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Letters

Impact of Aortic Valve Calcification and Sex on Hemodynamic Progression and Clinical Outcomes in AS

Aortic valve calcification (AVC) is the main culprit lesion of calcific aortic valve stenosis (AS) and is a strong determinant of AS severity and powerful risk factor for mortality (1,2). Multidetector computed tomography (MDCT) provides accurate, reproducible quantitation of AVC. Recent studies reported that AVC measured by MDCT is helpful to corroborate hemodynamic severity and enhance risk stratification in patients with AS (1,2). However, it remains unclear whether the assessment of AVC by MDCT might have an incremental value over clinical and echocardiographic variables to predict rapid AS hemodynamic progression and associated AS events.

We recruited 323 patients with AS and preserved left ventricular (LV) ejection fraction who underwent comprehensive Doppler echocardiography and MDCT exams within 3 months and a second echocardiographic exam ≥6 months thereafter, at 2 academic centers: 167 patients at Quebec Heart and Lung Institute and 156 patients at the Mayo Clinic. The recruitment, echocardiographic, and MDCT procedures were previously described (2,3). For this analysis, patients were excluded if they had a decrease in LV function or flow parameters during follow-up: that is, LV ejection fraction <50%, decrease in stroke volume index >5 ml/m^2, or decrease in mean transvalvular flow rate >20 ml/s. Of note, the LV outflow tract diameter was considered constant between the 2 echocardiographic examinations. AVC and density of AVC (AVCd) were measured using noncontrast MDCT (2).

The primary endpoint was the hemodynamic progression of AS, assessed by the annualized increase in mean gradient (MG). The secondary endpoint was the composite of aortic valve replacement or cardiovascular death after the second echocardiographic examination.

Among the 323 patients enrolled (68 ± 3 years of age; 70% men), baseline age, and comorbidities including hypertension, dyslipidemia, diabetes, coronary artery disease, atrial fibrillation, and chronic obstructive pulmonary disease were similar between the rapid progressors group (i.e., MG progression rate ≥3.0 mm Hg/year, median for the cohort) and the slow progressors group (all $p \geq 0.24$). However, the rapid progressors had higher prevalence of renal disease (25% vs. 16%; $p = 0.03$) and a trend toward worse New York Heart Association functional class III or IV (10% vs. 4%; $p = 0.08$). Median baseline AVC (1,209 [25th to 75th percentile: 615 to 2,065] arbitrary units [AU] vs. 689 [25th to 75th percentile: 323 to 1,187] AU; $p < 0.0001$) and AVCd (322 [25th to 75th percentile: 160 to 508] AU/cm^2 vs. 175 [25th to 75th percentile: 84 to 309] AU/cm^2; $p < 0.0001$) were 2-fold higher in the rapid progressors group compared with the slow progressors group. Median baseline AVC (531 [25th to 75th percentile: 224 to 1,098] AU vs. 1,019 [25th to 75th percentile: 571 to 1,921] AU; $p < 0.0001$) and AVCd (162 [25th to 75th percentile: 73 to 347] AU/cm^2 vs. 250 [25th to 75th percentile: 141 to 454] AU/cm^2; $p = 0.0002$) were significantly lower in women versus men, whereas hemodynamic severity was similar in both sexes (MG women 24 ± 13 vs. MG men 22 ± 10 mm Hg; $p = 0.48$).

The mean echocardiographic follow-up was 2.3 ± 1.6 years. Baseline AVC and AVCd were significantly associated with annualized increase in MG ($p < 0.0001$). Patients with severe AVC (≥2,000 AU in men and ≥1,200 AU in women) (3) at baseline had 3-fold faster progression rate of MG compared with those with nonsevere AVC (6.1 [25th to 75th percentile: 2.9 to 10.0] mm Hg/year vs. 2.1 [25th to 75th percentile: 0.5 to 4.8] mm Hg/year; $p < 0.0001$) (**Figure 1A**). Similarly, patients with severe AVCd (≥470 AU/cm^2 in men and ≥290 AU/cm^2 in women) (3) at baseline had 3-fold faster progression rate of MG (6.1 [25th to 75th percentile: 3.3 to 9.6] vs. 2.0 [25th to 75th percentile: 0.5 to 4.8] mm Hg/year; $p < 0.0001$). After adjustment for clinical risk factors and hemodynamic AS severity, AVC or AVCd were independent predictors of hemodynamic progression rate of AS (all $p \leq 0.01$). Adding MDCT variables to the multivariable models significantly improved the predictive value of all models (likelihood ratio test, all $p < 0.05$), suggesting an incremental value of AVC load to predict hemodynamic progression rate of AS.

Despite a comparable hemodynamic progression rate of AS in women versus men (MG: 3.4 [25th to 75th

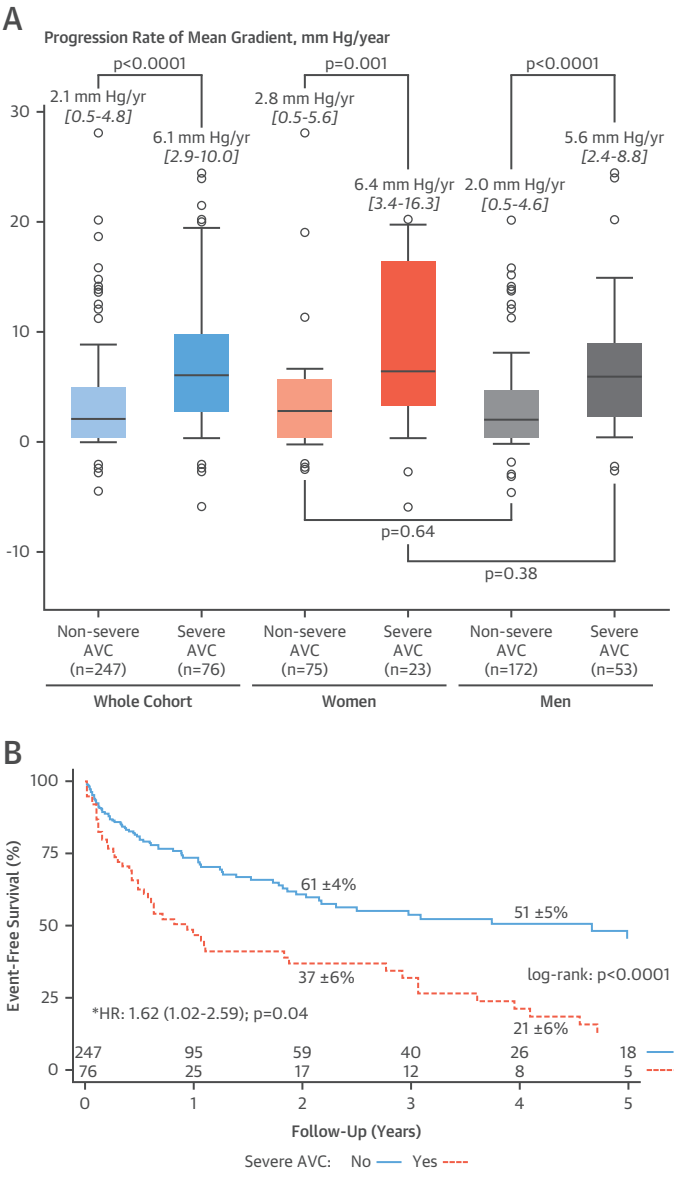
percentile: 0.7 to 6.4] mm Hg/year vs. 2.5 [25th to 75th percentile: 0.8 to 5.7] mm Hg/year; p = 0.48), the slopes of correlation between MG progression and AVC or AVCd were steeper in women than in men (all p [analysis of covariance] ≤ 0.003), suggesting a greater impact of AVC load on hemodynamic progression of AS in women. This could be linked to the greater amount of collagen fibers in women compared to men with similar degree of AS (4). Nevertheless, sex was not associated with hemodynamic progression of AS in multivariable analyses (all p ≥ 0.46).

During a mean follow-up of 1.4 ± 1.9 years after the second echocardiographic examination, 132 valve-related events occurred (124 aortic valve replacements and 8 cardiovascular deaths). Four-year event-free survival was lower in patients with severe AVC compared with those with nonsevere AVC (21 ± 6% vs. 51 ± 5%; p < 0.0001) (**Figure 1B**). Similar results were observed with severe versus nonsevere AVCd (p < 0.0001). After comprehensive multivariable adjustment using Cox proportional hazards analyses, severe AVC (hazard ratio: 1.62; 95% confidence interval: 1.02 to 2.59; p = 0.04) or AVCd (hazard ratio: 2.25; 95% confidence interval: 1.44 to 3.52; p < 0.0001) were independent predictors of valve-related events, provided additive value in all models (likelihood ratio test; all p < 0.05), and improved patients classification in predicting 4-year event-free survival (net reclassification index >20%; both p < 0.01).

In summary, AVC load measured by MDCT provides incremental prognostic value to predict faster hemodynamic AS progression and subsequent occurrence of valve-related events. Women have less AVC than men, but for a given degree of calcium load, they have faster hemodynamic progression. However, using the sex-specific thresholds, severe AVC is associated with the same rate of hemodynamic progression of AS in women versus men. These results support the usefulness of AVC in the risk stratification process and clinical management of patients with AS.

Lionel Tastet, MSc
Maurice Enriquez-Sarano, MD
Romain Capoulade, PhD
Joseph Malouf, MD
Phillip A. Araoz, MD
Mylène Shen, BSc
Hector I. Michelena, MD
Éric Larose, MD, MSc
Marie Arsenault, MD
Élisabeth Bédard, MD
Philippe Pibarot, DVM, PhD
***Marie-Annick Clavel, DVM, PhD**

FIGURE 1 Impact of AVC Load on Hemodynamic Progression Rate of Aortic Stenosis and Valve-Related Events



Annualized change in **(A)** mean gradient and **(B)** Kaplan-Meier curves of valve-related event-free survival according to the presence or absence of severe aortic valve calcification (AVC) (≥1,200 arbitrary units in women and ≥2,000 arbitrary units in men). HR = hazard ratio.

*Institut Universitaire de Cardiologie et de Pneumologie de Québec
2725 Chemin Sainte-Foy
Québec City, Québec
Canada
G1V-4G5
E-mail: marie-annick.clavel@criucpq.ulaval.ca

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Ticagrelor Versus Clopidogrel on Myocardial Infarct Size in Patients Undergoing Primary Percutaneous Coronary Intervention

Compared with clopidogrel, ticagrelor improves clinical outcomes in patients with acute coronary syndrome (1). However, the mechanism of ticagrelor's benefits has not been fully elucidated. Although recent animal studies demonstrated that ticagrelor reduces reperfusion injury and limits myocardial infarct size (2,3), ticagrelor did not improve ST-segment elevation resolution in patients with ST-segment elevation myocardial infarction (STEMI) (4). This study sought to compare the effects of ticagrelor and clopidogrel on myocardial infarct size in patients with STEMI undergoing primary percutaneous coronary intervention (PCI).

We conducted a 2-center, prospective, randomized, open-label, blinded endpoint study. The institutional review board approved the protocol (NCT01738100), and written informed consent was obtained. From January 2013 to June 2016, a total of 110 patients with STEMI undergoing primary PCI were randomly assigned to the ticagrelor group (180-mg loading dose, 90 mg twice daily thereafter) or the clopidogrel group (600-mg loading dose, 75 mg daily thereafter) at a 1:1 ratio. Patients with Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 or 1 were randomly assigned to intracoronary injection of morphine sulfate or saline at a 1:1 ratio to concurrently investigate morphine-induced cardioprotection. These second randomization data will be reported separately. The primary endpoint was myocardial infarct size assessed by cardiac magnetic resonance (CMR) imaging. Imaging acquisition and measurement of CMR were performed within 5 days after the index event as previously reported protocol in our center (5).

Evaluable CMR images were available in 45 and 50 patients of the ticagrelor and clopidogrel groups, respectively. There were no significant differences in baseline characteristics between the ticagrelor and clopidogrel groups. Angiographic and procedural findings were well balanced except pre-procedural TIMI flow grade (33 [73.3%] in the ticagrelor group vs. 42 [84.0%] in the clopidogrel group; $p = 0.20$). There was no significant difference in morphine use between the groups (48.6% vs. 55.6%; $p = 0.54$). Myocardial infarct size, the primary endpoint, and the extent of microvascular obstruction were significantly smaller in the ticagrelor group (**Table 1**). In exploratory subgroup analysis, a beneficial effect of ticagrelor was consistent regardless of morphine use (p for interaction = 0.33). Final TIMI flow grade and myocardial blush grade were comparable between the 2 groups. Although the frequency of complete ST-segment elevation resolution did not differ between the groups, peak creatinine kinase-myocardial band fraction level was also reduced in the ticagrelor group. Of patients with pre-procedural TIMI flow grade 0 to 1, beneficial effects of ticagrelor were consistent (infarct size: 22.6 ± 9.7% vs. 28.1 ± 11.0%, $p = 0.02$; microvascular obstruction: 4.4 ± 4.1% vs. 7.1 ± 6.3%, $p = 0.03$).

Platelet inhibition was comparable between the groups just before reperfusion, which was supported

TABLE 1 Study Endpoints

	Ticagrelor (n = 45)	Clopidogrel (n = 50)	p Value
Infarct size, % LV	21.5 ± 10.9	26.5 ± 11.3	0.03
Microvascular obstruction, % LV	3.0 (0-9.2)	5.3 (0.5-10.9)	0.02
Mean transmurality score	1.9 ± 0.5	2.1 ± 0.4	0.06
LV ejection fraction, %	55.2 ± 9.5	52.8 ± 8.7	0.21
Final TIMI flow grade 3	43 (95.6)	44 (88.0)	0.19
Myocardial blush grade 2/3	39 (86.6)	37 (74.0)	0.89
Complete ST-segment elevation resolution	21 (46.7)	24 (48.0)	0.90
Peak CK-MB fraction, ng/mL	170.4 (80.5-267.4)	232.7 (117.1-310.2)	0.04
$P2Y_{12}$ reaction unit	216.1 ± 83.6	231.0 ± 64.0	0.34

Values are mean ± SD, median (interquartile range), or n (%).

CK-MB = creatinine kinase-myocardial band; LV = left ventricular; TIMI = Thrombolysis In Myocardial Infarction.