Aortic valve calcification using multislice CT

After several decades in which the incidence of valvular heart disease decreased significantly owing to the introduction of antibiotics, mitral and aortic stenosis (AS) continues to be observed in the adult population. Indeed, AS remains the most common valvular heart disease in Western Europe, and its prevalence is going to increase dramatically with the aging of the population [1]. Management of patients with AS relies on accurate assessment of symptoms, AS severity and left ventricular ejection fraction (EF) [2–4]. The clinical utility of measuring the stenosis severity is threefold: to ensure that the valve disease is the cause of the patient’s symptoms, to reliably predict the optimal timing of valve replacement and to schedule the frequency of follow-up visits to the physician. Evaluation of AS severity is currently based on transthoracic echocardiographic measurements of maximal aortic peak velocity, mean transaortic pressure gradient and aortic valve area (AVA), calculated using the continuity equation. Transesophageal echocardiography has been excluded as an essential tool for evaluation of AS. Cardiac CT has recently demonstrated its ability to assess valve disease [5]. The calcium burden shown with MSCT is well correlated with the degree of hemodynamic severity and anatomic surface of aortic stenosis. MSCT is also useful for monitoring valvular calcifications, by evaluating the progression of the disease and the effect of treatments. In parallel, simultaneous MSCT assessment of coronary artery and mitral valve calcifications can help achieve a better overview of the risks of cardiovascular events in these patients.

Methods for AVC assessment

Aortic valve calcification is the leading process in the development of AS [8–10]. Valvular calcification is the structural mechanism behind the stenosis. Fluoroscopy has long been used to assess the severity of AS, calcification being suggestive of a significant AS. Ultrasound has also been used [8], but this method is subjective, semiquantitative, dependent on the settings used (gains and harmonic frequency) and, in our experience,
overestimates, by at least one rank, the importance of calcification in nearly a quarter of cases (classified into four grades: absent, slight, moderate and severe calcifications). Measurement of the degree of AVC using electron-beam CT (EBCT) has previously been validated as a complementary method for the evaluation of AS severity [9]. To quantify the amount of calcification with CT, measurements are obtained off-line using dedicated semi-automated software. Calcification is defined as four adjacent pixels with a density greater than 130 Hounsfield units. The degree of AVC is defined as the calcium score according to Agatston (calculated by multiplying the lesion area by an attenuation factor derived from the maximal Hounsfield units within the area), and expressed in arbitrary units (AU). AVC is defined as calcification within the valve leaflets, aortic annulus or aortic wall immediately adjacent to leaflet or annular calcification [10,11]. However, whether thresholds defined with EBCT could be extrapolated to multislice CT (MSCT) measurements is unknown because of the absence of a direct comparison between the two techniques, even if more recent studies have shown accurate AVC measurements with MSCT [10,11]. In addition, despite being theoretically interesting, the diagnostic value of AVC measurements in differentiating severe AS from nonsevere AS in patients with depressed EF is an important topic that has recently been evaluated [10].

Calcification burden in AS

Aortic stenosis is related to the gradual accumulation of calcium deposits resulting in a decrease in the surface area of the aortic orifice and a ventricular outflow obstruction [9,10]. However, these calcifications were, paradoxically, seldom studied. However, MSCT is the method of choice for studying calcification regardless of location, not only for coronary but also for valvular calcification (Figures 1 & 2).

CT is the modality of choice to evaluate tissue calcification. Unlike ultrasound and fluoroscopy, a CT scan allows an objective measurement and quantification of calcification. It is frequently used to locate and quantify coronary calcification as a marker of cardiovascular risk and was recently validated in AS [6–7]. Of 30 samples collected after aortic valve replacement for aortic valvular AS or aortic regurgitation, the calcium score measured by CT was compared with the

Figure 1. Non-enhanced CT of mild aortic valve calcification. Mild aortic valve calcification burden seen in (A) axial and (B) coronal views, and (C) reformatted in the plane of the aortic valve.
amount of calcium (weight) measured directly by tissue digestion. There was an excellent correlation between calcium score and the weight of calcium [9].

The degree of AVC measured by EBCT was compared at different ultrasound severity indexes of AS (area and peak velocity). In total, 100 patients were evaluated. The calcium score increased with the degree of hemodynamic severity and there was a good correlation between peak velocity and calcium score surface. A score of 1100 could predict severe stenosis with good sensitivity and good specificity. A score of more than 500 reliably ruled out stenosis (negative predictive value: 100%), while a score of more than 2000 was strongly predictive of stenosis [9]. Clinical applications of calcium burden measurements may be particularly useful in patients with left ventricular dysfunction.

However, the correlation between calcium score and ultrasound indices of severity of stenosis is not linear but curvilinear, suggesting that CT and ultrasound measurements are not equivalent and could provide additional prognostic information. Indeed, after adjusting for age, sex, functional class, EF and valve area, the calcium score was an independent prognostic factor for cardiovascular events [9]. Therefore, the degree of calcification can identify patients who are most at risk, especially in those with stenoses. Measuring the degree of calcification should be part of the evaluation of patients with AS. In particular, the European Society of Cardiology recommends operating on patients with tight AS, who are asymptomatic but with moderate or severe calcification (without specifying the threshold or the evaluation method) [2,16]. It is important to note that the evaluation of calcifications does not require an injection of iodine and that the values cited previously were derived from EBCT and should be validated with MSCT.

To answer these two questions (i.e., regarding the accuracy of MSCT for the assessment of calcification burden and diagnostic value in patients with left ventricular dysfunction), a recent study was performed on patients with mild-to-severe AS who prospectively underwent MSCT and transthoracic echocardiography within 1 week [10]. Severe AS was defined as an AVA of less than 1 cm². In 179 patients with an EF greater than 40% (validation set), the relationship between AVC and AVA was evaluated. The best threshold of AVC for the diagnosis of severe AS was then evaluated in a second subset (testing set) of 49 patients with low EF (≤40%). In this subgroup, AS severity was defined based on mean gradient, natural history or dobutamine stress echocardiography.

A good correlation was observed between AVC and hemodynamic parameters, either assessed using the valve area (absolute or indexed), the mean gradient or the peak velocity (correlation

![Figure 2. Non-enhanced CT of severe aortic valve calcification.](image-url)
coefficient r between 0.63 and 0.79; p < 0.0001); area under the curve of the receiving characteristic analysis for severe AS was excellent (between 0.86 and 0.92), demonstrating the good diagnostic value of AVC measurements (Table 1). It is worth noting that its diagnostic value remained excellent despite the inclusion of 14% of patients with atrial fibrillation. An AVC score of less than 700 AU excluded severe AS with high negative predictive value, whereas a score above 2000 AU was highly suggestive of severe AS [10]. A threshold of 1651 AU was the best compromise, with 82% sensitivity, 80% specificity, 88% negative predictive value and 70% positive predictive value. In the testing set (patients with low EF), this threshold correctly differentiated patients with severe AS from nonsevere AS in all but three cases. These three patients had an AVC score close to the threshold (1206, 1436 and 1797 AU).

Interestingly, this threshold was higher than the one previously reported using EBCT (1200 AU), reinforcing the need for the validation of thresholds that are specific to the technique used.

With regard to the high operative risk of those patients, it seems reasonable to corroborate AS severity with two different methods. In addition, contrast-enhanced CT is crucial in the work-up of patients referred for transcatheter aortic valvular implantation [17] and can be combined with AVC measurements. Finally, patients with paradoxical low flow and preserved EF are a recently described entity [18] in which AVC may also be of interest, but this deserves further investigation.

Evaluation of disease progression

Pathophysiological implications

Aortic stenosis is related to the gradual accumulation of calcification in the valve, which is now recognized as an active inflammatory and potentially modifiable pathology, with similarities to atherosclerosis. Therefore, its assessment can judge the progression of the disease and the effect of certain treatments.

For a long time, this process of calcification has been considered a degenerative process, related to age –’wear and tear of the valve’– but much work, both experimental and clinical, has shown that it is an active, biologically regulated process. In particular, similarities with atherosclerosis have been identified and cholesterol may play a central role. Several studies have evaluated the effect of cholesterol on the progression of AS. The results are discordant [19–24]. Two studies used CT to measure the progression of the disease [21–22], and a third also assessed the effect of cholesterol on the progression of aortic calcification measured by CT [25]. A total of 262 patients, constituting a representative sample of the North American population (Olmsted County, MN, USA), were prospectively followed for approximately 4 years. There was an association between the presence of aortic calcification and cardiovascular risk factors (e.g., lipids, hypertension, male gender, renal failure and diabetes). There was also a correlation between the small but significant presence of aortic calcification and the presence and degree of coronary calcification. These data confirmed the link between atherosclerosis and AVC, and could explain the excess mortality observed in the coronary Cardiovascular Health Study among participants with AS (defined as a reworking of ultrasound without valvular stenosis hemodynamics) [26]. On the other hand, no effect of plasma cholesterol levels (total or low-density lipoprotein fraction) on the progression of AVC was observed. Conversely, cholesterol promoted the development of calcification. Once they were established, they seemed to grow exponentially, but independently of risk factors to cardiovascular diseases.

### Table 1. Diagnostic value for severe aortic stenosis of various thresholds of aortic valve calcification score with multidetector CT.

<table>
<thead>
<tr>
<th>AVC score (AU)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
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AU: Arbitrary units; AVC: Aortic valve calcification.

Data taken from [10].
The effect of statins on the progression of AVC has also been evaluated [22–24,27–30], including in two randomized studies [22,30]. In the Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE) study, 77 patients were treated with atorvastatin, and 78 were on placebo [22]. The mean follow-up was approximately 25 months. Progression of AS was evaluated by ultrasonography and CT. Statin therapy was not accompanied by any effect on the progression of stenosis hemodynamics and degree of calcification. The study by Rossebo et al. demonstrated similar results [30], that is, simvastatin and ezetimibe did not reduce the composite outcome of combined aortic valve events and ischemic events in patients with AS. Such therapy reduced the incidence of ischemic cardiovascular events but not events related to aortic valve stenosis.

These results show that CT, through an objective and quantitative assessment of valvular calcification, can evaluate the progression of aortic stenosis, the effect of treatment and progress in understanding the pathophysiological mechanisms involved in AS.

**Relationships with coronary, thoracic aortic & mitral valve calcium scoring**

Several other studies have attempted to demonstrate that thoracic aortic calcium (TAC), AVC and coronary artery calcium (CAC) are associated with cardiovascular event risk. AVC can be quantified upon the same CT examination as CAC. Although CAC is an established predictor of cardiovascular events, limited evidence is available for an independent predictive value for AVC.

Wong et al. examined the prevalence of TAC and AVC in relation to the presence and extent of CAC, cardiovascular risk factors and estimated risk of coronary heart disease in 2740 subjects without known coronary heart disease. A close correspondence of TAC and AVC was observed with CAC. TAC and AVC increased with age; by the eighth decade of life, the prevalence of TAC was similar to that of CAC (>80%), and 36% of men and 24% of women had AVCs. Older age, male gender and low-density lipoprotein cholesterol were directly related to the likelihood of CAC, TAC and AVC; higher diastolic blood pressure and cigarette smoking additionally predicted CAC. BMI and higher systolic and lower diastolic blood pressures were also related to TAC, and higher BMI and lower diastolic blood pressure were related to AVC. Calculated risk of coronary heart disease increased with the presence of AVC and TAC across levels of CAC. TAC and AVC provided incremental value over CAC in association with the 10-year calculated risk of coronary heart disease [31]. Nothing is known about the responsibility of AVC alone in associated CAC.

Another group studied the association of AVC and mitral annular calcification (MAC) with coronary atherosclerosis using 64-detector MSCT in a cohort of 322 patients. Valvular calcification and the extent of calcified coronary atherosclerotic plaque (CAP), mixed coronary atherosclerotic plaque (MCAP) and noncalcified coronary atherosclerotic plaque in accordance with the 17 coronary segments model was assessed. The vulnerable characteristics of coronary plaque with positive remodeling, low-density plaque (CT density: ≤38 Hounsfield units) and the presence of adjacent spotty calcification were also under the scope of this study. In 49 patients with both AVC and MAC, the segment numbers of CAP and MCAP were larger than in those with a lack of valvular calcification and an isolated AVC (p < 0.001 for both). Multivariate analyses revealed that a combined presence of AVC and MAC was independently associated with the presence (odds ratio: 9.36; 95% CI: 1.55–56.53; p = 0.015) and extent (β-estimate: 1.86; p < 0.001) of overall coronary plaque. When stratified by plaque composition, aortic valve calcification was associated with the extent of CAP (β-estimate: 1.77; p < 0.001) and MCAP (β-estimate: 1.04; p < 0.001), but not with noncalcified coronary atherosclerotic plaque. Moreover, it was also related to the presence of coronary plaque with all three vulnerable characteristics (odds ratio: 4.87; 95% CI: 1.85–12.83; p = 0.001). The combined presence of AVC and MAC was highly associated with the presence, extent and vulnerable characteristics of coronary plaque [32].

Blaha et al. recently studied a cohort of 8401 asymptomatic subjects (mean age: 53 ± 10 years; 69% men) who were free of known coronary heart disease and were referred to CT for assessment of subclinical atherosclerosis [33]. The patients were followed for a median of 5 years (range: 1–7 years) for the occurrence of mortality from any cause. Multivariate Cox regression models were developed to predict all-cause mortality according to the presence of AVCs. A total of 517 patients (6%) had AVC on EBCT. During follow-up, 124
patients died (1.5%), and a more than two-fold risk of mortality was observed in patients with AVC after adjusting for age and gender (hazard ratio: 2.08; 95% CI: 1.27–3.38). After adjustment for age, gender, hypertension, dyslipidemia, diabetes mellitus, smoking and a family history of premature coronary heart disease, AVC remained a significant predictor of mortality (hazard ratio: 1.82, 95% CI: 1.11–2.98). Likelihood ratio statistics demonstrated that the addition of AVCs contributed significantly to the prediction of mortality in a model adjusted for traditional risk factors ($\chi^2 = 5.03; p = 0.03$), as well as traditional risk factors plus the presence of CAC ($\chi^2 = 3.58; p = 0.05$). Overall, AVC was associated with increased all-cause mortality, independent of the traditional risk factors and the presence of CAC [33].

Multidetector CT assessment before transcatheter aortic valve implantation

Recently, transcatheter aortic valve implantation (TAVI) has emerged as a less invasive alternative to surgical aortic valve replacement in patients with severe AS at high risk for surgery [34]. Despite being less invasive than open-chest surgery, TAVI remains associated with the potential for serious complications, such as stroke, malapposition, aortic root rupture and paravalvular leak. A recent report by John et al. revealed that aortic calcification in the device ‘landing zone’, as assessed by MSCT, is associated with acute procedural success in patients undergoing TAVI [35]. In this study, calcification in the aortic valve device landing zone displayed a significant positive correlation with paravalvular aortic regurgitations after TAVI. Furthermore, the need for ‘second maneuvers’ (i.e., postdilation after initial device release) could be predicted by these calcification scores. Thus, the usefulness of the evaluation of AVC, as well as thoracic aortic calcification may be of interest from the viewpoint of risk assessment for TAVI.

Radiation exposure issues

The current population with AS includes mainly elderly patients, in whom the radiation exposure issues are less crucial than in younger patients. Moreover, AVC is currently assessed using prospectively gated CT acquisitions of which the radiation dose remains low, at a level of less than 2 mSv.

In a TAVI population, several dose-reduction regimens are used because of the length of CT acquisition, encompassing the thorax, the abdomen and the pelvis, from subclavian to common femoral arteries. In an effort to minimize the radiation dose from CT, several methods for dose reduction are available. These include automated tube-current modulation, electrocardiographic modulation, prospective axial triggering, reduced tube voltage and iterative reconstruction techniques. The combination of these techniques can result in more than a 90% radiation dose reduction to less than 1 mSv [36]. Nevertheless, the penetration of these techniques into widespread clinical practice outside of specialized centers has not yet occurred, and radiation dose associated with CT remains excessively high. A recent multicenter, single-state registry [37] showed that educational interventions to current CT practice reduced radiation by almost 50%, suggesting that instruction regarding and implementation of radiation techniques can effectively lower the radiation dose and potentially improve patient safety [38].

Executive summary

Calcification burden in aortic stenosis

- Quantitative assessment of aortic valve calcifications with CT is accurate, as well with previous electron-beam CT systems and present multidetector CT systems. The amount of aortic valve calcification is well correlated to the degree of stenosis and to future cardiac events.

Evaluation of disease progression: pathophysiological implications

- There is no robust proof of the efficacy of medical therapies to slow or stop the evolution of aortic valve stenosis.

Relationships with coronary, thoracic aortic & mitral valve calcium scoring

- There is close correlation between the severity of aortic valve, mitral valve and coronary artery calcifications, all of them being the result of ongoing atherosclerosis.

Multidetector CT assessment before transcatheter aortic valve implantation

- The location of aortic valve calcification at multidetector CT is of primary importance before transcatheter aortic valve implantation.

Radiation exposure issues

- Radiation dose is acceptable in this population, with the help of dose-reduction methods.
Conclusion
Multidetector CT assessment of AVC is an accurate means to stage the severity of aortic valve stenosis, as well as to monitor the progression of the disease and the effect of medical strategies against atherosclerotic processes, despite not having been demonstrated at the present time.

Future perspective
Multidetector CT takes part in a modern network of allied diagnostic technologies, improving the work-up of patients with aortic valve stenosis. Knowing the amount and location of valvular calcifications may help select candidates for open surgery or transcatheter aortic valve implantation, a role in which multidetector CT will probably grow in for the next years.

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Bibliography


