Prevalence of aortic valve stenosis in patients with ST-segment elevation myocardial infarction and effect on long-term outcome

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Prevalence of Aortic Valve Stenosis in Patients With ST-Segment Elevation Myocardial Infarction and Effect on Long-Term Outcome

Gurpreet K. Singh, MD[a], Pieter van der Bijl, MD, PhD[a], Laurien Goedemans, MD[a], E. Mara Vollema, MD[a], Rachid Abou, MD[a], Nina Ajmone Marsan, MD, PhD[a], Jeroen J. Bax, MD, PhD[a,b], and Victoria Delgado, MD, PhD[a,*]

Several studies have shown an association between aortic valve stenosis (AS), atherosclerosis and cardiovascular risk factors. These risk factors are frequently encountered in patients with ST-segment elevation myocardial infarction (STEMI). The aim of this study was to evaluate the prevalence and the prognostic implications of AS in patients presenting with STEMI. A total of 2041 patients (61 ± 12 years old, 76% male) admitted with STEMI and treated with primary percutaneous coronary intervention were included. Patients with previous myocardial infarction and previous aortic valve replacement were excluded. Echocardiography was performed at index admission. Patients were divided in 3 groups: 1) any grade of AS, 2) aortic valve sclerosis and 3) normal aortic valve. Any grade of AS was defined as an aortic valve area ≤2.0 cm^2. The primary endpoint was all-cause mortality. The prevalence of AS was 2.7% in the total population and it increased with age (1%, 3%, 7% and 16%, in the patients aged <65 years, 65 to 74 years, 75 to 84 years and ≥85 years, respectively). Patients with AS showed a significantly higher mortality rate when compared to the other two groups ($p < 0.001$) and AS was independently associated with all-cause mortality, with a HR of 1.81 (CI 95%: 1.02 to 3.22; $p = 0.04$). In conclusion, AS is not uncommon in patients with STEMI, and concomitant AS in patients with first STEMI is independently associated with all-cause mortality at long-term follow up. **(Am J Cardiol 2021;153:30−35)**

Aortic valve stenosis (AS) is the most common valve disease requiring surgical or transcatheter intervention and the prevalence increases with age.[1−3] Acquired AS encompasses the range of disease from alterations of the cell biology of the leaflets to deposits of calcium and bone formation causing left ventricular (LV) outflow obstruction.[4] Several studies have shown an association between AS, atherosclerosis and cardiovascular risk factors.[1,5] These same risk factors are frequently encountered in patients with ST-segment elevation myocardial infarction (STEMI). The frequency of AS in patients with acute coronary syndrome (ACS) is much larger than that observed in the general population: 1.5 to 2.7% versus <1%, respectively.[6−8] Echocardiography is recommended during admission for STEMI to evaluate residual LV systolic function, diastolic dysfunction and concomitant valvular heart disease. Little is known about the frequency of concomitant AS during admission for STEMI and the prognostic implications of concomitant AS. The pressure overload imposed on the already compromised LV may facilitate adverse remodelling and heart failure during follow-up. However, this has not been thoroughly investigated. Therefore, the present study evaluated the frequency and the prognostic implications of AS in STEMI patients.

Methods

From an ongoing clinical registry of patients admitted with STEMI, the frequency of any grade of AS was assessed. Patients were treated with primary percutaneous coronary intervention and underwent 2-dimensional (2D) transthoracic echocardiography within the first 48 hours of admission. The echocardiograms of patients admitted with STEMI between February 2004 and May 2013, at the Leiden University Medical Center (Leiden, The Netherlands) were evaluated to identify the presence of any grade of AS. Patients were divided into three groups: 1) any grade of AS, 2) aortic valve sclerosis and 3) normal aortic valve. Patients with prior myocardial infarction, prior aortic valve replacement or incomplete echocardiographic data to determine the severity of AS were excluded. Electronic records (EPD Vision, version 12.3.5.0, Leiden, The Netherlands) were used to collect clinical and demographic data. The institutional review board waived the need for patient written informed consent, for retrospective analysis of clinically acquired data which were anonymously handled.

Transthoracic echocardiography was performed in patients at rest. Images were obtained with the patient in the left decubitus position using commercially available ultrasound systems (Vivid 7, E9 and E95 GE Healthcare,

[a]Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands; and [b]Heart Center, Turku University Hospital and University of Turku, Turku, Finland. Manuscript received March 7, 2021; revised manuscript received and accepted May 11, 2021.

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*Corresponding author: Tel: +3175262020; fax: +31715266809

E-mail address: v.delgado@lumc.nl (V. Delgado).

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Horten, Norway) equipped with 3.5-MHz or M5S transducers. Standard 2D, M-mode, colour, pulsed- and continuous-wave Doppler images in parasternal and apical views were acquired. Data were stored digitally and retrospectively analysed offline using EchoPac software (version BT13; GE Medical Systems, Horten, Norway). The apical 2- and 4-chamber views were used for the measurement of LV volumes, and using the biplane method of Simpson, LV ejection fraction (LVEF) was calculated.[9] On the parasternal long-axis view, LV dimensions were measured and LV mass was calculated according to Devereux's formula.[9] The aortic valve morphology was based on visual analysis on short-axis images to identify the number of cusps, and to describe cusp thickness and calcification.[10] Using continuous-wave Doppler on the 3- or 5-chamber LV apical views, peak aortic jet velocity, aortic valve mean and peak gradients were measured with the simplified Bernoulli equation. On the same apical views, pulsed-wave Doppler images of the LV outflow tract were obtained and the aortic valve area (AVA) was calculated using the continuity equation.[10] Any grade of AS was defined as an AVA $\leq$2.0 cm^2. The presence of aortic valve sclerosis was diagnosed if the cusps were thickened, there were isolated (larger) spots or extensive calcification of all cusps.

The endpoint of the present study was all-cause mortality. Mortality data were collected through medical files of patients from the outpatient clinic containing up-to-date information on mortality. Follow-up data were available for all patients of this study.

Categorical data are presented as frequencies and percentages, and were analysed using the chi-square test. Continuous variables with a normal distribution are presented as mean $\pm$ standard deviation and were analysed using the ANOVA-test. Non-normally distributed data are presented as median and interquartile range, and were analysed using the Kruskal-Wallis test. Kaplan-Meier analysis was performed to calculate the all-cause mortality event rates and Cox proportional hazards regression analyses were performed to evaluate the clinical and echocardiographic characteristics that were independently associated with all-cause mortality. All statistical analyses were two-sided and a p-value of <0.05 was considered statistically significant. All analyses were conducted using SPSS software (version 25.0; IBM, Armonk, NY, USA).

Results

Baseline clinical and echocardiographic characteristics of the overall population and the 3 subgroups are shown in Table 1 and Table 2, respectively. A total of 2041 STEMI patients (mean age 61 $\pm$ 12 years, 76% male) were included. AS was present in 55 (2.7%) patients, including 32 patients with mild AS, 17 with moderate AS and 6 with severe AS. Aortic valve sclerosis was present in 1610 (79%) patients. The prevalence of AS increased with age (Figure 1). Patients with AS were significantly older compared to the other two subgroups. Cardiovascular risk factors were equally distributed, with the exception of a family history of cardiovascular disease. Statin use in the total population was low, reflecting the first admission to the hospital and no previous history of atherosclerotic cardiovascular disease in the majority of the patients. Bicuspid valve morphology and a lower LVEF was more common in patients with AS.

Table 1
Baseline clinical characteristics

Variable	Total population (n = 2041)	Normal aortic valve (n = 376)	Aortic valve sclerosis (n = 1610)	Aortic valve stenosis (n = 55)	p value
Men	1545 (76%)	261 (69%)	1248 (76%)	36 (65%)	0.001
Age (years)	61 $\pm$ 12	58 $\pm$ 12	61$\pm$ 12	71 $\pm$ 13	<0.001
Body surface area (m^2)	2.0 $\pm$ 0.2	2.0 $\pm$ 0.23	2.0 $\pm$ 0.2	1.9 $\pm$ 0.2	0.064
Creatinine (μmol/L)	77 (67 to 89)	74 (64 to 84)	77 (67 to 90)	76 (68 to 94)	<0.001
Systolic blood pressure (mm Hg)	136$\pm$ 26	136 $\pm$ 26	136 $\pm$ 26	128 $\pm$ 26	0.131
Diastolic blood pressure (mm Hg)	82 $\pm$ 17	83 $\pm$ 18	81 $\pm$ 17	77 $\pm$ 15	0.031
Multivessel coronary disease	1068 (53%)	182 (49%)	844 (53%)	42 (79%)	<0.001
Killip class $\geq$2, (%)	76 (4 %)	12 (3%)	59 (4%)	5 (9%)	0.096
Diabetes mellitus	196 (10%)	38 (10%)	151 (9%)	7 (13%)	0.663
Hypertension	721 (35%)	132 (35%)	564 (35%)	25 (45%)	0.293
Dyslipidaemia	373 (18%)	58 (15%)	304 (19%)	11 (20%)	0.285
Smoker					0.055
Never	835 (41%)	137 (37%)	674 (42%)	24 (44%)	
Former	238 (12%)	37 (10%)	192 (12%)	9 (17%)	
Current	942 (47%)	198 (53%)	723 (45%)	21 (39%)	
Family history of CVD	847 (42%)	171 (47%)	660 (427%)	16 (30%)	0.045
Medication before STEMI					
Aspirin	227 (11%)	38 (10%)	178 (11%)	11 (20%)	0.092
β-blockers	301 (15%)	46 (12%)	241 (15%)	14 (25%)	0.031
ACE-inhibitor/ARB	269 (13%)	46 (12%)	208 (13%)	15 (27%)	0.007
Statin	264 (13%)	52 (14%)	203 (13%)	9 (16%)	0.618

Diabetes mellitus was defined as having a history of diabetes mellitus and medical therapy with insulin, oral glucose-lowering drugs or diet; Hypertension was defined as a systolic blood pressure of >140 mm Hg and/or a diastolic blood pressure of >90 mm Hg or prior use of antihypertensive medication; Dyslipidaemia was defined as previous statin use and/or having a documented history of dyslipidaemia.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CVD = cardiovascular disease; STEMI = ST-elevation myocardial infarction.

Table 2
Baseline echocardiographic characteristics

Variable	Total population (n = 2041)	Normal aortic valve (n = 376)	Aortic valve sclerosis (n = 1610)	Aortic valve stenosis (n = 55)	p value
Aortic valve anatomy					<0.001
Tricuspid morphology	2033 (99.6%)	375 (99.7%)	1607 (99.8%)	51 (93%)	
Bicuspid morphology	0 (0.2%)	0 (0%)	1 (0.1%)	4 (7%)	
LV outflow tract diameter (cm)	2.2 (2.1 to 2.4)	2.3 (2.1 to 2.4)	2.2(2.1 to 2.3)	2.1(2.0 to 2.3)	0.001
VTI LV outflow tract (cm)	19.8 ± 4.7	19.7 ± 4.6	19.8 ± 4.7	20.2 ±5.7	0.747
Stroke volume index (ml/m^2)	40 ± 11	40 ± 11	40 ± 11	37 ± 10	0.234
LV mass (g/m^2)	199 (161 to 242)	193 (150 to 255)	200 (164 to 242)	207 (169 to 227)	0.043
LV end-diastolic volume (ml)	102 (83 to 124)	100 (82 to 120)	102 (84 to 124)	101 (92 to 119)	0.510
LV end-systolic volume (ml)	53 (42 to 67)	51 (41 to 66)	53(42 to 67)	56 (48 to 71)	0.220
LV ejection fraction (%)	47 ± 9	47 ± 9	47 ± 9	44 ± 9	0.029
Peak aortic jet velocity (m/s)	1.2 (1.1 to 1.4)	1.2 (1.1 to 1.4)	1.2 (1.1 to 1.4)	2.4 (2.0 to 2.9)	<0.001
Aortic valve mean gradient (mm Hg)	4 (3 to 5)	4 (3 to 4)	3 (3 to 4)	13 (9 to 20)	<0.001
Aortic valve peak gradient (mm Hg)	6 (5 to 8)	6 (5 to 9)	6 (5 to 8)	24 (16 to 33)	<0.001
Aortic valve area (cm^2)	3.1 ± 0.8	3.2 ± 0.7	3.2 ± 0.7	1.5 ± 0.4	<0.001
Severity of aortic valve stenosis					
Mild	32 (1.6%)	-	-	32 (58%)	-
Moderate	17 (0.8%)	-	-	17 (31%)	-
Severe	6 (0.3%)	-	-	6 (11%)	-

LV = left ventricular; VTI = velocity time integral.

After a median follow-up of 108 (interquartile range 90 to 108) months, 299 (15%) patients died. Patients with AS experienced a significantly higher mortality rate, compared to the other two subgroups (Figure 2). Uni- and multivariable Cox regression analyses were performed to evaluate an independent association of the presence of AS and all-cause mortality (Table 3). After adjusting for female sex, age, creatinine, diastolic blood pressure and LVEF, the presence of AS remained independently associated with all-cause mortality. In addition, a sensitivity analysis was performed to assess if there was a linear relationship between the severity of AS and all-cause mortality.

Respectively, hazard ratios of 1.640 (CI: 0.941 to 2.859; p = 0.81) and 1.623 (CI: 0.839 to 3.414; p = 0.151) were detected for the univariate and multivariate analyses.

Discussion

The present study shows that AS is not uncommon in patients admitted with a first STEMI and that it is independently associated with reduced survival.

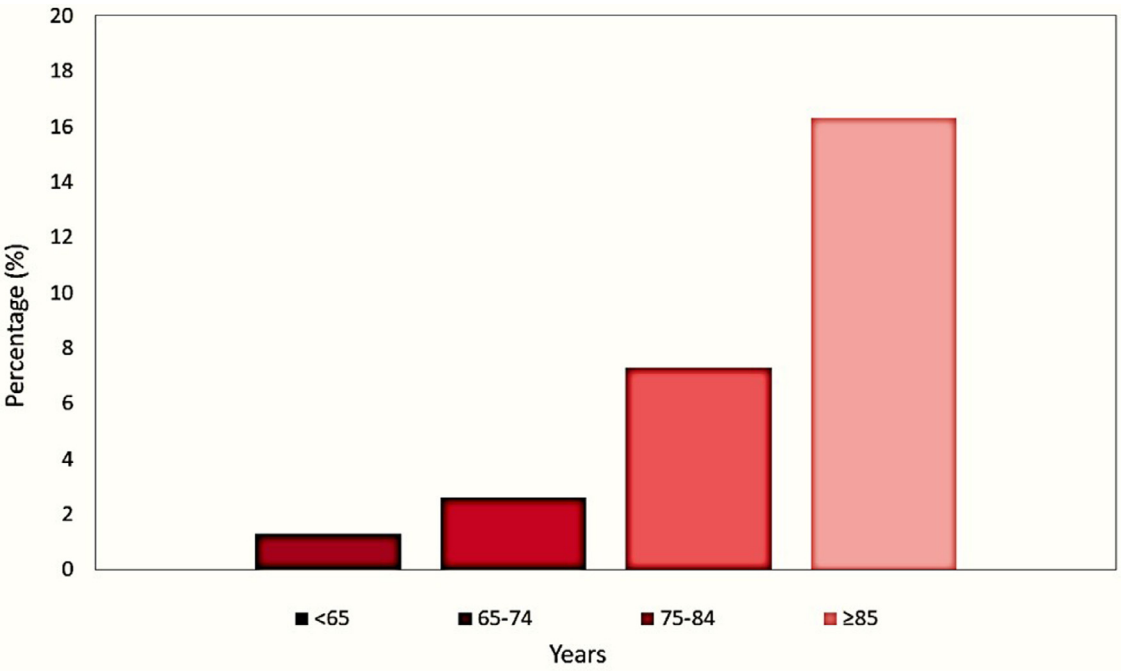

Figure 1. Prevalence of aortic valve stenosis in patients after ST-segment elevation myocardial infarction divided by age.

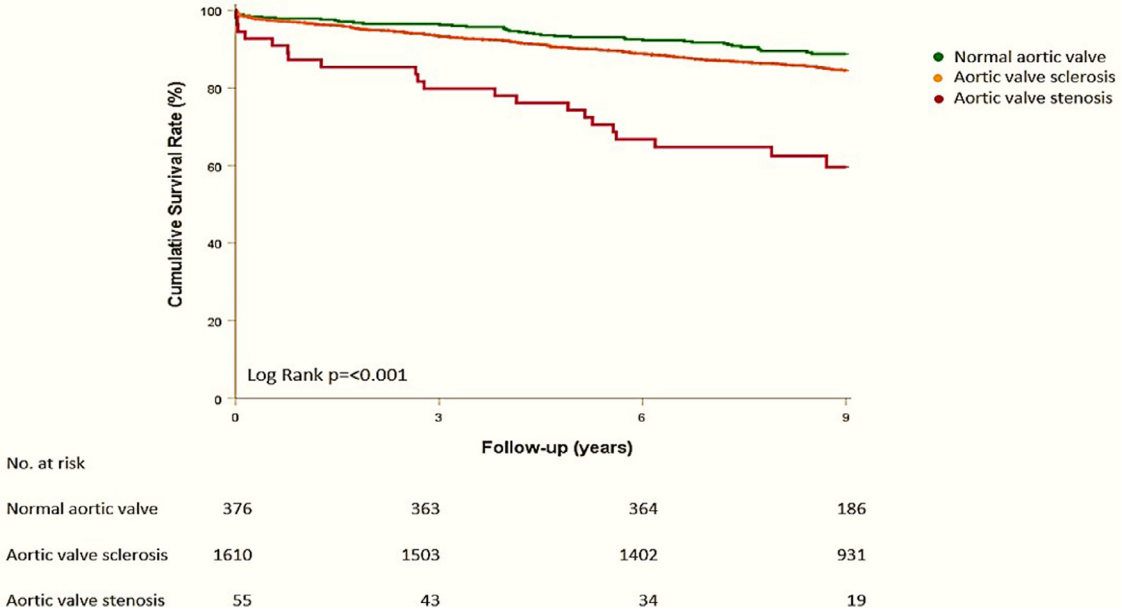

Figure 2. Comparison of all-cause mortality between aortic valve stenosis, aortic valve sclerosis and a normal aortic valve.

Several studies have assessed the prevalence of AS among patients with ACS.[6,8] Hasdai et al [8] reported a prevalence of 1.5% for moderate-to-severe AS among ACS patients. In a cohort of 1443 patients with ACS, the prevalence of AS was 2.7% (1.8% with only moderate-to- severe AS and 0.9% with both moderate-to-severe AS and mitral regurgitation).[6] These frequencies contrast with those reported in the population-based studies by Nkomo et al[7] and Stewart et al[11] Nkomo et al[7] reported a prevalence of <1% of at least moderate AS in the general population. The prevalence increased with age, from <1% in patients <65 years, to 1.3% in those aged 65 to 74 years, and 2.8% in patients ≥75 years. Stewart et al[11] reported a prevalence of 2% of AS in the general population aged 65 years or older. However, in the current study, by taking age into consideration, we found a higher frequency of AS compared to the studies including patients with ACS and the general population studies.[6–8,11] Differences in the definition of AS and in the patient population may explain the differences observed across the studies. Hasdai et al[8], defined AS based on the information extracted from medical chart review, as well as from self-reporting by the patient. No confirmation of the diagnosis of a valvular lesion by echocardiography or other imaging modalities was performed. Therefore, it is possible that this prevalence was underestimated. Furthermore, in our study we included mild AS, which would lead to a higher frequency of AS. However, when focusing only on patients with at least moderate AS, the present study also demonstrates a higher prevalence than that reported by Nkomo et al[7] and Crimi et al[6]

Table 3
Uni- and multivariable analyses to evaluate an independent association with all-cause mortality

	Univariable analysis			Multivariable analysis		
Variable	Hazard Ratio	95% Confidence Interval	p value	Hazard Ratio	95% Confidence Interval	p value
Female sex	1.445	1.131 to 1.846	0.003	0.995	0.759 to 1.304	0.972
Age (years)	1.083	1.072 to 1.095	<0.001	1.074	1.062 to 1.087	<0.001
Creatinine (μmol/L)	1.013	1.010 to 1.016	<0.001	1.008	1.005 to 1.011	<0.001
Diastolic blood pressure (mm Hg)	0.989	0.982 to 0.997	0.003	0.997	0.990 to 1.004	0.422
Family history CVD	0.512	0.397 to 0.662	<0.001			
β-blockers	1.638	1.242 to 2.160	<0.001			
ACE-inhibitor/ARB	1.447	1.075 to 1.947	0.015			
Bicuspid morphology	0.050	0.000 to 1139.958	0.558			
LV mass (g/m^2)	1.000	0.9981 to 0.002	0.933			
LV outflow tract diameter (cm)	1.074	0.9790 to 1.179	0.131			
LV ejection fraction (%)	0.952	0.940 to 0.964	<0.001	0.958	0.947 to 0.971	<0.001
AVR during follow-up	1.915	0.714 to 5.136	0.197			
Normal aortic valve	Reference			Reference		
Aortic valve sclerosis	1.416	1.013 to 1.979	0.042	1.181	0.828 to 1.685	0.358
Aortic valve stenosis	4.440	2.618 to 7.531	<0.001	1.813	1.019 to 3.224	0.043

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; AVR = aortic valve replacement; CVD = cardiovascular disease; LV= left ventricular.

(Supplementary Table 1). While Nkomo et al[7] analysed the general population, the present study included patients with very high cardiovascular risk, since all patients were admitted with STEMI. Several studies have demonstrated common pathophysiological mechanisms of AS and cardiovascular atherosclerosis.[12–15] In addition, it has been shown that there is an association between AS and cardiovascular risk factors, such as diabetes mellitus, dyslipidaemia, and hypertension.[5,11]

The prognostic implications of AS in patients with first STEMI were evaluated in several studies. Crimi et al[6] showed in a cohort of 1443 patients with ACS that moderate-to-severe AS were independently associated with the composite primary endpoint of all-cause death, myocardial infarction, disabling stroke and re-hospitalization for heart failure at 1 year follow-up. In contrast, moderate-to-severe AS did not show an association with the secondary endpoint of cardiovascular death.[6] The present study included 2041 patients, a larger population than that of the study by Crimi et al[6], and demonstrated that patients with any grade of AS have a worse outcome, when compared to patients without AS.

The present study also assessed the survival of patients without AS and those with aortic valve sclerosis, since it is known that aortic valve sclerosis is associated with atherosclerosis and cardiovascular death.[16–19] Our study showed that aortic valve sclerosis was not associated with all-cause mortality when AS was taken into consideration. A possible explanation for these results is that AS represents a more advanced stage of the disease, which may have a stronger association with outcome than aortic valve sclerosis.

In patients with STEMI, the presence of AS requires further follow-up to detect fast progression to severe AS and it remains unclear how the effect of LV outflow obstruction can impact LV remodelling in these patients. Future studies are needed to investigate if early intervention is needed in patients with STEMI and concomitant AS.

The present study has some limitations. First, our study is a single center study with a retrospective design. Second, there exists the potential for selection bias by having focussed only on patients with STEMI and excluding those with non-STEMI. Third, this study had a modest number of AS patients. Fourth, inter- and intra-individual analysis were not available, however the echocardiographic measurements were performed by an experienced echocardiographer. Fifth, we have adjusted for the most important confounders for the endpoint all-cause mortality. But we cannot exclude that there are residual confounders where we have not adjusted for. Finally, the specific cause of death could not be reported in the current analysis since systematic documentation was not available.

CRediT author statement

GKS: Conception and design of the study; collection, analysis and interpretation of data; drafting of the manuscript; final approval of the manuscript. Pvan derB: Conception and design of the study; collection, analysis and interpretation of data; drafting of the manuscript; final approval of the manuscript. LG: Conception and design of the study; drafting of the manuscript; final approval of the manuscript. EMV: Conception and design of the study; drafting of the manuscript; final approval of the manuscript. RA: Conception and design of the study; drafting of the manuscript; final approval of the manuscript. NAM: Conception and design of the study; collection, analysis and interpretation of data; drafting of the manuscript; final approval of the manuscript. JJB: onception and design of the study; collection, analysis and interpretation of data; drafting of the manuscript; final approval of the manuscript. VD: Conception and design of the study; collection, analysis and interpretation of data; drafting of the manuscript; final approval of the manuscript.

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.05.012.

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