# Impact of Aortic Valve Calcification, as Measured by MDCT, on Survival in Patients With Aortic Stenosis

## Results of an International Registry Study

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## ABSTRACT

**BACKGROUND** Aortic valve calcification (AVC) load measures lesion severity in aortic stenosis (AS) and is useful for diagnostic purposes. Whether AVC predicts survival after diagnosis, independent of clinical and Doppler echocardiographic AS characteristics, has not been studied.

**OBJECTIVES** This study evaluated the impact of AVC load, absolute and relative to aortic annulus size ($AVC_{density}$), on overall mortality in patients with AS under conservative treatment and without regard to treatment.

**METHODS** In 3 academic centers, we enrolled 794 patients (mean age, $73 \pm 12$ years; 274 women) diagnosed with AS by Doppler echocardiography who underwent multidetector computed tomography (MDCT) within the same episode of care. Absolute AVC load and $AVC_{density}$ (ratio of absolute AVC to cross-sectional area of aortic annulus) were measured, and severe AVC was separately defined in men and women.

**RESULTS** During follow-up, there were 440 aortic valve implantations (AVIs) and 194 deaths (115 under medical treatment). Univariate analysis showed strong association of absolute AVC and $AVC_{density}$ with survival (both, $p < 0.0001$) with a spline curve analysis pattern of threshold and plateau of risk. After adjustment for age, sex, coronary artery disease, diabetes, symptoms, AS severity on hemodynamic assessment, and LV ejection fraction, severe absolute AVC (adjusted hazard ratio [HR]: 1.75; 95% confidence interval [CI]: 1.04 to 2.92; $p = 0.03$) or severe $AVC_{density}$ (adjusted HR: 2.44; 95% CI: 1.37 to 4.37; $p = 0.002$) independently predicted mortality under medical treatment, with additive model predictive value (all, $p \leq 0.04$) and a net reclassification index of 12.5% ($p = 0.04$). Severe absolute AVC (adjusted HR: 1.71; 95% CI: 1.12 to 2.62; $p = 0.01$) and severe $AVC_{density}$ (adjusted HR: 2.22; 95% CI: 1.40 to 3.52; $p = 0.001$) also independently predicted overall mortality, even with adjustment for time-dependent AVI.

**CONCLUSIONS** This large-scale, multicenter outcomes study of quantitative Doppler echocardiographic and MDCT assessment of AS shows that measuring AVC load provides incremental prognostic value for survival beyond clinical and Doppler echocardiographic assessment. Severe AVC independently predicts excess mortality after AS diagnosis, which is greatly alleviated by AVI. Thus, measurement of AVC by MDCT should be considered for not only diagnostic but also risk-stratification purposes in patients with AS. (J Am Coll Cardiol 2014;64:1202–13) © 2014 by the American College of Cardiology Foundation.

Calcific aortic stenosis (AS) occurs frequently, and aortic valve implantation (AVI), surgical or percutaneous, is the only effective treatment (1,2). According to U.S. and European guidelines, AVI is indicated in severe symptomatic AS (1,2) on the basis of classic studies showing poor outcomes after symptom onset (3,4). However, in recent decades, AS etiology has fundamentally evolved to become predominantly "degenerative" (5). Thus, nowadays, AS affects elderly patients, in whom the evaluation and interpretation of symptoms and even the interpretation of valvular hemodynamic data can be puzzling (6), requiring other objective markers of diagnosis and risk.

Because valvular calcification is the intrinsic mechanism leading to AS development, and because it can be accurately measured by computed tomography (CT) (7), aortic valve calcification (AVC) load assessment generates considerable interest. In the general population, screening studies (8) and a meta-analysis of data from smaller series (9) suggest that AVC qualitative assessment may be of prognostic importance. More specifically, in patients with AS, physiological studies advance that because AVC quantification is strongly but nonlinearly (7) associated with hemodynamic measures of AS severity, it may add incremental value to Doppler echocardiography. We gained improved interpretation of quantified AVC load with the demonstration that the association between AVC and hemodynamic data is robust but different in men and women (10), leading to sex-specific thresholds for defining severe AVC compared with Doppler echocardiographic hemodynamic AS severity (11).

Although the physiological and diagnostic values of AVC in AS are now better supported, particularly in patients with discordant gradients (11), the impact on survival of AVC load, as measured by multidetector computed tomography (MDCT) after AS diagnosis, remains undefined. Initial qualitative studies using echocardiography were encouraging (12,13) but remain isolated. Pilot CT studies suggested that AVC load may be linked to cardiovascular events, particularly AVI indications, but with inconsistent and non–sex-differentiated thresholds (7,14). These pilot studies generated potential clinical interest and the hypothesis that in patients with AS, AVC load may be a determinant of survival after diagnosis as a major and categorically definable endpoint, independent of and incremental to valvular hemodynamic data obtained by Doppler echocardiography. The present study took advantage of the large patient volume of our multicenter international registry of calcified aortic valve diseases to evaluate the impact of quantitatively defined AVC load, absolute and relative to left ventricular (LV) outflow tract size (AVC$_{density}$), on overall mortality in patients under conservative treatment. This study's secondary aim was to evaluate the impact of AVC on overall survival regardless of treatment.

## METHODS

We prospectively recruited 794 adult patients with at least mild AS (defined as a mean gradient [MG] $\geq$15 mm Hg, peak aortic jet velocity [V$_{max}$] $\geq$2.0 m/s, or aortic valve area [AVA] $\leq$2 cm$^2$) who underwent comprehensive Doppler echocardiography and MDCT within the same episode of care (<3 months between evaluations) at 1 of 3 academic centers: the Mayo Clinic (Rochester, Minnesota), Bichat Hospital (Paris, France), or the University Institute of Cardiology and Pneumology (IUCPQ) (Quebec, Quebec, Canada). We excluded patients age <18 years and those with identified rheumatic valve disease or endocarditis, congenital heart disease (except bicuspid aortic valve), moderate or severe aortic regurgitation or mitral valve disease, and/or a history of valve repair or implantation. Informed consent was obtained according to approval by each institutional review board.

**DOPPLER ECHOCARDIOGRAPHY MEASUREMENTS.**
Doppler echocardiographic data were obtained according to recommendations of echocardiographic societies (15), and included left ventricular (LV) dimensions and ejection fraction, V$_{max}$, MG by modified Bernoulli formula, stroke volume measured

in the LV outflow tract, and AVA, calculated using the continuity equation as absolute AVA or indexed to body surface area (AVAi).

**MDCT MEASUREMENTS.** Noncontrast CT was performed using multidetector scanners (Sensation or Somatom, Siemens AG Healthcare, Erlangen, Germany; MX 8000 IDT 16, Philips Healthcare, Andover, Massachusetts). The 3 centers used the same methodology of image acquisition and interpretation, which was previously described (11,16). AVC measurements were performed off-line on dedicated workstations using validated software (HeartBeat CS [Philips Healthcare] or Aquarius iNtuition [TeraRecon, Inc., Foster City, California]) by the Agatston method (17) and expressed in arbitrary units (AU).

We previously showed that AVC values of ≥1,274 AU in women and ≥2,065 AU in men were the best cutoff values to define severe AVC according to Doppler echocardiographic evaluation of AS (11). Moreover, to account for interindividual variability in body size, we showed that indexing AVC to the cross-sectional area of the aortic annulus was the preferable indexation and that the best thresholds for $AVC_{density}$ were 292 and 476 $AU/cm^2$ in women and men, respectively (11). Thus, we dichotomized AVC and $AVC_{density}$ in severe and nonsevere calcification using these previously defined thresholds.

In a subset of 635 patients, the entire heart was visible on MDCT scanning; coronary artery calcium load was calculated and considered severe when greater than the median value in our population.

Technologists and cardiologists performing CT acquisitions and measurements were kept blinded to the clinical, Doppler echocardiographic, and outcomes data. The median time between Doppler echocardiography and MDCT was 1 day (interquartile range: 0 to 9 days).

**SYMPTOM STATUS.** Patients were considered symptomatic if they presented with dyspnea, New York Heart Association functional class III or IV, angina (Canadian Cardiovascular Society class III or IV), presyncope, or syncope. Among patients considered asymptomatic, some had minor symptoms (dyspnea or angina with vigorous physical activity).

**STUDY ENDPOINTS.** The primary endpoint was overall survival under medical treatment. Hence in patients who underwent AVI, the AVI date was used to compute the duration of follow-up under medical management, but AVI was not an endpoint. Secondary endpoints were cardiovascular death under medical management and the overall and cardiovascular survival during the entire follow-up, regardless of AVI status. Outcomes data were obtained from patient visits or records, mailed questionnaires, or scripted telephone interviews with patients or physicians, and death certificates when applicable. Follow-up to death, AVI, or ≥5 years post-diagnosis was completed in 762 patients (96%).

**STATISTICAL ANALYSIS.** Results are expressed as mean ± SD, median (interquartile range), or percentages when appropriate. Continuous variables were tested for normality by the Shapiro-Wilk test. AVC, $AVC_{density}$, and coronary artery calcium load were not normally distributed. We used a square-root

| TABLE 1  Baseline Clinical, Echocardiographic, and MDCT Characteristics | | | | |
|---|---|---|---|---|
| | **Study Groups** | | | |
| | Nonsevere $AVC_{density}$*  (n = 384) | Severe $AVC_{density}$†  (n = 410) | p Value | All Patients (N = 794) |
| **Clinical data** | | | | |
| Age, yrs | 70 ± 13 | 76 ± 11 | <0.0001 | 73 ± 12 |
| Female | 122 (32) | 152 (37) | 0.12 | 274 (35) |
| Body mass index, kg/m² | 28.2 ± 5.4 | 28.4 ± 6.5 | 0.69 | 28.3 ± 5.9 |
| Body surface area, m² | 1.90 ± 0.23 | 1.91 ± 0.25 | 0.46 | 1.90 ± 0.24 |
| Systolic blood pressure, mm Hg | 131 ± 18 | 127 ± 19 | 0.01 | 129 ± 19 |
| Diastolic blood pressure, mm Hg | 72 ± 11 | 70 ± 11 | 0.11 | 71 ± 11 |
| Heart rate, beat/min | 66 ± 13 | 69 ± 13 | 0.001 | 68 ± 13 |
| Heart failure symptoms | 51 (13) | 160 (39) | <0.0001 | 211 (27) |
| Hypertension | 266 (69) | 278 (68) | 0.66 | 544 (69) |
| Coronary artery disease | 153 (40) | 194 (47) | 0.04 | 347 (44) |
| Diabetes | 82 (21) | 98 (24) | 0.38 | 180 (23) |
| Hyperlipidemia | 265 (69) | 269 (66) | 0.30 | 534 (67) |
| Previous CABG | 81 (21) | 102 (25) | 0.23 | 183 (23) |
| **Echocardiographic data** | | | | |
| Peak aortic jet velocity, m/s | 3.0 ± 0.7 | 4.4 ± 0.8 | <0.0001 | 3.7 ± 1.0 |
| Mean gradient, mm Hg | 22 ± 11 | 47 ± 17 | <0.0001 | 35 ± 19 |
| Aortic valve area, cm² | 1.34 ± 0.39 | 0.87 ± 0.21 | <0.0001 | 1.10 ± 0.39 |
| AVAi, cm²/m² | 0.71 ± 0.20 | 0.46 ± 0.11 | <0.0001 | 0.58 ± 0.20 |
| LV outflow tract diameter, cm | 2.25 ± 0.20 | 2.22 ± 0.22 | 0.10 | 2.23 ± 0.21 |
| LV ejection fraction, % | 62 ± 10 | 58 ± 14 | <0.0001 | 60 ± 12 |
| LV mass index, g/m² | 108 ± 26 | 127 ± 37 | <0.0001 | 118 ± 33 |
| **MDCT data** | | | | |
| Aortic valve calcification, AU | | | | |
| Men | 1,070 (575–1,531) | 3,403 (2,662–4,458) | <0.0001 | 2,022 (1,042–3,397) |
| Women | 436 (211–782) | 1,879 (1,355–2,774) | <0.0001 | 1,103 (495–2,028) |
| $AVC_{density}$, $AU/cm^2$ | | | | |
| Men | 257 (136–364) | 790 (630–1,011) | <0.0001 | 473 (256–789) |
| Women | 127 (58–215) | 553 (401–819) | <0.0001 | 318 (142–593) |
| Coronary artery calcium load,‡ AU | 362 (39–1,199) | 920 (235–2,322) | <0.0001 | 719 (107–1,916) |

Values are mean ± SD, n (%), or median (interquartile range). *Defined as <292 $AU/cm^2$ in women and <476 $AU/cm^2$ in men. †Defined as ≥292 $AU/cm^2$ in women and ≥476 $AU/cm^2$ in men. ‡Measurable in a subset of 635 patients.

AU = arbitrary unit(s); AVA = aortic valve area; AVAi = aortic valve area indexed to body surface area; AVC = aortic valve calcification; CABG = coronary artery bypass graft surgery; LV = left ventricular; MDCT = multidetector computed tomography.

transformation to normalize AVC and $AVC_{density}$, and all analysis of AVC or $AVC_{density}$ as continuous variables used square-root-transformed levels that well-normalized distributions, with a *W*-statistic of Shapiro-Wilk test of ≥0.997 and p ≥ 0.08.

Differences between patients with nonsevere or severe $AVC_{density}$ were analyzed using the Student *t* test for continuous normally distributed variables, the Wilcoxon rank sum test for continuous non-normally distributed variables, and the chi-square test for nominal variables.

Differences of classification between graphically determined thresholds and previously calculated thresholds (11) of severe absolute AVC and $AVC_{density}$ were assessed by the McNemar test.

The effect of clinical, Doppler echocardiographic, and MDCT variables on overall survival under medical treatment was assessed using the Cox proportional hazards model. Clinically relevant variables and/or variables with a p value of ≤0.05 on individual analysis were included in background multivariate models (i.e., age, sex, heart failure [HF] symptoms, diabetes, history of coronary artery disease [CAD], AVAi, MG, and LV ejection fraction). For each endpoint, MG was replaced by peak aortic jet velocity in secondary models to assess whether this substitution affects the association of AVC and survival. For subgroup analysis, stepwise backward methods from general models were used. To analyze the secondary endpoints, AVI was used as a time-dependent covariate in the Cox models. Results of the Cox models are presented as hazard ratios (HRs) and 95% confidence intervals (CIs).

To determine whether severe $AVC_{density}$ offered value in predicting 1-year mortality under medical treatment (primary endpoint) beyond traditional risk factors, the incremental value of severe $AVC_{density}$ was assessed using the net reclassification index (NRI). Logistic regression was used to determine predicted probabilities for 1-year all-cause mortality under medical management in each patient, using the background model. The probabilities were then ranked and categorized into tertiles (<4%, 4% to <15%, and ≥15%). After severe $AVC_{density}$ was added into the model, patients were reclassified according to the predicted probability of death at 1 year. The NRI quantified the net improvement in risk reclassification (higher predicted probability of death in 1-year nonsurvivors; lower predicted probability of death in 1-year survivors). A p value ≤0.05 was considered statistically significant. Statistical analyses were performed with SPSS 20.0 software (SPSS Inc., Chicago, Illinois).

## RESULTS

**BASELINE CHARACTERISTICS.** The baseline characteristics of the 794 patients included in this study (Mayo Clinic: 535; IUCPQ: 137; Bichat Hospital: 122) are presented in **Table 1**. On stratification of patients by $AVC_{density}$, patients with severe $AVC_{density}$ were older (p < 0.0001), but comorbid clinical conditions were within ranges similar to those in patients with nonsevere $AVC_{density}$. As expected, patients with severe $AVC_{density}$ had more severe AS and presented more often with symptoms (**Table 1**).

**PATTERN OF MORTALITY ACCORDING TO AVC LOAD.** During the mean follow-up of 3.1 ± 2.6 years, there were 440 AVIs and 194 deaths. Overall 5-year survival after diagnosis was 65 ± 3% under medical management and 68 ± 2% with medical and/or surgical management for the entire cohort. The quantitative links between the levels of AVC load expressed as continuous variables (absolute AVC load and $AVC_{density}$) and survival after diagnosis were analyzed separately in men and women due to the differential calcification between sexes previously reported (10).
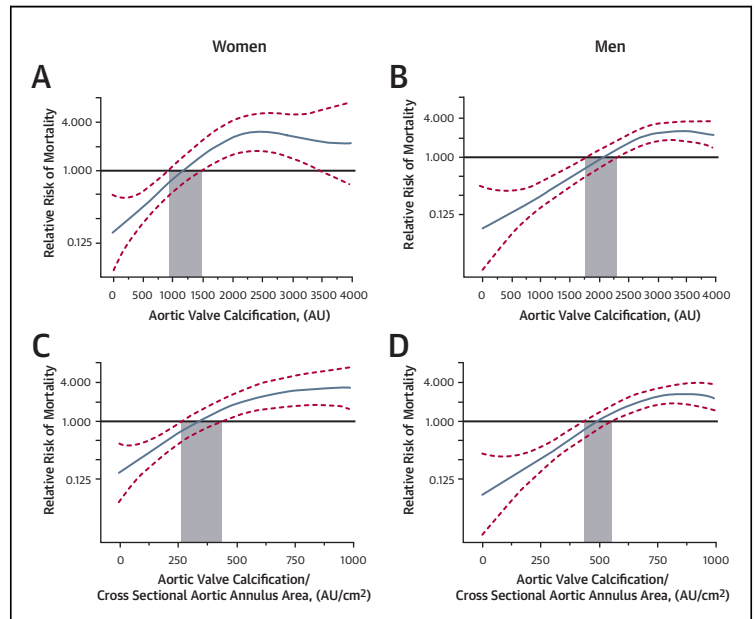


**FIGURE 1** Impact of AVC Burden on Mortality in Patients With AS, by Sex

Spline curve analysis of absolute aortic valve calcification (AVC) **(A and B)** and $AVC_{density}$ (ratio of absolute AVC index to cross-sectional area of aortic annulus) **(C and D)**, in women **(A and C)** and in men **(B and D)** with aortic stenosis (AS). The spline curve **(solid lines)** is presented with 95% confidence interval **(dotted lines)**. The *x*-axis represents the AVC load; the *y*-axis, the relative risk (RR) for mortality. The **horizontal line** at RR = 1 represents the mean risk in the cohort. The **grey zone** represents the range of AVC loads corresponding to the 95% bracket of the spline curve when it crosses the line at RR = 1. AU = arbitrary unit(s).

Thus, on univariate Cox proportional hazards analysis, both absolute AVC and $AVC_{density}$ were strong predictors of mortality in men as well as in women (all, p < 0.0001). The pattern linking AVC severity and mortality was analyzed in spline curves (of relative risk [RR] on the *y*-axis vs. AVC severity on the *x*-axis), whereby a RR of 1 represents the cohort's mean risk. These spline curves (for absolute AVC and $AVC_{density}$ in men and women) are presented in **Figure 1** and show clearly the high risk associated with a high AVC load.

Furthermore, specific patterns of association between AVC load and mortality risk are noteworthy. First, in terms of thresholds of risk, as shown in **Figures 1A and 1B**, absolute AVC negatively impacted

survival under medical management, with thresholds (crossing of the RR line of 1.0) of 1,180 AU in women and 2,050 AU in men. These thresholds are not different from those previously defined as associated with hemodynamic markers of severe AS (both, p > 0.12). Similarly, **Figures 1C and 1D** illustrate that $AVC_{density}$ negatively impacts survival, with thresholds of 300 $AU/cm^2$ in women and 475 $AU/cm^2$ in men, not different from those previously defined as associated with hemodynamic markers of severe AS (both, p > 0.24).

Second, the links between absolute AVC and $AVC_{density}$ and mortality shown in **Figure 1** were not linear and reached a plateau. To document this pattern, we analyzed data from patients with absolute AVC and $AVC_{density}$ higher than the thresholds of risk and categorized them as having absolute AVC and $AVC_{density}$ higher (highly severe) and lower (simply severe) than the medians in this high-risk subset. In this analysis, patients with highly severe and simply severe absolute AVC showed similar mortality under medical management of AS (p = 0.36). Similarly, patients with highly severe versus simply severe $AVC_{density}$ incurred similar mortality (p = 0.21). In view of this pattern of threshold and plateau regarding the links between AVC load (both absolute AVC and $AVC_{density}$) and mortality after diagnosis in men and women, subsequent analyses categorized patients as having high versus low AVC load (with specific thresholds in men and women), which allowed for a combined analysis of survival in men and women together. The Kaplan-Meier survival curves according to the presence or absence of severe absolute AVC and $AVC_{density}$ show that irrespective of the measure used, patients with high AVC load had lower survival (all p <0.0001) under medical management (**Figure 2**) or with medical/surgical management (**Figure 3**).
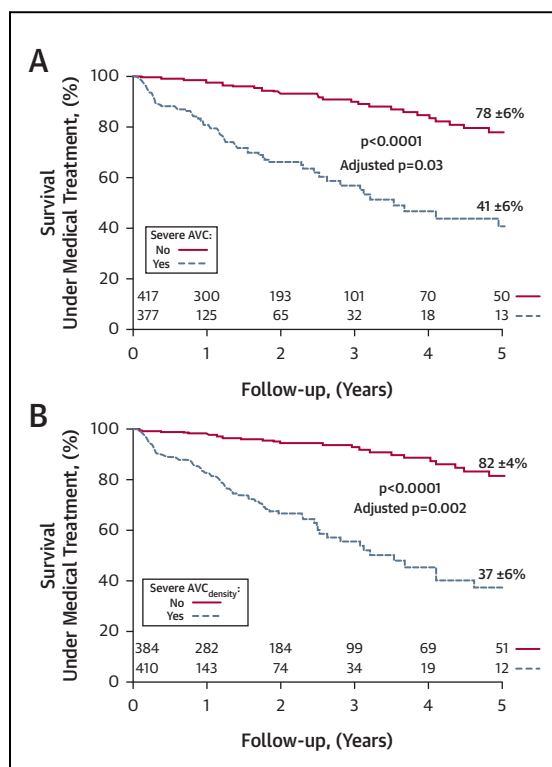


**FIGURE 2**   **Effects of AVC Burden on Survival in Patients With AS Under Medical Treatment**

Kaplan-Meier curves of survival, according to the presence **(solid red line)** or absence **(dashed blue line)** of severe absolute AVC (≥1,274 AU in women and ≥2065 AU in men) **(A)**, and the presence **(dashed blue line)** or absence **(solid red line)** of severe $AVC_{density}$ (≥292 $AU/cm^2$ in women and ≥476 $AU/cm^2$ in men) **(B)**. Note the considerable excess mortality associated with severe calcification load. Adjusted for age, sex, New York Heart Association functional class ≥III, diabetes, coronary artery disease, aortic valve area indexed to body surface area (AVAi), mean gradient (MG), and left ventricular (LV) ejection fraction. Abbreviations as in **Figure 1**.

**INCREMENTAL PROGNOSTIC VALUE OF SEVERE AVC ON MORTALITY IN MEDICALLY MANAGED PATIENTS.** During a mean follow-up of 1.7 ± 2.0 years under medical treatment, there were 115 deaths; 82 were considered cardiovascular related. In view of the association of higher AVC load with somewhat older age and definitely tighter AS (**Table 1**), it is essential to determine the incremental nature of the association of AVC load with survival. On adjustment for age, sex, HF symptoms, diabetes, CAD, AVAi, MG, and LV ejection fraction, severe absolute AVC (HR: 1.75; 95% CI: 1.04 to 2.92; p = 0.03) and severe $AVC_{density}$ (HR: 2.44; 95% CI: 1.37 to 4.37; p = 0.002) predicted mortality under medical management (**Table 2**).

When absolute AVA replaced AVAi in multivariate models, the predictive values of absolute AVC (HR: 1.71; 95% CI: 1.05 to 2.84; p = 0.03) and $AVC_{density}$ (HR: 2.21; 95% CI: 1.26 to 3.98; p = 0.005) were unaffected. Replacing $V_{max}$ with MG in multivariate models did not affect the predictive value of absolute AVC (HR: 1.71; 95% CI: 1.02 to 2.90; p = 0.04) or $AVC_{density}$ (HR: 2.31; 95% CI: 1.30 to 4.21; p = 0.004). Similarly, AVC and $AVC_{density}$ also predicted cardiovascular-related death (HR: 2.14 [95% CI: 1.08 to 4.45; p = 0.03] and 2.28 [95% CI: 1.11 to 4.95; p = 0.02], respectively). Moreover, after further adjustment for severe coronary artery calcification, severe $AVC_{density}$ remained predictive of mortality (HR: 2.41; 95% CI: 1.22 to 4.77; p = 0.01).

In all models, severe AVC (p ≤ 0.04) and severe $AVC_{density}$ (p ≤ 0.02) provided significant additive value (incremental to all clinical and Doppler echocardiographic variables) to the prediction of mortality under medical treatment in AS. After adding severe $AVC_{density}$ to the background model, the NRI in predicting 1-year mortality was 12.5% (p = 0.04). Interestingly, the most important reclassification was achieved among nonsurvivors at 1 year, with a reclassification of 50% of these patients from the intermediate risk to the higher-risk category (data not shown).

On comparison of multivariate models, those using $AVC_{density}$ were more powerful than were those utilizing absolute AVC in predicting mortality under medical treatment (all, p < 0.03). In the analysis of the prognostic impact of AVC in subgroups stratified by AS severity (guideline-based thresholds), $AVC_{density}$ was predictive of mortality under medical management in patients with severe AS (HR: 3.11; 95% CI: 1.64 to 6.70; p = 0.0002) or without severe AS (HR: 5.69; 95% CI: 2.89 to 11.03; p < 0.0001) (Figure 4). After adjustment for age and sex, $AVC_{density}$ remained significantly predictive of mortality in both groups (HR: 2.08 [95% CI: 1.07 to 4.53; p = 0.02] and 3.35 [95% CI: 1.60 to 6.85; p = 0.002] in patients with and without severe AS, respectively). With comprehensive adjustment, $AVC_{density}$ came out as independently predictive of mortality under medical management in patients with severe AS (HR: 2.79; 95% CI: 1.45 to 5.36; p = 0.002) and without severe AS (HR: 2.93; 95% CI: 1.35 to 6.19; p = 0.008) (Figures 4 and 5).

The impact of severe $AVC_{density}$ was consistent across multiple AS subsets: It was predictive of mortality under medical treatment in women as well as men (both, adjusted p ≤ 0.04), in patients with and without HF symptoms (both, adjusted p ≤ 0.03), in patients with MG higher or lower than 40 mm Hg

| TABLE 2 | Effects of Severe Absolute AVC and Severe $AVC_{density}$ on Survival: Univariate and Multivariate Analyses | | | |
|---|---|---|---|---|
| | **Severe Absolute AVC*** | | **Severe $AVC_{density}$†** | |
| | HR (95% CI) | p Value | HR (95% CI) | p Value |
| **Overall survival with medical treatment, all patients (N = 794)** | | | | |
| Univariate | 5.63 (3.82-8.46) | <0.0001 | 7.06 (4.66-11.02) | <0.0001 |
| Multivariate‡ | 1.75 (1.04-2.92) | 0.03 | 2.44 (1.37-4.37) | 0.002 |
| **Overall survival with medical/ surgical treatment** | | | | |
| All patients (N = 794) | | | | |
| Univariate | 3.04 (2.20-4.19) | <0.0001 | 3.76 (2.58-5.22) | <0.0001 |
| Multivariate‡§ | 1.71 (1.12-2.62) | 0.01 | 2.22 (1.40-3.52) | 0.001 |
| Subgroup with coronary calcium scoring (n = 635), multivariate‡§‖ | 1.58 (1.02-2.47) | 0.04 | 1.89 (1.14-3.09) | 0.01 |

*Defined as ≥1,274 AU in women and ≥2,065 AU in men. †Defined as ≥292 $AU/cm^2$ in women and ≥476 $AU/cm^2$ in men. ‡Adjusted for age, sex, New York Heart Association functional class ≥III, diabetes, coronary artery disease, AVAi, MG, and LV ejection fraction. §Further adjusted for aortic valve implantation as a time-dependent variable. ‖Further adjusted for severe coronary artery calcification.

HR = hazard ratio; MG = mean gradient; other abbreviations as in Table 1.

(both, adjusted p ≤ 0.04), and in patients with AVAi higher or lower than 0.6 $cm^2/m^2$ (both, adjusted p ≤ 0.02). Thus, despite stratification causing smaller subsets and wider CIs, high $AVC_{density}$ was independently associated with excess mortality after diagnosis in all subsets (Figure 5). Finally, in a combined subgroup with ≥1 criterion for severe AS (by AVA, AVAi, MG, or $V_{max}$) and without HF symptoms (n = 308), $AVC_{density}$ was independently associated with excess mortality (HR: 2.59; 95% CI: 1.02 to 8.01; p = 0.04).

## IMPACT OF SEVERE AVC ON MORTALITY WITH MEDICAL/SURGICAL TREATMENT. On analysis of overall mortality and cardiovascular-related mortality (138 deaths) during the entire follow-up, severe AVC (all, HR: ≥1.58; p ≤ 0.04) and severe $AVC_{density}$ (all, HR: ≥1.89; p ≤ 0.01) were each independent predictors of overall mortality (Table 2, Figure 3) and cardiovascular-related mortality, and significantly improved multivariate models (all, p ≤ 0.01), with or without adjustment for severe coronary artery calcification. $AVC_{density}$ demonstrated superiority (all, p < 0.04) beyond absolute AVC for predicting overall mortality.

Analysis of AVI benefit (time-dependent variable) in strata of AVC load showed that AVI was a powerful independent predictor of improved survival in patients with severe $AVC_{density}$ (HR: 0.37; 95% CI: 0.25 to 0.56; p < 0.0001), whereas AVI effect did not reach statistical significance in the stratum with nonsevere $AVC_{density}$ (HR: 0.63; 95% CI: 0.25 to 1.61; p = 0.33). Thus, in patients with severe $AVC_{density}$, AVI was
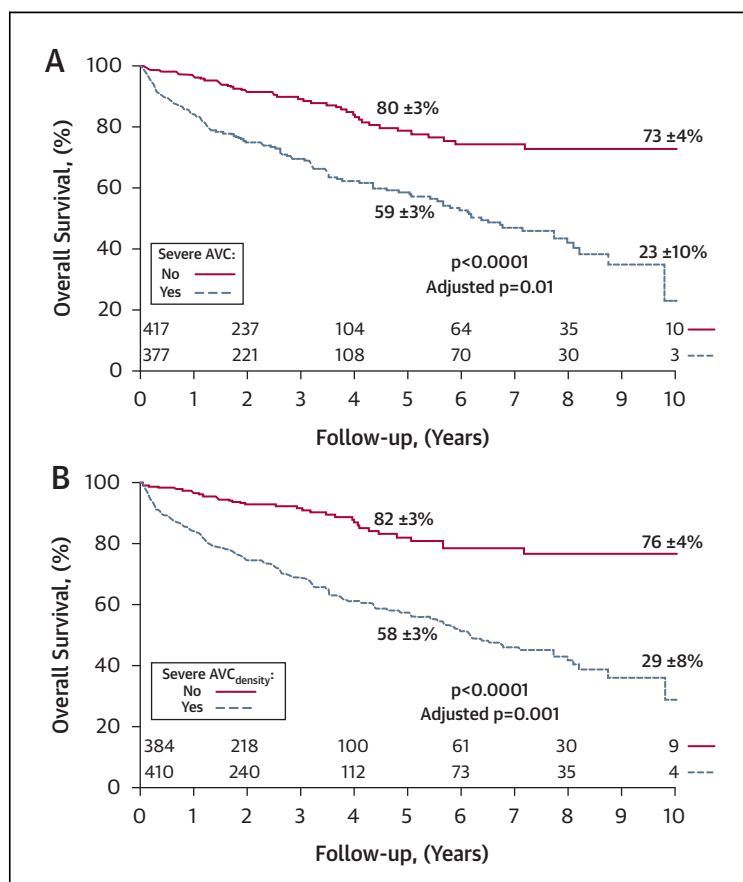
**FIGURE 3  Overall Survival, by AVC Burden, in Patients With AS**

Kaplan-Meier curves of overall survival according to the presence **(dashed blue line)** or absence **(solid red line)** of severe absolute AVC (≥1,274 AU in women and ≥2,065 AU in men) **(A)**, and the presence **(dashed blue line)** or absence **(solid red line)** of severe $AVC_{density}$ (≥292 $AU/cm^2$ in women and ≥476 $AU/cm^2$ in men) **(B)**. Curves include post-operative survival. Note the considerable excess mortality associated with severe calcification load, supporting the analysis in patients under medical management. Adjusted for age, sex, New York Heart Association functional class ≥III, diabetes, coronary artery disease, AVAi, MG, LV ejection fraction, and aortic valve implantation as a time-dependent variable. Abbreviations as in **Figures 1 and 2**.

associated with considerable alleviation of mortality risk, confirming that the $AVC_{density}$-survival link directly depends on the AS.

## DISCUSSION

This study, conducted on the basis of a large international registry of calcified aortic valve disease, is the first to show that in a pure population of patients with AS, AVC load, as measured by MDCT, independently predicts mortality after AS diagnosis, with or without regard to treatment (**Central Illustration**). This strong impact on mortality persists even after adjustment for hemodynamic characteristics,

including AVAi and MG (or alternatively AVA and $V_{max}$), and even accounting for clinical history of CAD or MDCT-measured coronary artery calcification. The AVC-mortality link is incremental in all clinical and Doppler echocardiographic measures with a notable NRI and persists in patients with hemodynamically severe AS. The pattern of the AVC-mortality link involves thresholds similar to those defining severe aortic valve disease in comparison to hemodynamic data by Doppler echocardiography for both absolute AVC and $AVC_{density}$ (11), followed by a plateau of risk. Thus, whereas the thresholds defining severe AVC are different in men and women, the presence of severe AVC defined by these thresholds holds similar survival implications in both sexes. Furthermore, $AVC_{density}$ indexed to cross-sectional area of aortic annulus was a more powerful survival predictor than was absolute AVC, and its impact was consistent among all subsets of AS, irrespective of initial presentation. Finally, survival was improved by AVI in patients with severe $AVC_{density}$, emphasizing the direct link between the valvular anatomic alteration and its implications on outcome.

**AVC IN AS.** In the general population, there is growing evidence that calcified aortic valve disease is prognostically significant (8,9), but AS is naturally calcified, so the significance of calcifications within that specific valvular condition remains uncertain. In current U.S. clinical guidelines (1), severe or moderate-severe AVC is mentioned as a parameter to be considered in AS management, although there are no recommendations on specific definitions or implications. This recommendation is made on the basis of echocardiographic data regarding AS progression (18) and cardiovascular events (12). However, calcification by echocardiography is diagnosed on the basis of video qualitative assessment, which grossly correlates with AVC quantified by CT but with wide overlap between echo "calcification" grades (7). The imprecise aortic valve "calcium" scoring on echocardiography has not allowed for the detection of crucial differences between men and women; MDCT, taking advantage of the unequaled value of x-ray calcium assessment, provided definitions of severe AVC load specific to men and women, with lower thresholds in women (10,11). Thus, this imprecise echo evaluation of valvular "density" has not been duplicated in terms of outcome and has not been reported as a crucial measure to be performed in patients with AS (1,2). The present study, by using the hard endpoint of survival and quantitative assessment of valvular calcium by MDCT, extends our
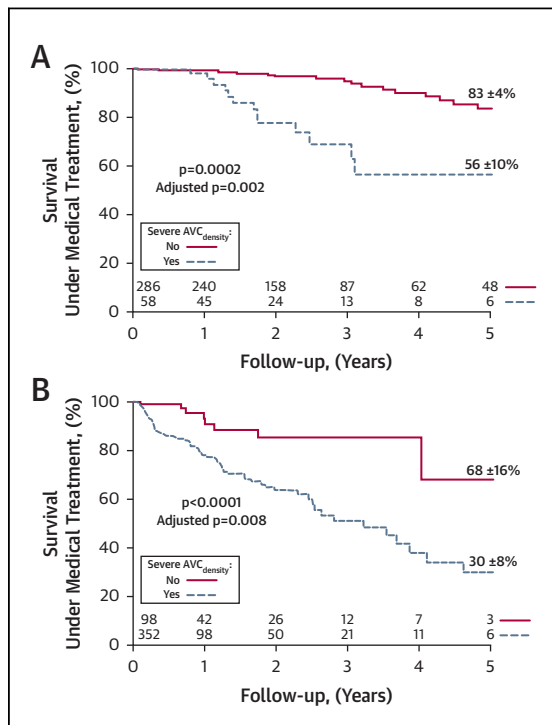
**FIGURE 4** Effects of AVC Burden on Survival in Patients With AS Under Medical Treatment, Stratified by Severity of AS on Hemodynamic Assessment

Kaplan-Meier curves of survival, according to AVC burden, in patients with nonsevere **(A)** and severe **(B)** aortic stenosis (AS), as evaluated by guideline criteria (1). Severe AS is define by an MG $\geq$40 mm Hg, $V_{max}$ $\geq$4 m/s, or AVA $\leq$1 cm². In both strata of severity of AS on hemodynamic assessment, severe AVC$_{density}$ ($\geq$292 AU/cm² in women and $\geq$476 AU/cm² in men) is associated with lower survival. Both unadjusted and adjusted p values for the comparison of the presence **(dashed blue lines)** versus the absence **(solid red lines)** of severe AVC$_{density}$ are presented for each stratum. Adjusted using stepwise backward Cox analysis. Abbreviations as in **Figures 1 and 2**.
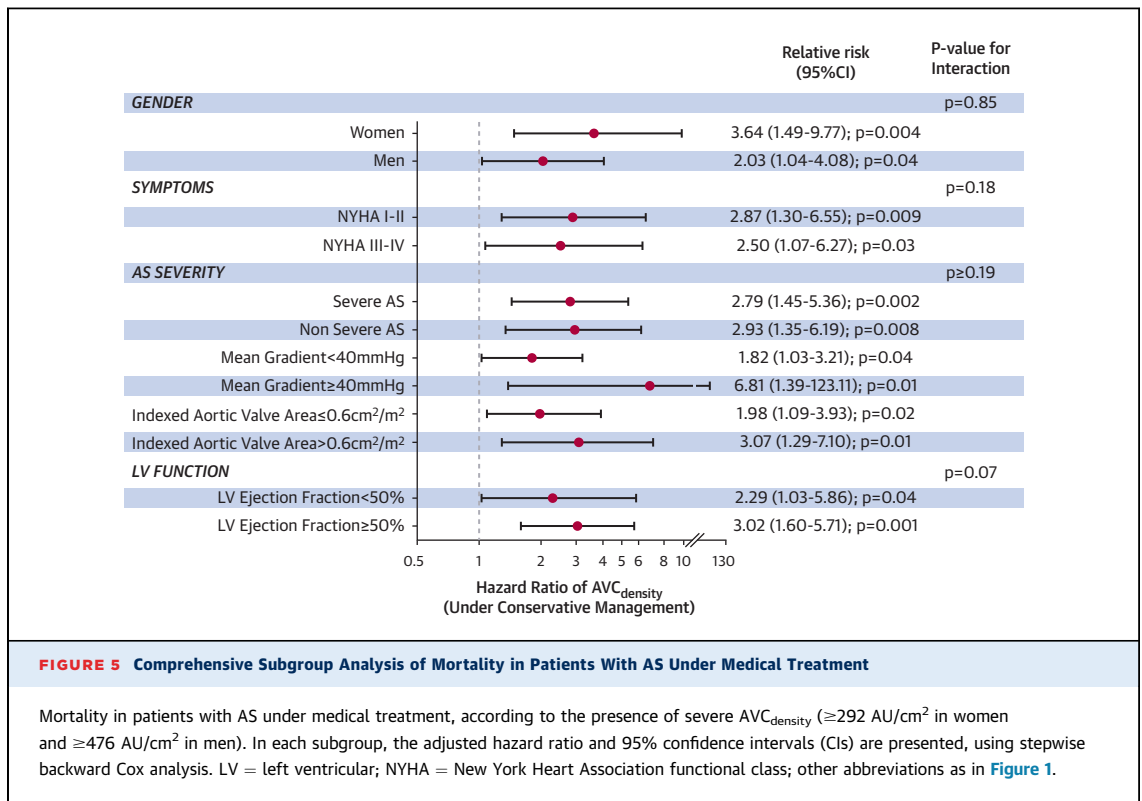
findings regarding the hemodynamic significance of AVC load in men and women, showing that even after normalization for aortic annulus cross-sectional area, the impact on mortality occurs at lower scores in women compared with men. Thus, defining *severe AVC* as absolute AVC $\geq$1,274 AU in women and $\geq$2,065 AU in men or as AVC$_{density}$ $\geq$292 AU/cm² in women and $\geq$476 AU/cm² in men not only strongly suggests severe hemodynamic AS (11) but also defines severe calcified aortic valve disease for subsequent mortality. Previous studies with CT, including our pilot study of 2004 (7), linked valve calcification to cardiovascular events following diagnosis, dominated by performance of AVI, and the pitfalls of this endpoint may explain why this measure has not yet gained wide acceptance. Furthermore, different thresholds

were used (16,18), no sex-specific threshold was defined, and due to the strong association between AVC and valve hemodynamic data, the incremental value of AVC remained unclear. The present study is thus the first to link AVC load, objectively and quantitatively measured, to the simple and crucially important outcome of mortality. Hence, we believe that such an observation is essential in emphasizing the importance of AVC load measurement in clinical practice and in recommending specific thresholds. MDCT measurement of AVC load represents a test added to classic Doppler echocardiography, but demonstration of its incremental prognostic information is essential vis-à-vis cost, whereas it is routine before transcatheter AVI (19).

The concept that AVC load provides information incremental in hemodynamic measures of AS severity is not completely intuitive, as the hemodynamic load is considered the ultimate cause of death (20). However, AVC, although long known to be present on the valve and considered a scarring phenomenon (21), has been shown to appear early in valve lesions as an integral part of the disease process (22). Furthermore, calcification is a nonlinear process that increases exponentially (23) and accelerates disease progression (24). With this in mind, we see that the implications of AVC load on survival do not represent a statistical artefact but are coherent with the biology of AVC deposition (25). It is thus logical, from a pathophysiological standpoint, that a severe amount of calcium in the aortic valve will lead to faster disease progression (23), adverse events, and ultimately mortality. The initial low mortality in moderate AS, even with severe AVC, is consistent with previous data on AS outcome (6), but over time severe AVC imposes excess mortality in all AS severity grades. As shown in our study, survival was largely improved by AVI selectively in patients with severe AVC, underscoring the coherent biological and outcome rationale of AVC load as a marker of AS outcome.

**AVC AND AS MANAGEMENT.** In view of its implications on diagnosis and survival, AVC load can be used as an objective marker of severity in patients in whom clinical assessment is confusing. Given that AS today typically results from calcific "degenerative" etiology and is diagnosed in the mid-seventh decade (6), it is commonly associated with symptoms or markedly reduced activity. Concomitant comorbidities also may cause symptoms, making a patient's risk quite difficult to interpret. In this challenging clinical context, objective markers of outcome are crucial in stratifying risk at diagnosis

**FIGURE 5** Comprehensive Subgroup Analysis of Mortality in Patients With AS Under Medical Treatment

Mortality in patients with AS under medical treatment, according to the presence of severe $AVC_{density}$ ($\geq$292 $AU/cm^2$ in women and $\geq$476 $AU/cm^2$ in men). In each subgroup, the adjusted hazard ratio and 95% confidence intervals (CIs) are presented, using stepwise backward Cox analysis. LV = left ventricular; NYHA = New York Heart Association functional class; other abbreviations as in **Figure 1**.

and for this AVC load may play a very important role once its link to survival is ascertained. Specifically, measuring AVC load by MDCT may be crucial in patients with discordant Doppler echocardiographic markers of AS severity.

Indeed, between 30% and 70% of patients diagnosed with AS present with low MG despite tight AVA (6,26,27). This hemodynamic presentation is highly heterogeneous with or without low flow, often with preserved ejection fraction, and stems from possible measurement errors (28), asymmetry of the LV outflow tract (29), and/or decreased systemic arterial compliance (30). Irrespective of the reason, this hemodynamic presentation proves challenging in terms of diagnosis and therapeutic decision making. Tight AVA suggests severe AS and favors AVI, whereas low gradient is rather consistent with moderate stenosis and favors conservative management. Although in patients with low ejection fraction, dobutamine echocardiography is valuable to detect pseudosevere AS (31-33), it is unclear how useful the test is in patients with preserved ejection fraction and low flow and its utility is even less likely in patients with normal flow (34-37). In the context of the uncertainty of hemodynamic status, obtaining an independent and direct measure of aortic valve

lesion severity such as AVC load is crucial. Uncertainty with regard to clinical status is no less frequent than is that of hemodynamic status. A trial of percutaneous treatment of AS demonstrated great benefit but also showed that AS treatment may be futile when comorbidity blurs symptom interpretation (38). This frequent clinical situation, and that regarding the decision of whether moderate AS deserves AVI simultaneously with coronary artery bypass surgery (1), represent conundrums in which the independent evaluation of aortic valve disease is crucial. In addition to its diagnostic value, severe AVC load, independently and incrementally linked to lower survival alleviated by AVI, as measured by MDCT may be an essential candidate "tie-breaker" and indicator of follow-up frequency when AVI is delayed. The prognostic impact of AVC in various AS subsets (i.e., reduced or preserved ejection fraction, with low or high MG or AVA) makes AVC a versatile clinical tool in most situations warranting the consideration of AVI.

**STUDY LIMITATIONS.** MDCT measurements were done in each institution, and this international collaboration was challenging in terms of exchanging images among centers. However, the training for
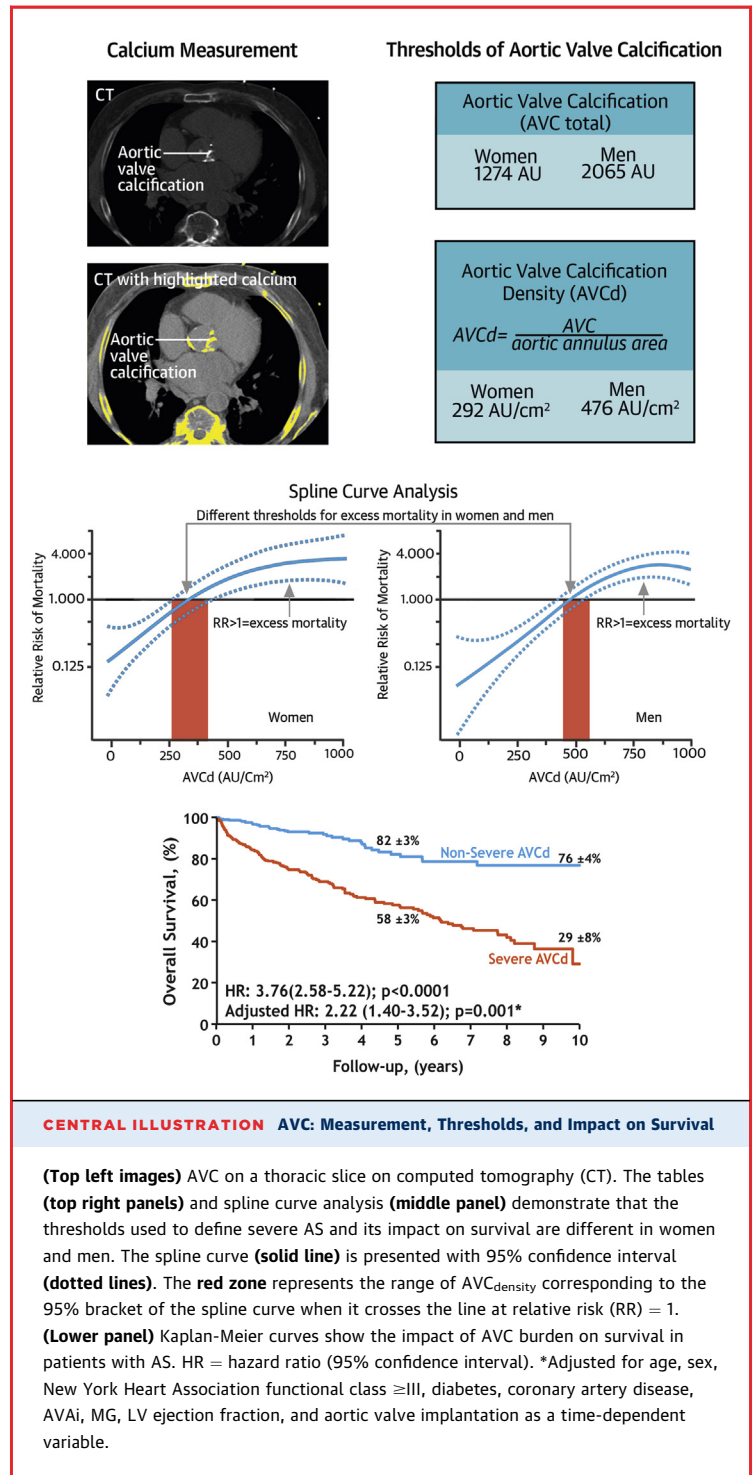
calcium measurement was common and standardized in the 3 centers, and we arranged intercenter investigators' visits to address interobserver variability (10). The possibility of a "center effect" on the AVC-mortality link was unlikely, with no interaction between centers and AVC in determining all-cause or cardiovascular mortality (all, p > 0.80). The thresholds defining severe $AVC_{density}$ may not have been easy to remember in clinical practice. Simple rounded thresholds of 300 AU/cm$^2$ in women and 500 AU/cm$^2$ in men may be considered in clinical practice. Although not exactly data defined, hemodynamic based, or outcomes based, these rounded thresholds of severe AVC load provided prediction of mortality under medical management that was not significantly inferior to that of data-defined thresholds (p = 0.36).

AVC may have different levels of additive prediction value in different AS subsets (e.g., discordant, low-gradient AS), but studies in larger sample sizes should be planned in the future for all AS subset analyses.

**CLINICAL IMPLICATIONS.** In the elderly AS population, whose lack of symptoms may be related to inactivity or orthopedic ailments, or whose symptoms may be due to comorbid conditions, gathering objective outcomes markers is essential. AVC as measured by MDCT is low risk, noninvasive, and highly reproducible for that purpose in most patient subsets. MDCT is not indispensable in patients with an obvious surgical indication of AVI but is essential in considering transcatheter AVI. In patients with borderline indications, particularly with doubtful hemodynamic data, severe AVC load may be a crucial element of a difficult decision. When the indication of an intervention is clearly not present, AVC load may influence the frequency of follow-up. The pattern of the impact of AVC on mortality showed distinctly that once the threshold is reached, the risk for death increases. This threshold is different and lower in women compared with that in men, even after adjustment for aortic annulus area. Thus, patients with an $AVC_{density}$ ≥300 AU/cm$^2$ (women) or ≥500 AU/cm$^2$ (men) should be considered as having severe AS and treated accordingly, whereas those with lower amounts of calcification should be considered as having moderate AS and followed closely as the level of calcification approaches the threshold.

## CONCLUSIONS

This large-scale, international outcomes study shows that measuring AVC load by MDCT provides important



**CENTRAL ILLUSTRATION** AVC: Measurement, Thresholds, and Impact on Survival

**(Top left images)** AVC on a thoracic slice on computed tomography (CT). The tables **(top right panels)** and spline curve analysis **(middle panel)** demonstrate that the thresholds used to define severe AS and its impact on survival are different in women and men. The spline curve **(solid line)** is presented with 95% confidence interval **(dotted lines)**. The **red zone** represents the range of $AVC_{density}$ corresponding to the 95% bracket of the spline curve when it crosses the line at relative risk (RR) = 1. **(Lower panel)** Kaplan-Meier curves show the impact of AVC burden on survival in patients with AS. HR = hazard ratio (95% confidence interval). *Adjusted for age, sex, New York Heart Association functional class ≥III, diabetes, coronary artery disease, AVAi, MG, LV ejection fraction, and aortic valve implantation as a time-dependent variable.

incremental prognostic value for survival after AS diagnosis beyond that obtained from clinical and Doppler echocardiographic data. Severe $AVC_{density}$, although defined differently in men and women, holds similar independent prognostic value in both

sexes and in all possible AS subsets. The excess mortality associated with severe AVC$_{density}$ is greatly alleviated by AVI. Thus, the measurement of AVC by MDCT should be considered for not only diagnostic but also risk-stratification purposes in the evaluation of and therapeutic decision making in patients with AS.

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**PERSPECTIVES**

**COMPETENCY IN MEDICAL KNOWLEDGE:** The extent of aortic valve calcification correlates with the hemodynamic severity of aortic stenosis.

**TRANSLATIONAL OUTLOOK:** Additional studies are needed to quantify the incremental value of MDCT over echocardiographic and hemodynamic assessments in selecting symptomatic patients with aortic stenosis for valve replacement when the valve orifice area and pressure gradient are discordant.

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