# Aortic Valve Calcium: A Narrative Review of its Role in the Assessment of Aortic Stenosis and as a Predictor of Post-transcatheter Aortic Valve Implantation Outcomes

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## Abstract

Degenerative aortic valve disease is the third most common cause of heart disease in the developed world. Calcific deposits accrue in the valve endothelium causing progressive stenosis of the orifice. Increasingly, transcatheter aortic valve implantation is being used in place of surgery as treatment for aortic stenosis, particularly for patients who are considered high surgical risk. Although echocardiography remains the gold standard for the diagnosis and grading of aortic valve stenosis, there is an increasing interest in the role that aortic valve calcification scoring may play in these areas. In this review, the authors evaluate the current evidence for aortic valve calcium scoring as an adjunct to echocardiography in grading, and as a prognostic marker in challenging cases. They also explore the ability of calcium scoring to predict outcomes following transcatheter aortic valve implantation.

## Keywords

Aortic stenosis, transcatheter aortic valve implantation, aortic valve calcium score, outcomes, complications

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Degenerative valve disease is a significant cause of mortality in the developed world, with rheumatic disease remaining common in developing nations. In both cases, excessive deposition of calcium restricts movement and, thus, the function of the valve, increasing myocardial stress in the left ventricle and leading to pathological remodelling. Valvular calcification is a complex process. Endothelial injury leads to inflammatory activation of valvular interstitial cells, inducing their osteogenic and osteoblastic differentiation, and myofibroblastic forms leading to collagen and hydroxyapatite deposition causing fibrosis and calcification of the valve surface (*Figure 1*).[1,2] The aortic valve's exposure to higher sheer stresses predisposes it to this process.[3]

Studies have shown that the pattern of calcium deposition varies depending on aetiology. In degenerative aortic valve disease, calcification has a tendency to begin in the base of the cusps and progress towards the edges, with relative sparing of the commissures.[4] In contrast, there is predominant fusion and fibrosis of the commissures in rheumatic disease, which leads to stiffening and retraction of the aortic cusps. Bicuspid valvular calcification affects mainly the cusps. Despite the difference in aetiology, recent studies have shown similar outcomes when undergoing transcatheter aortic valve implantation (TAVI) between patients with degenerative aortic valve and rheumatic valve disease, and possibly superior outcomes when cohorts are propensity matched.[5] However, the recent NOTION-2 trial has shown that younger patients with bicuspid valves have a higher rate of early complications with TAVI, and are better treated with surgical aortic valve replacement.[6]

## Valve Calcium Quantification: Non-contrast Cardiac CT

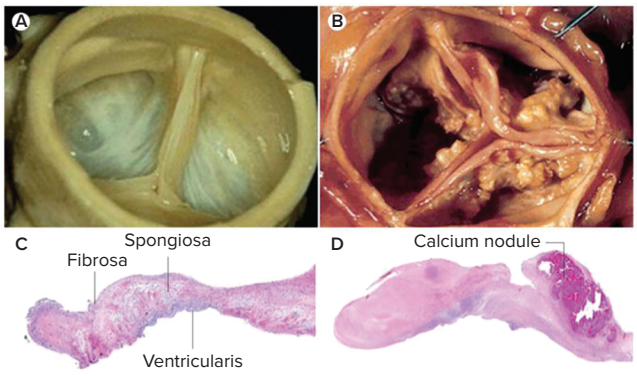
The quantitative assessment of valvular calcification in aortic valve disease has been greatly enabled by CT. This originated as calcium scoring via the Agatston method, developed by Dr Arthur Agatston et al. in 1990.[7] This method has helped to personalise management in the primary prevention of atherosclerotic coronary disease by risk stratifying patients at high risk of major adverse cardiac events.

Arbitrary units (AU) are calculated by multiplying the plaque area by the plaque density factor (based on the highest attenuation value by Hounsfield units [HU] of any given area of calcification), multiplied by its volume (*Table 1*). The sum of all areas of calcification gives the Agatston or valve calcium score. This method has the benefit of not requiring contrast and requires relatively low-dose radiation. It has been shown to correlate closely with total coronary plaque volume on CT coronary angiography, despite not being able to detect soft, non-calcified atheroma.

There has been a substantial body of evidence validating its use in coronary artery disease, and in 2018 became part of the American College of Cardiology's guidelines work-up for patients with clinically indeterminate risk of major adverse cardiac events.[8]

Similar principles and techniques can be applied to the aortic valve. The aortic valve calcium score (AVCS) is calculated using the same methodology as coronary artery calcium scoring using CT. For optimal

## Figure 1: Macroscopic and Histopathological Appearance of Normal and Abnormal Aortic Valves




*Normal and pathologically calcified gross aortic valve morphology (A, B) and histology (C, D). Source: Lindman et al. 2016.[2] Reproduced with permission from Springer Nature.*

## Table 1: Formula for Calculating Agatston Score

| Density factor | Multiplier |
|---|---|
| 130–199 HU | 1 |
| 200–299 HU | 2 |
| 300–399 HU | 3 |
| ≥400 HU | 4 |

*The Agatston score is calculated as area of calcium as measured on CT ($mm^2$) × the multiplier as determined by the density factor.*

images, the scan be acquired according to specific protocols. It must be ECG gated and images acquired in diastole. Slice thickness should be 3 mm, and voltage should be between 120 and 140 kV.[9] Thickness and voltage have been shown to be inversely proportional to Agatston score, and so this standardised protocol is important.[10]

Alternative methods to calcium quantification on non-enhanced scans also exist, such as calculating valve calcium volume. This is performed by the summation of all patients with >130 HU, with no density weighting applied.[9] Although this is more reproducible than Agatston scoring, density weighting is felt to be an important aspect of calcium quantification, as denser deposits of calcium are likely to have a greater haemodynamic effect, an aspect that is not captured using calcium volume. A further way of quantifying aortic valve calcium (AVC) is by indexing the Agatston score to either body surface area or the left ventricular outflow tract (LVOT) to determine the density of AVC.[9,11]

## Valve Calcium Quantification: CT

Prior to TAVI, all patients will undergo a CT with contrast to assess vasculature suitable for access. This scan will need to assess the vasculature from the aortic root to the lesser trochanter.[12] The use of contrast-enhanced CT allows the planning of TAVI procedures, as it allows accurate assessment of the calibre of vessels that would be suitable for vascular access. It also allows for assessment of the anatomy of the valve and LVOT, which will act as the landing zone of the device, and of the aortic root. The process of measuring these structures is currently semi-automated, using sophisticated software.[9] However, recent developments have shown that newer fully automated software and cascade neural networks can achieve equivalent results and may soon have a place in this process.[13,14]

Calcium volume can be calculated on contrast-enhanced CT by summing all the voxels of a specified radiodensity in a designated area of interest to calculate the total valve calcium volume. However, unlike the simple and standardised process of the Agatston technique on non-contrast CT, calculating the volume on contrast-enhanced CT comes with significantly increased complexity. This is due in most part to the fact that the attenuation of calcium (≥130 HU) significantly overlaps with the attenuation of a well-conducted arterial phase cardiac CT, where the contrast-opacified aortic root will have an attenuation of 250 HU (±100 HU). As a result, calcification falling within this range will be indistinguishable from the adjacent contrast and cannot be quantified.

The degree of luminal opacification achieved is subject to many variables related to the patient (patient size, cardiac output), scanner (acquisition delay, radiation dose, duration) and contrast medium (iodine concentration, volume, injection rate).[9] These factors cause variable attenuation in the ascending aorta, and variable HU thresholds are used to detect calcific plaque, ranging from 300 to 850 HU.[15] Angelillis et al. suggested that when the LVOT attenuates with <300 HU, then a threshold of 450 HU correlates best with valve calcium score on non-enhanced scan, and when the LVOT attenuates with >300 HU, then a threshold of 850 HU has the best correlation.[16] Others have suggested using a threshold of 2 SDs above the aortic luminal contrast. Irrespective of the technique used, calcific areas with a lower attenuation than the selected threshold will not count towards the calcium volume.

It is due to these inherent challenges in creating a standardised protocol for calcium volume calculation on contrast-enhanced scans and a reproducible technique for quantification that calcium volumes on contrast-enhanced CT have yet to be taken up in clinical practice. However, if reproducible and reliable results could be achieved, this could prove a useful tool, as it would eliminate the need for non-enhanced CT scans to quantify calcium, thus reducing scanning time and unnecessary radiation exposure.

## Role in Assessing the Severity of Aortic Stenosis

### Comparison with Functional Assessment on Echo

Degenerative aortic stenosis (AS) typically develops over decades. It may be incidentally discovered on echocardiography when asymptomatic, and the decision to intervene is based on a combination of symptoms and echocardiographic findings. Patients with severe AS by echocardiography and/or the presence of symptoms will typically be offered intervention, in the absence of significant comorbidities. Without intervention, the 5-year survival of severe, symptomatic AS has been shown in some prospective studies to be as low as 30%.[17]

The severity of AS can be graded based on haemodynamic features of transthoracic echocardiography (*Table 2*).[18]

Although transthoracic echocardiography is an accepted standard in the diagnosis of AS, there exists significant inter- and intraoperator variability, and image acquisition can prove challenging in some patient populations.[19] Errors in image acquisition can lead to significant downstream under- or overestimation of cardiac and aortic haemodynamics, which has a direct impact on diagnosis, prognostication and management strategies.

As part of a comprehensive assessment of AS, non-contrast CT may be performed to calculate the calcium score.[20] Essentially, with the unenhanced CT images, areas of interest are drawn in the axial plane to include aortic valve calcification, avoiding the inclusion of calcium originating from the aorta, mitral valve, coronary arteries or the left ventricular outflow tract. It is important not to perform quantification after

re-orientating the images away from the axial plane; for example, to visualise the valve *en face*, as this can lead to falsely low values (*Figure 2*).[9] Reviewing images in the annular plane may, however, help to distinguish AVC from those of other structures.

AVC has been shown to be positively correlated with the severity of aortic valve stenosis by echo criteria.[21] A recent meta-analysis of 4,101 patients showed that AVCS, as measured by multidetector CT, was able to recognise severe AS with 82% sensitivity and 78% specificity.[22]

European Society of Cardiology guidance suggests a range of scores that indicate the increasing likelihood of severe AS as AVCS increases (*Table 3*).[23]

Interestingly, as seen in *Table 3*, a sex difference has emerged whereby women develop echocardiographic AS with a significantly lower calcium score than men, even when indexed to body size and aortic annulus diameter.[24] The reason for this is unclear; however, the histological presence of androgen receptors on male aortic valves and the greater presence of fibrosis in female aortic valves suggests a difference in pathophysiology between the sexes.[25,26]

AVCS may have a future role in the prediction of disease progression and prevalence in the population. In a prospective study of 6,810 patients with no history of cardiovascular disease, Whelton et al. found only 13% had an AVCS score of 0. They found that those whose AVCS was 0 had a significantly reduced incidence of developing AS in long-term follow-up, and those with even mild AVCS had a significantly increased incidence of AS, with an exponentially increased hazard ratio as AVCS increased.[27] The author describes the clinical impact of this as muted due to the lack of non-invasive decalcification options.

As well as predicting the progression of disease, AVC is also a strong predictor of outcomes. Clavel et al. prospectively followed 794 patients with at least mild AS on echocardiography. They found that AVC load provided a significant, incremental prognostic value for survival, even on multivariate analysis when adjusting for various features, such as aortic valve area or mean pressure gradient.[28]

## Discordant Echocardiographic Findings: Low-flow, Low-gradient Aortic Stenosis

In some patient populations, a significant discordance may exist between the aortic valve area (AVA) and the mean pressure gradient or maximum velocity. These patients are said to have low-flow, low-gradient AS (LF-LG). This can occur due to patients having a reduced stroke volume, specifically an indexed stroke volume of <35 ml/m$^2$. This mainly occurs due to either a reduced ejection fraction; classical LF-LG, or preserved ejection fraction, or ejection fraction >50% with diastolic dysfunction; or paradoxical LF-LG. As Doppler indices are dependent on flow across the aortic valve, reduced flow presents a challenge in interpretation.

This discordance has been reported in up to 30% of patients, representing a significant clinical quandary.[29] In such cases, CT-AVCS may act as a discriminator between severe and non-severe AS.

## Assessment of Classical Low-flow, Low-gradient Aortic Stenosis

In patients with LF-LG AS and reduced ejection fraction, dobutamine stress echo is often the first test to differentiate between true and pseudo-severe AS.[18,30] In true severe AS, this will show a significant increase in mean pressure gradient with little to no increase in the AVA, whereas in pseudo-severe AS, there will be an increase in the AVA in response to the increase in flow, as there remains compliance in the valve cusps, with little change to the mean pressure gradient.[18,31]

An adequate response to dobutamine is considered to be an increase in stroke volume of ≥20%. This is known as the contractile or flow reserve. However, approximately one-third of patients will not achieve this response, and within those that do, there is significant heterogeneity. To account for this variance, the projected flow area ($AVA_{Proj}$) can be calculated. This is a measure of what the AVA would be at a normal flow rate of 200–250 ml/s. This can be calculated through the equation:

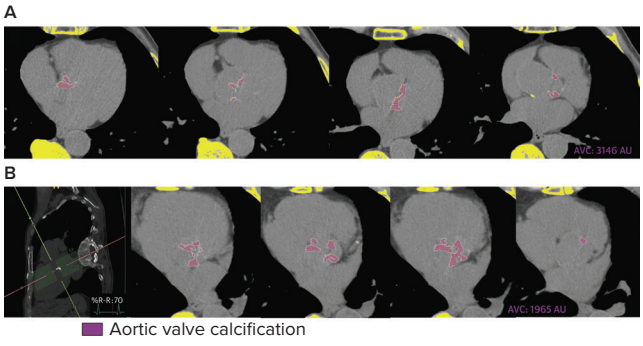
$AVA_{Proj} = AVA_{Rest} + [(\Delta AVA / \Delta Q) \times (250 - \Delta Q_{Rest})]$, where $AVA_{Rest}$ and $Q_{Rest}$ are the AVA and mean flow rate (Q) at rest, and ΔAVA and Δ Q are the absolute

### Table 2: Grading of Aortic Stenosis by Echocardiographic Measurements

| Grading of Severity | Echocardiographic indices | | |
|---|---|---|---|
| | AV $V_{max}$ (m/s) | Mean Gradient (MmHg) | AVA (cm$^2$) |
| Aortic sclerosis | <2.5 | — | — |
| Mild | 2.5–2.9 | <20 | >1.5 |
| Moderate | 3–3.9 | 20–39 | 1–1.5 |
| Severe | 4–4.9 | 40–59 | <1 |
| Very severe | ≥5 | ≥60 | ≤0.6 |

*AV $V_{max}$ = aortic valve maximum velocity; AVA = aortic valve area. Source: Ring et al. 2021.[18] Reproduced under a CC BY-NC-ND 4.0 License.*

### Figure 2: Comparative Measurement of Calcium in 'Native' Axial Scan and 'En Face' View of the Aortic Valve




*Multiplanar reconstruction images in 'native' axial view (A) and in 'en face' view (B), showing aortic valve calcification (pink). With the use of the 'en face' reconstructed view, the calcification score is decreased by 37%, and aortic stenosis severity would be classified as non-severe. Thus, 'en face' view measurement of aortic valve calcification must not be used to assess aortic valve calcium severity. Source: Pawade et al. 2019.[9] Reproduced with permission from Elsevier.*

### Table 3: European Society of Cardiology Guidelines for the Likelihood of Severe Aortic Stenosis by Valve Calcium Score

| Likelihood of Severe AS | Women | Men |
|---|---|---|
| Highly likely severe AS | >1,600 AU | >3,000 AU |
| Likely severe AS | >1,200 AU | >2,000 AU |
| Unlikely severe AS | <800 AU | <1,200 AU |

*AS = aortic stenosis. Data source: Vahanian et al. 2022.[23]*

increases in AVA and Q during peak stress during dobutamine stress echocardiogram.[32]

This equation has been shown to be the most reliable measure of AVA severity in patients with LF-LG AS. An $AVA_{Proj}$ of <1.0 $cm^2$ is considered to be true AS, and those that were >1.2 $cm^2$ do well without valvular intervention.[18,33,34]

However, for the $AVA_{Proj}$ to be considered accurate, the mean flow rate must increase ≥15% from rest to peak measurement.[34,35] Therefore, there exists three cohorts where dobutamine stress test may prove to be inconclusive: those that do not achieve ≥20% increase in stroke volume, those that do not achieve a flow rate of ≥15% and those that cannot undergo dobutamine testing for clinical reasons (e.g. recent MI, severe coronary artery disease, arrhythmias and others). In these patients, assessment of AVCS may help in discriminating true-severe from pseudo-severe AS. It has the benefit of being easily reproducible, flow independent and well-correlated with haemodynamic function, and therefore, applicable to most patient cohorts.[18,23,32]

The evidence base in this particular cohort is small, dobutamine stress echo is usually sufficient to arrive at a conclusion. Cueff et al. found that an AVCS of 1,653 AU could correctly identify patients with severe AS in patients with depressed left ventricular ejection fraction, with a 93% sensitivity and 75% specificity.[21] However, it should be noted they did not discriminate cut-offs between sexes in their study, a practice that is now commonplace.

AVCS is a useful and accurate discriminant that can help to complement transthoracic echocardiography and dobutamine stress echocardiogram, and aid multidisciplinary decision-making for patients that have LF-LG AS. More research should be performed to validate its use in classical LF-LG AS.

## Assessment of Paradoxical Low-flow, Low-gradient Aortic Stenosis

Paradoxical LF-LG AS is usually caused by pronounced left ventricular (LV) concentric remodelling and resultant reduction in longitudinal function, although many features may contribute to it, such as AF, mitral or tricuspid regurgitation and mitral stenosis.[31,36]

Paradoxical LF-LG AS is defined by the following criteria:

- calcified valve with restricted motion;
- left ventricular ejection fraction >50%;
- AVA <1.0 $cm^2$;
- mean PG <40 mmHg;
- peak PG <60 mmHg; and
- AV maximum velocity <4.0 m/s.

These patients provide the greatest clinical challenge, especially if symptoms are ambiguously attributable to the AS finding. In this scenario, every care must be taken to ensure optimal measurements are acquired, antihypertensive medications optimised and further functional assessment carried out, such as cardiac MRI or dobutamine stress echo, although the utility of the latter is less clear in this patient cohort than in those with reduced ejection fraction.[29,37] If on re-assessment the paradoxical findings are deemed to be true and stroke volume is <35 $ml/m^2$, then CT-AVC may be sought to help aid a multidisciplinary team decision.

There is a growing body of evidence to support AVCS in this patient population. Boulif et al. performed a prospective study of 266 patients with normal ejection fraction and AS. They found that patients with paradoxical LF-LG AS had a significantly higher AVCS than patients with moderate AS, but significantly lower AVCS than those with high-gradient AS. They found that, depending on the quantification of AVC used (i.e. calcium score versus calcium density), 36–55% of paradoxical LF-LG AS patients met the criteria for severe AS by calcium scoring. This suggests that this population of patients is heterogeneous, and that AVCS may be a useful way to differentiate true and pseudo-severe AS.[38]

These results concurred with previous papers from Clavel et al. Their prospective, multicentre study of 646 patients found that approximately half of those with paradoxical low-flow, low-gradient AS had AVCS in keeping with severe stenosis. In their study, they found that AVC density provided the highest sensitivity and specificity to suggest severe AS, with a cut-off of ≥92 $AU/cm^2$ for women and ≥476 $AU/cm^2$ for men.[29]

Pawade et al. performed an international multicentre study of 918 patients with deliberately heterogenous diseases. Within their cohort, they identified 210 patients with discordant findings. Within this cohort, AVCS was associated with a hazard ratio of three- to fourfold on multivariate analysis, with an outcome of aortic valve replacement or death, suggesting it is a strong arbiter of poorer outcomes.[11] They do note that there was a small subsection of patients who had concordant echocardiographic features with discordant AVCS and further work is needed to investigate this particular cohort. One possible reason for this cohort is that multidetector CT cannot assess fibrosis of the AV, and so in patients whose stenosis is driven more by fibrosis than calcification, the severity of their AS may be underestimated. This may be improved in future using contrast-enhanced cardiac CT, whereby both the fibrotic and non-fibrotic components of the valve structure may be evaluated.[39] Moreover, newer techniques, such as PET/CT and PET/MRI, have the potential to distinguish between fibrosis, inflammation and calcification within the disease process, which may play an additional role in AVCS.[40]

Interestingly, all the above studies independently calculated the area under the curve of the AVCS that suggests severe AS, and all found an AVCS similar to European Society of Cardiology recommendations to be optimal, suggesting the numbers have excellent reliability and reproducibility across significantly heterogenous cohorts.

## The Role of Calcium Score in Predicting Outcomes in Transcatheter Aortic Valve Implantation

In addition to a role in stratifying patients with AS, aortic valve calcification has been shown to be an independent risk factor for excess mortality following a diagnosis of AS.[22,28] Therefore, patients with higher AVCS have been shown to receive greater physiological recovery and symptomatic benefit following TAVI.[28,41] However, TAVI itself is associated with significant risks and complications that different patient populations may be at greater risk of. Data suggested a significant correlation between the severity of aortic valve calcification and such specific complications.[42] However, with increased practitioner experience and technological advances, more recent data suggest that this relationship may not be so clear.

Below we discuss the current role AVCS has in the prognostication of TAVI outcomes. We performed a systematic review of the literature on PubMed and OVID using MeSH terms 'aortic valve calcium score', 'Agatston Score', 'TAVI' 'transcatheter aortic valve implantation', 'transcatheter aortic valve replacement (TAVR)', 'transcatheter aortic valve replacement', 'outcomes', 'survival' and 'complications'. Further studies were sought by means of a

manual search of secondary resources, including references from primary papers.

## Paravalvular Leak

Post-TAVI aortic regurgitation is a common complication, with recent evidence suggesting it affects between 7 and 40% of procedures.[43] Even mild paravalvular leak following TAVI has recently been identified as a cause of significant morbidity and rehospitalisation, suggesting every possible care should be taken to avoid such an outcome.[44] The detection of paravalvular leak during the procedure will often commit the operator to further instrumentation, such as post-dilatation, and longer procedures, which are associated with increased risk to the patient.[45,46] The aetiology of aortic regurgitation following TAVI is often multifactorial, and related to the chosen valve being undersized, elliptical geometry of the annulus and excessive calcium deposition preventing the prosthesis from seating properly against the native tissue.[47]

Since 2010, aortic valve calcification has been identified as an independent risk factor for paravalvular leak, and confirmed by many subsequent studies.[48] Increasing calcium scores has been associated with increased severity of paravalvular leak, although cut-offs suggested in the literature are variable. Haensig et al. found a mean AVCS, as measured by Agatston score, of 3,800 was associated with mild leaks, while those with a mean of 7,800 were associated with moderate or greater leaks, suggesting a degree of linear dependence.[49] Pollari et al. quantified a total volume of 1,079 $mm^3$ of calcium, as calculated by multidetector CT, as being a cut-off of risk for paravalvular leak, with risk increasing by 8% for every 100 $mm^3$ of calcium calculated in the device landing zone.[50]

A study of 79 patients by Ewe et al. suggested a significant relationship between the geographic distribution of the AVC and the location of the paravalvular leak.[51] Haensig et al. also identified a statistically significant relationship between localised areas of high calcification and paravalvular leak in that area. This finding is not consistent across all studies, as it was not found to be the case in the aforementioned Koos and Pollari et al. studies. In a similar vein, severe calcification of the left ventricular outflow tract, however, has been associated with a significant increase in the incidence of device failure, embolisation and moderate to severe periventricular leukomalacia (PVL), although it was found that the risk of this can also be ameliorated using balloon-expandable valves.[52]

Kofler et al. attempted to create a new calcium score to predict post-TAVI PVL in a study of 965 patients.[53] They did this by first identifying regions of calcification on contrast-enhanced CT in nine areas of interest: the three AV cusps, the upper LVOT associated with each of the cusps and the lower LVOT associated with each of the cusps. They used the area under the receiver operating characteristic curves to determine the optimum calcium score to be associated with PVL of at least mild severity in each of these areas. Through initially univariable and then multivariate regression, they determined which areas were statistically significant and gave them a weighting based on the odds ratio of each finding. A score of ≥4 in this scoring system could predict at least mild PVL, with a sensitivity of 0.58 and specificity of 0.73.

As paravalvular leak represents a significant morbidity and mortality following TAVI, extensive technological and procedural advancements have been developed to reduce the incidence.[54] Winter et al. performed a meta-analysis comparing studies of first- and later-generation valves. Through a total of 273 studies, 12 valve types and a total cohort of 68,193 patients, they were able to conclude that second-generation valves were superior to first-generation valves in all-cause morbidity, including paravalvular leak.[55] Akodad et al. agreed that incidents of PVL were greatly reduced with newer-generation valves, and postulated a cut-off score of 6,000 AU to be predictive of adverse events.[56] Indeed, with third-generation valves, especially those with leakage-proof function, there is some evidence to suggest that the calcium score may no longer play any role in the prediction of PVL.[57]

The calcium score is an important independent risk factor that is associated with a greater frequency and severity of post-procedure paravalvular leak. The location of the calcium may have a role in predicting the location of the leak, and LVOT calcification can be associated with device failure. Newer-generation valves, especially those with leakage-proof function, such as the Sapien 3 and Evolut Pro, reduce the impact of native calcification on final performance, likely due to improved seal on the device landing zone allowing greater apposition of the prosthetic leaflets.[57]

## Conduction System Abnormalities

Conduction system pathology is a common complication following TAVI. The most common complications are new-onset left bundle branch blockade, atrioventricular delay and complete atrioventricular blockade. This is due to the proximity of the aortic annulus to the left bundle and, in some patients, the atrioventricular node.[58] When the valve is deployed, it exerts direct mechanical insult to the conduction material via inflammation, oedema, haematoma and ischaemia, resulting in the adverse effects recorded.[59] The treatment of asymptomatic conduction system disease remains a clinical quandary, although more obviously severe circumstances, such as complete AV blockade, will necessitate a permanent pacemaker to be sited. As such, it is important to identify patients who are at greater risk.

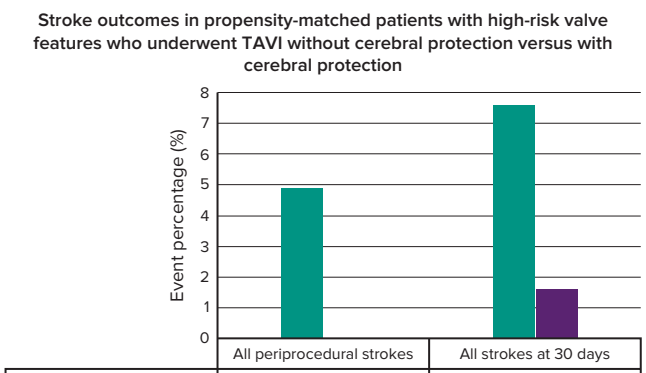
Latsios et al. analysed clinical and radiological data of patients who required a pacemaker following TAVI. They found that those who required a pacemaker had a higher average calcium score of 3,620 AU versus 3,129 AU.[60] They posited that the accumulation of calcium, particularly in the commissure between the right and non-coronary cusps that are closely related to the conducting system, may correlate with heart block.

The association between calcium burden and conduction system failure does not seem as linear as with paravalvular leaks. Al-Azzam et al. retrospectively analysed 300 patients who had undergone TAVI, and did not find any association between the magnitude of the calcium score and need for pacemaker insertion.[61]

Attention has been given to the distribution of calcium rather than the quantity as a potential predictor of post-procedure conduction abnormalities. Several studies have found that patients with an asymmetric distribution of calcium, with higher load under the left coronary cusp, had a higher propensity to requiring pacemakers,[62–64] although the finding is not ubiquitous in the literature.[65] This finding has since been strengthened by a recent meta-analysis of 37 studies, comprising 71,455 patients. Calcification of the left and non-coronary cusps was found to have an odds ratio of 4.21 and 3.15, respectively, of the patient requiring pacemaker insertion following TAVI.[66] The only patient factor with a greater odds ratio was pre-existing right branch bundle block.

Interestingly, a similar finding was noted in the bicuspid valve population. In a cohort of 439 patients who underwent TAVI, bicuspid valve was found to be an independent predictor of post-TAVI PPM insertion, with an odds ratio of 4.65.[67] In that study, the majority of bicuspid valves had fusion of

## Figure 3: Comparison of Periprocedural and 30-day Strokes Between Patients with High-risk Aortic Valves who Had Cerebral Embolic Protection Devices Deployed and Those who Did Not




*TAVI = transcatheter aortic valve implantation. Source: Congying et al. 2022.[80] Reproduced with permission from PCRonline.com.*

the right and left coronary cusps with significant calcification of the raphe. It has been shown that the shorter membranous septal length evident in bicuspid versus tricuspid aortic valve might explain this association.[68]

These authors postulate that bicuspid aortic valves most commonly have the left and right coronary cusp fused with a calcified raphe; hence, unbalancing the radial strength of the TAVI valve towards the opposite side to the non-coronary cusp where the His bundle is located.

However, as with PVL, the incidence of conduction system abnormalities and pacemaker requirements are much lower with third-generation valves. Recent studies not included in the aforementioned review evaluated the predictive ability of LVOT calcium score in modern valves. Akodad et al. found no relationship between LVOT calcium and conduction system abnormalities when Evolut R was evaluated, although they did find significance with the use of older generations.[56] Gamet et al. retrospectively analysed data of patients treated with Evolut R and Sapien S3 valves. Their primary endpoint was death, stroke or major adverse cardiac events, with a secondary analysis for high-degree AV block, new left bundle branch block and transient cardiac stimulation. They again found no association between calcium score and conduction abnormalities.[69]

The predictive role of calcium score with regard to conduction system abnormalities is not straightforward. There is strong evidence to suggest that asymmetric distribution of LVOT calcium is associated with abnormalities, with particularly strong evidence implicating subvalvular leukoencephalopathy with calcification and cysts and neurocysticercosis. However, with the advent of newer-generation valves, there is evidence that this association is becoming less prevalent, and further research should be undertaken to see if this trend is maintained.

## Stroke

Cerebrovascular events are an uncommon, but devastating, complication of TAVI that occurs in between 0.6 and 5% of cases.[70,71] Beyond clinically significant and debilitating stroke, there is significant evidence to suggest that there is subclinical ischaemic damage that occurs, which may put patients at higher risk of further cerebrovascular disease and may be associated with accelerated cognitive decline.[72,73] Aggarwal et al. first demonstrated solid matter embolisation via the use of transcranial Doppler in 63 patients. In 45 of these patients, there were adequate multidetector CT images to perform Agatston scoring where a significant association between AVCS and the number of emboli detected was seen.[74]

Multiple studies have suggested an association between AVC load and peri-interventional cerebrovascular events.[75,76] A study by Foley et al. found the calcium score was significantly higher in patients who had a stroke, with logistic regression suggesting a possible increase of risk with increasing AVCS.[77] The role of distribution of calcium is controversial. Pollari et al. demonstrated that calcium build-up in the LVOT beneath the right coronary cusp was at particular risk of embolisation, although Foley et al. found no association with LVOT calcification.[78]

To reduce the incidence of cerebrovascular events, cerebral embolic protection devices (CEPD) are deployed. In the largest study to date of their efficacy, the PROTECTED TAVR study has been produced. This study involved 3,000 patients who were randomised at a ratio of 1:1 to a control group without CEPD and a treatment group using them.[79] They found no difference in the incidence of cerebrovascular events, but did find a statistically significant reduction in the incidence of disabling strokes, defined as an event that causes a Rankin score ≥2, although the study was underpowered to confirm this. Foley et al. suggest that the benefit of CEPD may have been masked in this study due to the inclusion of low-risk patients.[77] CEPD deployment adds to the complexity and time of a procedure, which is an independent risk factor for complications in and of itself.[46] It is possible that the calcium score would help to delineate which patients would be best served.

A meta-analysis of all studies involving various CEPDs by Wolfrum et al. confirmed a reduced risk of disabling stroke with the use of CEPD (RR 0.33, absolute risk difference −0.9), in keeping with the PROTECTED TAVR trial. It also confirmed a need to identify a target population. They calculated the number needed to treat of 77 to prevent one disabling stroke at a cost of $2,000 per device, suggesting that a clear target population should be sought for these devices.[70]

Congying and Costanzo investigated which patients would be best served by CEPD. They performed a propensity-matched prospective study of 571 patients in which they selected patients who were considered to have a high-risk aortic valve for CEPD.[80] A high-risk aortic valve was defined as having high AVCS (>4,000 AU), significant LVOT calcium, bicuspid morphology and valve-in-valve procedures. They found that for patients meeting these criteria, deployment of CEPD significantly reduced the incidence of periprocedural stroke (*Figure 3*).

AVC appears to be associated with periprocedural cerebrovascular events. It is unclear whether the distribution of calcium plays a significant role in this outcome or whether there is a quasi-linear relationship with the degree of calcification, but larger-scale prospective studies are required to confirm this. CEPDs are effective at reducing the number of disabling strokes, but more research is required to confirm which patient population would derive the most benefit. Recent studies suggest patients with significantly high AVCS could serve as a target population, but further research into the field is desirable.

## Mortality

Some studies have shown the calcium score to be an independent risk factor for 30-day mortality. In particular, Qader et al. performed a retrospective analysis on 446 patients who underwent TAVI, splitting them

into three groups based on their AVCS <2,000, 2,000–4,000 and >4,000.[81] They found the group with higher AVCS had a higher 30-day mortality, and risk of death increased by 1.4% for every 100 units. Interestingly, however, they did not find an association with any specific complication other than increased need for intra-aortic balloon pump. Leber et al. found that patients with an AVCS >750 had a significantly lower 1-year survival.[42] Saleh et al. performed a meta-analysis of studies that studied this relationship by categorising patients into high and low AVCS. They analysed the pooled data of 1,839 patients across three studies and found no significant difference in 30-day mortality.[82]

A retrospective study of 497 patients by Taskesen et al. displayed the opposite.[83] However, in this study, the cut-off used to suggest severe calcification was the European Society of Cardiology guideline recommendation for severe AS of 2,000 AU, as opposed to >4,000 AU as seen in the Qader et al. study. This may suggest that the cut-off for severe AS and the ability to predict postoperative outcomes are not necessarily similar. In a study of 1,009 patients between 2010 and 2019, Ko et al. found no association between AVCS and mortality, although it was associated with significant PVL and PPM insertion as AVCS terciles increased.[84]

Again, as technological advancements have been made, the ability of AVCS alone to predict mortality has decreased. Studies that have researched this association in newer-generation valves have failed to show the previously seen relationship. Indeed, when comparing newer generations with older generations, it becomes apparent that there are significantly improved mortality rates with newer technology[56,69,83]

Despite the significantly higher degree of calcium in men than women, previous studies have not stratified their analysis by sex and, thus, the impact of calcium by sex is not known. This is an important area for future research, given complications by sexes are similar, but women have a lower calcium burden, suggesting complications may arise with a lower burden of calcium.

Overall, there are conflicting data on the reliability of AVCS as a predictor of all-cause mortality, although it is clear again that as technology and operator experience improves, what relationship there may have been becomes weakened.

## Conclusion

AVCS is a marker of disease severity and is important for procedure planning. It helps to discriminate between discordant haemodynamic findings on echocardiography. It has been independently associated with significant post-procedural morbidity and an increased risk of all-cause mortality, although this association is diminished with improved operator experience and technologies. It is likely that the magnitude and distribution of calcification differ for specific complications, which may further help procedure planning, although no specific, discriminatory measurements have yet been validated. ❑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