

Letters

RESEARCH LETTER

Analysis of Calcium Scores in Severe Aortic Stenosis Patients With and Without Cardiac Amyloidosis

The CAUSATIVE Study

Transthyretin amyloid cardiomyopathy (ATTR-CM) frequently coexists with degenerative aortic stenosis (AS), with prevalence estimates up to 25% in contemporary cohorts of elderly patients undergoing valve replacement.¹ Both diseases share overlapping echocardiographic features, making the diagnosis of either condition more challenging.

Cardiac computed tomography (CCT)-derived aortic valve calcium scoring (CS) is widely used to confirm the severity of AS, particularly in low-flow, low-gradient phenotypes commonly observed in the presence of ATTR-CM.² However, clinical observations suggest that patients with ATTR-CM may develop severe AS despite a modest calcification burden, raising concerns about the reliability of guideline-based CS thresholds in this setting.³

The CAUSATIVE (Analysis of Calcium Score of Severe Aortic Stenosis in Patients With and Without Cardiac Amyloidosis; [NCT06066632](#)) study tested the hypothesis that patients with dual pathology exhibit significantly lower CS than do those with isolated AS.³ This multicenter observational study enrolled consecutive patients ≥ 65 years with symptomatic severe AS and an indication for valve replacement across 9 European amyloidosis referral centers: Italy: Ferrara, Trieste, Bologna, Milan, Ancona, Cotignola, Florence, and Pisa; Austria: Vienna. The Institutional Review Board approved the protocol at each participating center. Patients were enrolled in the study if they met the following inclusion criteria: 1) age ≥ 65 years, 2) diagnosis of symptomatic severe AS; 3) indication for aortic valve replacement; and 4) presence of at least 1 red flag suggestive of ATTR-CM. The red flags considered included septal wall thickness ≥ 18 mm, E/A ratio > 1.4 , persistently elevated high-sensitivity troponin, carpal tunnel syndrome, right bundle branch block, and Sokolow-Lyon index < 1.9 mV.

The diagnosis of severe AS was based on current echocardiographic guidelines and defined as a

functional aortic valve area $< 1 \text{ cm}^2$. All patients underwent systematic screening for ATTR-CM using bone scintigraphy and TTR genotyping. The diagnosis of ATTR-CM was established on the basis of myocardial uptake on bone scintigraphy with either pyrophosphate or diphosphonate tracers (ie, Perugini score grade 1, 2, or 3): 1) in the absence of biochemical evidence of plasma cell dyscrasia; or 2) with biopsy-proven TTR amyloid in the presence of plasma cell dyscrasia.

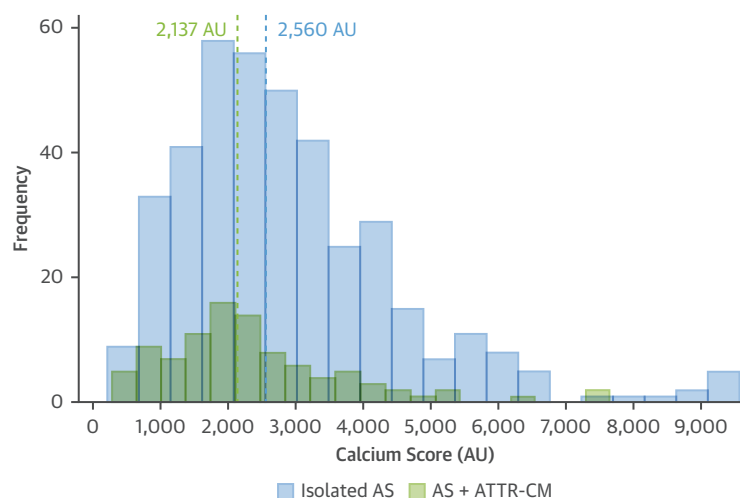
Noncontrast electrocardiogram-gated CCT was performed in all patients. CS was quantified by a blinded core laboratory using the Agatston method. The primary endpoint was the difference in CS between isolated AS and dual pathology (AS + ATTR-CM). Group comparisons were performed using nonparametric tests and multivariable quantile regression adjusted for age, sex, renal function, and AS phenotype. A total of 504 patients were included: 400 (79.4%) with isolated AS and 104 (20.6%) with concomitant ATTR-CM. The mean age was 81.1 ± 5.9 years; 53.6% were male ([Figure 1A](#)). Patients with dual pathology were older and more frequently male, with a higher prevalence of atrial fibrillation and heart failure history. A total of 187 patients (37.1%) had low-flow, low-gradient AS (137 [34.2%] with isolated AS and 50 [48.1%] with concomitant ATTR-CM; $P = 0.009$).

The primary endpoint analysis showed significantly lower median CS in patients with concomitant ATTR-CM (2,137 arbitrary unit [AU] [Q1-Q3: 1,476-2,912 AU]) than did those with isolated AS (2,560 AU [Q1-Q3: 1,728-3,609 AU]) ($P = 0.007$), as well as lower calcium volume (1,617 mL vs 2,057 mL; $P < 0.001$) and lower indexed CS (per body surface area) (1,089 vs 1,362; $P = 0.002$) ([Figure 1](#)). In multivariable quantile regression, ATTR-CM remained independently associated with lower CS, with a median difference of -674 AU (95% CI: $-1,005$ to -343 AU; $P < 0.001$). These results demonstrate that patients with severe AS and concomitant ATTR-CM exhibit markedly lower aortic valve CS than do those with isolated AS. This difference persisted after adjustment for key confounders, including AS phenotypes.

Our findings have 2 key clinical implications: 1) In the context of dual pathology, valvular obstruction may be not driven solely by calcification. In some cases, amyloid infiltration of the valve and annulus

FIGURE 1 Baseline Characteristics and Distribution of Calcium Score**A**

	Isolated AS N = 400	AS and ATTR-CM N = 104	P-Value
Age-year (SD)	80.4 (±6.0)	83.8 (±4.6)	<0.001
Male-n (%)	199 (49.8%)	71 (68.3%)	<0.001
eGFR-mL/min/1.73 m ² (SD)	62.8 (±22.8)	56.8 (±22.0)	0.017
NT-proBNP-ng/L (IQR)	2,360.0 (706.0-5,420.2)	4,038.0 (1,494.0-7,453.0)	<0.001
Low flow-Low gradient phenotype-n (%)	137 (34.2%)	50 (48.1%)	0.009
Calcium Score-AU (IQR)	2,560.0 (1,728.0-3,609.0)	2,137.0 (1,476.0-2,912.0)	0.007
Calcium Volume-mL (IQR)	2,056.5 (1,361.5-2,849.0)	1,616.5 (1,105.0-2,137.0)	<0.001
Indexed Calcium Score -AU/m ² (IQR)	1,362.2 (999.0-1,985.0)	1,089.6 (807.9-1,534.0)	0.002

B

Baseline characteristics (A) and distribution of calcium score (B) in patients with isolated AS and those with dual pathology. AS = aortic stenosis; ATTR-CM = transthyretin amyloid cardiomyopathy; AU = arbitrary unit; eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

may contribute to stenosis severity, thereby explaining the reduced calcific burden observed in some patients. 2) According to the current ESC (European Society of Cardiology)/EACTS (European Association for Cardio-Thoracic Surgery) guidelines, sex-specific CS thresholds are recommended to confirm severe AS in patients with discordant echocardiographic findings.⁴ In the setting of dual

pathology, applying standard CS thresholds may underestimate stenosis severity in the presence of concomitant ATTR-CM.

Recognition of this limitation is crucial. In practice, patients with ATTR-CM may be denied valve replacement despite true severe AS, potentially missing the opportunity for improved symptoms and outcomes. Our findings therefore support the need

for disease-specific CS cutoffs or multiparametric approaches integrating CS with clinical, echocardiographic, and scintigraphic data.

The study lacked histological confirmation of valvular amyloid deposition, and advanced imaging (quantitative scintigraphy and single-photon emission computed tomography) was not mandatory. Nonetheless, the blinded core-laboratory analysis of CCT and the large, systematically screened cohort strengthen the validity of the primary endpoint findings. Furthermore, a previous histological study showed a high frequency of occult TTR deposition in aortic valves replaced for AS.⁵

In conclusion, in a large multicenter cohort of severe AS, patients with concomitant ATTR-CM exhibited markedly lower aortic valve CS than did those with isolated AS. These results highlight the need for ATTR-CM-specific diagnostic strategies when evaluating AS severity and call for reconsideration of CS cutoffs to avoid underrecognition of true severe AS in patients with dual pathology.

***Matteo Serenelli, MD**
Paolo Cimaglia, MD
Aldostefano Porcari, MD
Andrea Lalaro, MD
Marco Merlo, MD
Christian Nitsche, MD, PhD
Maximilian Autherith, MD, PhD
Laurenz Hauptmann, MD
Philipp Emanuel Bartko, MD
Simone Longhi, MD
Giulia Saturi, MD, PhD
Fabio Vagnarelli, MD, PhD
Carla Lofiego, MD, PhD
Rita Conti, MD
Alberto Aimo, MD, PhD
Michele Emdin, MD, PhD
Francesco Cappelli, MD
Giulia Nardi, MD
Alberico Del Torto, MD
Gianluca Pontone, MD, PhD

Guglielmo Gallone, MD, PhD
Gaetano Maria De Ferrari, MD
Arianna Morena, MD
Valentino Santori, MD
Carlo Tumscitz, MD
Beatrice Dal Passo, MD
Anna Cantone, MD
Jacopo Bonini, MD
Matteo Arzenton, MD
Federico Sanguettoli, MD
Federico Marchini, MD
Rita Pavasini, MD
Gianluca Campo, MD
Gianfranco Sinagra, MD

***Cardiology Unit**

Azienda Ospedaliero-Universitaria S.Anna
 Via A. Moro 8
 Cona (Ferrara), Italy
 E-mail: matteoserenelli@gmail.com

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

REFERENCES

1. Ternacle J, Krapf L, Mohty D, et al. Aortic stenosis and cardiac amyloidosis: JACC Review Topic of the Week. *J Am Coll Cardiol*. 2019;74(21):2638-2651.
2. Longhi S, Lorenzini M, Gagliardi C, et al. Coexistence of degenerative aortic stenosis and wild-type transthyretin-related cardiac amyloidosis. *JACC Cardiovasc Imaging*. 2016;9(3):325-327.
3. Hussain M, Hanna M, Griffin BP, et al. Aortic valve calcium in patients with transthyretin cardiac amyloidosis. *Circ Cardiovasc Imaging*. 2020;13(10):e011433.
4. Singal AK, Bansal R, Singh A, et al. Concomitant transthyretin amyloidosis and severe aortic stenosis in elderly Indian population. *JACC CardioOncol*. 2021;3(4):565-576.
5. Honda K, Tasaki M, Yamano T, et al. High frequency of occult transthyretin and apolipoprotein AI-type amyloid in aortic valves removed by valve replacement for aortic stenosis. *Amyloid*. 2025;32(1):22-28.