery ischaemia.<sup>42</sup> Perhaps that's why moderate/severe AR was significantly related to the risk of MI rather than the risk of stroke.

### Strengths and limitations

One strength of the current study is that patients with DAVD were recruited from a large population of North-eastern China. Moreover, our study was prospectively conducted and the clinical outcomes were identified during the follow-up period, which enables the inference of a causal relationship between AR severity and risk of clinical outcomes.

Despite the strengths mentioned above, our study has several limitations. First, the diagnoses of MI were made by the local cardiologists, and not all patients with MI underwent coronary angiography. This might have led to overdiagnosis of MI. Second, although there were 3576 patients with DAVD involved in the current study, the number of patients with DAVD with moderate/severe AR is relatively small (n=37), which limited the statistical power to some extent. Considering the fact that the

participants were enrolled from a general population, it is therefore not surprising. Finally, patients with DAVD who had a history of MI or stroke were not excluded at baseline, which restricted the causal inference. However, the sensitivity analysis showed that the associations between moderate/severe AR and risk of MI and MI mortality remained significant even after the exclusion of baseline MI.

### Conclusions

AR was the most prevalent concomitant VHD among patients with DAVD from a Chinese general population. Moderate/severe AR but not mild AR was strongly associated with the risk of MI and MI mortality, independent of traditional risk factors. However, there was no evidence that AR was significantly associated with stroke, irrespective of AR severity. As DAVD and share many common pathophysiological pathways with atherosclerosis,<sup>13</sup> secondary prevention strategies targeting these pathways should be taken to delay the progression of DAVD and thus reduce the incidence of MI.

### Author affiliations

<sup>1</sup>Department of Cardiology, The First Hospital of China Medical University, Shenyang, China

<sup>2</sup>Department of Medical Record Management Center, The First Hospital of China Medical University, Shenyang, China

<sup>3</sup>Department of Cardiovascular Ultrasound, The First Hospital of China Medical University, Shenyang, China

<sup>4</sup>Department of Clinical Epidemiology, Library, Shengjing Hospital of China Medical University, Shenyang, China

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### ORCID iDs

Guangxiao Li <http://orcid.org/0000-0003-0318-3490>

Liqiang Zheng <http://orcid.org/0000-0003-0101-9398>

Yingxian Sun <http://orcid.org/0000-0002-1961-899X>



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