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1 **MULTI-MODALITY IMAGING IN AORTIC STENOSIS AN EACVI CLINICAL CONSENSUS**

2 **DOCUMENT**

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16

17 **Abstract:**

18 In this EACVI clinical scientific update, we will explore the current use of multi-modality
19 imaging in the diagnosis, risk-stratification and follow-up of patients with aortic stenosis, with
20 a particular focus on recent developments and future directions. Echocardiography is and will
21 likely remain the key method of diagnosis and surveillance of aortic stenosis providing detailed
22 assessments of valve haemodynamics and the cardiac remodelling response. CT is already
23 widely used in the planning of transcatheter aortic valve implantation. We anticipate its
24 increased use as an anatomical adjudicator to clarify disease severity in patients with
25 discordant echocardiographic measurements. CT calcium scoring is currently used for this
26 purpose, however contrast computed tomography techniques are emerging that allow
27 identification of both calcific and fibrotic valve thickening. Additionally, improved assessments
28 of myocardial decompensation with echocardiography, cardiac magnetic resonance and

1 computed tomography will become more commonplace in our routine assessment of aortic
2 stenosis. Underpinning all of this will be widespread application of artificial intelligence. In
3 combination we believe this new era of multi-modality imaging in aortic stenosis will improve
4 the diagnosis, follow-up and timing of intervention in aortic stenosis as well as potentially
5 accelerate the development of the novel pharmacological treatments required for this disease.

6

7

8 **1. INTRODUCTION**

9 Aortic stenosis (AS) affects 12.4% of adults over the age of 75 years (1), already accounting
10 for substantial global morbidity and premature mortality, that is likely to increase with an ageing
11 population. Yet, the pathology of AS remains poorly understood, and there is no effective
12 medical therapy capable of slowing disease progression.

13

14 Non-invasive imaging, in combination with clinical assessment, has played a central role in
15 the assessment and management of AS for many decades. In particular, echocardiography
16 remains the reference standard, however other imaging modalities are now increasingly being
17 used, providing complementary information that is improving our understanding of the
18 underlying biology, and helping to guide clinical decision making. This consensus document
19 seeks to complement the recent European Society of Cardiology guidelines (2), providing
20 added detail on the role of multi-modality AS imaging in current clinical practice as well as a
21 focus on emerging applications and future developments.

22

1 **2. PATHOLOGY**

2 We believe it important to describe briefly the pathobiology of AS with respect to both the valve
3 and myocardium so that we can contextualise the information provided by each of the
4 individual imaging modalities. Recently, there has been a clear shift away from the paradigm
5 of passive “wear and tear” to considering aortic valve stenosis as a metabolically active, highly
6 regulated and potentially modifiable disease process (3). In brief, a model for AS is proposed
7 comprising both an initiation and propagation phase (4). The early *initiation phase* shares
8 many similarities with atherosclerosis. Mechanical stress and subsequent injury to the
9 endothelium of the valve leaflets triggers inflammatory cell infiltration and lipid deposition,
10 regions of which co-localise with microcalcification and areas of mineralisation (3). These
11 changes induce differentiation of valve interstitial cells into activated fibroblasts and
12 osteoblasts which promulgate progressive valve fibrosis and calcification. The trans-
13 differentiation of activated fibroblasts and osteoblasts signals the start of the *propagation*
14 *phase*. Here, progressive thickening and reduced pliability of the leaflets increases mechanical
15 stress and cellular injury, thereby establishing a self-perpetuating cycle of injury, inflammation
16 and fibro-calcific leaflet thickening. (4). The *propagation phase* is defined clinically by the
17 inexorable progression of AS, with baseline assessments of valve calcification consistently
18 serving as the most powerful predictors of AS progression, outperforming traditional
19 cardiovascular risk factors (5, 6).

20
21 The myocardial remodelling response to AS varies between individuals and has an important
22 influence on the development of symptoms, heart failure and long-term prognosis. AS causes
23 an increased afterload, triggering a hypertrophic remodelling response that restores wall
24 stress and cardiac performance for many years in accordance with the law of Laplace (7).
25 Importantly, the degree of left ventricular hypertrophy is not well predicted by AS severity
26 alone, being under the influence of multiple other factors including arterial hypertension, sex
27 and genetic polymorphisms (8). Eventually, the hypertrophic response decompensates and
28 patients transition to heart failure and the development of adverse clinical events. At the

1 pathological level, this left ventricular decompensation relates to progressive diffuse
2 myocardial fibrosis and myocyte cell death triggered by the hypertrophied myocardium
3 outgrowing its blood supply (9). Alongside, increased end diastolic pressures, capillary
4 rarefaction and arteriolar remodelling, these pathological changes characterise left ventricular
5 decompensation and the transition to heart failure, resulting in increased myocardial stiffness,
6 reduced contractility and impaired cardiac function.

7 Finally, it is increasingly appreciated that AS and transthyretin amyloidosis (ATTR) commonly
8 co-exist, (e.g. 16% of TAVI candidates (10), most likely reflecting the increasing prevalence
9 of the two conditions with advancing age (11, 12).

10

11 **3. ECHOCARDIOGRAPHY**

12 Echocardiography is the primary imaging modality for the diagnosis and assessment of AS.
13 The purpose of the echocardiographic examination in a patient with suspected AS is three-
14 fold: i) to confirm valve morphology and a diagnosis of AS ii) to grade AS severity; and iii) to
15 assess the structure and function of the left ventricle, the other cardiac chambers and the aorta
16 (Fig. 1).

17 **3.1. Assessments of the Aortic Valve**

18 *Aortic valve morphology*

19 Transthoracic echocardiography is able, in the majority of cases, to determine the valve
20 phenotype (tricuspid, bicuspid, unicuspid or other) according to Sievers classification (Type 0:
21 No raphe, type 1: 1 raphe, type 2 : 2 raphe) or a new classification recently proposed by an
22 international group of experts(13, 14). Transoesophageal echocardiography (TOE), computed
23 tomography (CT) or cardiac magnetic resonance (CMR) can be helpful to clarify aortic valve
24 morphology when transthoracic echocardiography is not diagnostic.

25

26

1 *Haemodynamic severity of AS*

2 The main echocardiographic parameters to define AS severity are the peak aortic jet velocity,
3 peak and mean transvalvular gradients, aortic valve area, and Doppler velocity index (DVI)
4 (15). Aortic valve area can be indexed for body surface area to account for differences in
5 height, particularly in those of shorter stature. It should be avoided in obese or very thin
6 patients, when indexing to height may be superior. Based on these echocardiographic
7 parameters, we can differentiate severe from non-severe AS (Table 1).

8
9 To avoid underestimation of AS severity, the continuous-wave Doppler beam must be aligned
10 parallel to the direction of the stenotic jet. This is not predictable from imaging or colour
11 Doppler data and so multiple measurements from different positions in the thorax must be
12 acquired. It is important to note that velocity and gradients are highly flow-dependent and may
13 underestimate AS severity in the presence of low-flow states for example in patients with
14 impaired systolic function or small cavity size. The aortic valve area, calculated from the
15 continuity equation, is widely used as a “less flow-dependent” parameter of AS severity that
16 can be employed to assess AS severity even in low flow states. It should be noted that aortic
17 valve area can be prone to measurement error, related predominantly to inaccuracies in
18 assessing the left ventricular outflow tract (LVOT) area (16) and the simplistic assumption
19 that the LVOT is circular rather than oval. Alternatives include the velocity time integral (VTI)
20 ratio, which provides a ratio of the VTI at the aortic valve and the left ventricular outflow tract
21 (17) and therefore avoids measurement of the left ventricular outflow tract area completely. In
22 addition, hybrid methods are being explored which calculate the aortic valve area using flow
23 velocities from Doppler, alongside measurements of the left ventricular outflow tract area from
24 TOE, CT or CMR (18). When using these hybrid methods, a larger cut-off value of aortic valve
25 area ($< 1.2 \text{ cm}^2$ vs. $< 1.0 \text{ cm}^2$) should be applied to define severe AS.

26

27

1 *Discordant grading of AS severity at echocardiography*

2 Up to 40% of patients with severe AS have an apparent discordance between the peak
3 velocity/mean gradient and aortic valve area: most commonly where the aortic valve area
4 indicates severe disease and the peak velocity or mean gradient suggest otherwise (19).
5 “Discordant grading” includes 3 main categories: (i) “classical” low-flow, low-gradient AS with
6 stroke volume index $<35 \text{ mL/m}^2$ and with reduced left ventricular ejection fraction ($<50\%$); (ii)
7 “paradoxical” low-flow, low-gradient AS with stroke volume index $<35 \text{ mL/m}^2$ but with
8 preserved left ventricular ejection fraction ($\geq 50\%$), and (iii) normal-flow, low-gradient AS with
9 stroke volume index $\geq 35 \text{ mL/m}^2$ and preserved left ventricular ejection fraction ($\geq 50\%$).

10

11 In cases of low-flow low gradient aortic stenosis with low ejection fraction, dobutamine stress
12 echocardiography is recommended (2, 20). True severe aortic stenosis is characterised by a
13 fixed aortic valve area ($\leq 1.0 \text{ cm}^2$) in the face of an increased flow rate. This will result in
14 higher gradients and velocities across the stenotic valve (transaortic velocity $\geq 4 \text{ m/s}$ and
15 mean pressure gradient across the valve of $>40 \text{ mmHg}$ at any stage of dobutamine stress
16 echocardiography). Another important parameter to assess is the change in stroke volume
17 with dobutamine administration. An increase of stroke volume of $<20\%$ is a marker of
18 reduced LV reserve and is associated with a worse prognosis and higher peri-operative risk
19 (21). This can help guide decision-making in these higher-risk patients, where TAVI would
20 be preferable to surgical AVR. However, recent data assessing the performance of the
21 above guideline measures against to the calculated projected AVA (AVA_{proj}) from the True or
22 Pseudo Severe Aortic Stenosis (TOPAS) study demonstrated that AVA_{proj} was superior to
23 the AVA and haemodynamic measures at distinguishing true severe AS from pseudo-severe
24 AS and at predicting mortality in medically managed patients(22). A multi-modality approach
25 is useful in patients where clinical ambiguity remains.

1 Assessments of pressure recovery can also be useful, particularly in smaller patients with an
2 ascending aorta diameter of less than 30mm. Using pressure recovery to adjust the aortic
3 valve area helps to reclassify patients with discordant echocardiography from severe to
4 moderate AS with corresponding improvements in prognosis observed(15, 23). The final
5 alternative which is being increasingly used in patients with discordant echocardiography and
6 which is recommended in the ESC guidelines is CT calcium scoring (Section 4). Figure 7
7 demonstrates a systematic approach to assessing these discordant patients (Section 4) (24).

9 **3.2. Assessment of the Myocardium**

10 Besides grading AS severity, echocardiography is useful in assessing the structure and
11 function of the left ventricle (Fig. 1) as well as the other cardiac chambers. Left ventricular wall
12 thickness is routinely measured on parasternal long-axis views and used to both derive left
13 ventricular mass measurements and to track progression of the hypertrophic response.
14 However, at present, the ejection fraction remains the only left ventricular measurement
15 recommended by the guidelines to guide clinical decision making and the timing of aortic valve
16 replacement.

17 Deterioration of left ventricular ejection fraction generally occurs late in the course of the
18 disease and is often preceded by the development of left ventricular diastolic dysfunction.
19 Indeed, left ventricular ejection fraction underestimates systolic dysfunction in the presence of
20 concentric remodelling or hypertrophy and may thus lack sensitivity in patients with AS. Recent
21 observational studies and UK National Institute for Health and Care Excellence (NICE)
22 guidelines (23) suggest applying a higher cut-off ejection fraction (<55%) to improve its
23 sensitivity in detecting subclinical left ventricular systolic dysfunction.

24 **3.4. Quality and standardisation of echocardiographic examination and reporting**

25 Echocardiography should be performed in patients with AS, according to European
26 Association of Cardiovascular Imaging expert advice for image acquisition and analysis (24).

1 A multi-parameter integrative approach should be used to grade the severity of AS and of
2 concomitant aortic regurgitation if any. The echocardiography report should include the
3 parameters outlined in Table 2.

4

5 **3.5 Developing techniques in the echocardiographic assessment of AS**

6 *Assessment of left ventricular function.*

7 Other echocardiographic techniques are emerging to provide more sensitive assessments of
8 left ventricular function in AS. Speckle tracking echocardiography provides assessment of
9 myocardial strain. In particular, global longitudinal strain appears to provide a more sensitive
10 marker of systolic dysfunction than ejection fraction. A threshold of < 15% is associated with
11 AS patients who have a higher risk of adverse outcomes (25).

12 The first phase of left ventricular ejection fraction (EF1), is the percentage change in left
13 ventricular volume from end-diastole to peak aortic valve flow. This has recently been
14 proposed for early identification of left ventricular dysfunction in AS, with a threshold of < 25%
15 being associated with an increased risk of adverse events (26).

16 Diastolic dysfunction is another important and relatively well-established component of overall
17 left ventricular function. Recent registry data demonstrated diastolic dysfunction of grade II
18 and above in 42% of severe AS patients, with more severe diastolic dysfunction incrementally
19 associated with cardiovascular mortality and hospitalisations (27). Similarly, left atrial strain,
20 another marker of left ventricular diastolic function, has demonstrated an association with
21 increased hospitalization and mortality in patients with moderate to severe aortic stenosis (28).

22 *Assessment of Other Cardiac Chambers*

23 Assessment of left atrial dilatation, pulmonary artery pressure, right ventricular dysfunction
24 and tricuspid regurgitation provides incremental information on the stage of disease and may

1 have important prognostic implications in patients with AS (29). On this basis a classification
2 for staging the extent of extra aortic valve cardiac damage and heart failure associated with
3 AS has recently been proposed integrating progressive involvement of the chambers of the
4 heart (30-32) (Fig. 2).

5 This echo assessment of cardiac chamber remodeling may also be useful in selecting the
6 optimal type and timing of aortic valve replacement with transcatheter aortic valve implantation
7 (TAVI) potentially preferred in patients with more advanced damage. Careful consideration
8 should be given to whether the cardiac chamber remodelling is due to AS or other co-
9 morbidities (e.g. pulmonary hypertension or right ventricular dysfunction) and therefore
10 whether improvement can be expected following aortic valve replacement.

11

12 *Next steps*

13 Large prospective outcome studies and randomised controlled trials are now required to
14 assess how these novel echocardiographic markers of left ventricular function and cardiac
15 damage might improve the assessment and care of patients with advanced AS. The ongoing
16 DANAVR randomised controlled trial is investigating whether echocardiographic assessments
17 of diastolic dysfunction might provide a more objective marker of left ventricular
18 decompensation in AS and optimise the timing of aortic valve replacement (clinicaltrials.gov
19 NCT03972644).

20

COMPUTED TOMOGRAPHY

4.1 CT calcium scoring

Discordant echocardiographic measurements are common and governed by complex interactions between the ventricle, the valve and systemic arterial compliance (33). It is therefore valuable to have an alternative, anatomical assessment of disease severity that is truly flow-independent, reliable, inexpensive and reproducible. Non-contrast CT aortic valve calcium scoring fulfils this role. As an anatomical measure of both valve calcium density and volume, a standardised method of assessment has been validated in multiple international cohorts, with established sex-specific thresholds for severe AS: 1200 AU in women (Positive predictive value of 93% and negative predictive value of 79%) and 2000 AU in men (positive predictive value of 88% and negative predictive value of 82%) (33, 34)(Fig. 3). CT aortic valve calcium scoring is now recommended by both European Society of Cardiology and American Heart Association/ American College of Cardiology Guidelines to help clarify stenosis severity when discordant echocardiographic assessments remain inconclusive (2, 35).

Aortic valve CT calcium scoring can be performed quickly with no iodinated contrast and a low dose of ionising radiation (~1 mSv) (36). Measurements are highly reproducible, demonstrate excellent agreement with concordant echocardiographic measurements, markers of left ventricular decompensation and provide powerful prediction of subsequent clinical events, (outperforming echocardiography in both regards) in all patient groups including those with discordant grading(37, 38). As with any technique there are limitations which include motion artifact in patients with fast heart rates and occasional difficulty in differentiating valve calcification from that in the aortic annulus, aortic root and mitral valve annulus. More fundamentally CT calcium scoring does not account for fibrotic aortic valve thickening, which can lead to underestimation of disease severity particularly in younger women with bicuspid valves. Finally, although calcium scoring is clinically useful as an arbiter of disease severity in

1 cases where echocardiographic measures are uncertain, borderline cases are often simply
2 that – borderline – and a single value close to the established thresholds should be regarded
3 within the broader clinical context.

4

5 **4.2 CT angiography**

6

7 CT angiography plays an important role in the work up of patients with AS being considered
8 for TAVI. An accurate pre-TAVI CT assessment is pivotal not only in determining a patient's
9 eligibility but also for precise procedure planning. Imaging is needed to assess the optimal
10 access route and to accurately select the optimal size of the valve bioprosthesis. The latter is
11 based on co-axial measurements of the annulus, a structure which is frequently
12 underestimated by 2D echocardiography measurements due to its oval shape. The aim is to
13 achieve appropriate anchoring and sealing of the device with the goal of mitigating
14 paravalvular leakage whilst minimizing the risk of annular rupture (39, 40). Over recent years,
15 cardiac CT has become the reference standard imaging modality for TAVI procedure planning.
16 Specific acquisition requirements have become standardised and image analysis is performed
17 using dedicated semi-automated approaches (40, 41) to assess coronary anatomy, select the
18 optimum type and size of bioprostheses and access route, with high intra- and inter-observer
19 reproducibility (Fig. 4) (42-47). In selected cases CT can also be used to provide useful
20 information about coronary anatomy prior to intervention.

21

22 **4.3 Developing applications**

23 Contrast-enhanced CT angiography holds promise in refining anatomic assessments of AS
24 severity, with advantages over non-contrast approaches. These include high spatial resolution
25 and improved anatomical definition which facilitates assessment of the valve in a uniform *en-*
26 *face* view and differentiation of valve pathology from that in adjacent structures. Importantly,
27 both non-calcific and calcific leaflet thickening can be quantified, a major potential advantage
28 over CT aortic valve calcium scoring (Fig. 3). Various cohorts have attempted to derive

1 thresholds and correct for variations in contrast load surrounding the valve (48, 49), Recent
2 studies have demonstrated good inter-observer reproducibility and confirmed that valve
3 fibrosis is more prominent in women than men (50). Moreover, indexed fibrocalcific volumes
4 have shown a close association with echocardiographic measures of valve
5 hemodynamics(33). Further work is now required to establish a rapid and generalisable
6 methodology as well as identifying appropriate severity thresholds to guide clinical decision
7 making.

8
9 Contrast-enhanced CT can also provide advanced assessment of the myocardium, including
10 the measurement of extracellular volume and global longitudinal strain. These demonstrate
11 good agreement with cardiac magnetic resonance (CMR) and echocardiographic
12 measurements respectively, may highlight dual pathology of AS and cardiac amyloidosis (51)
13 and correlate with adverse outcomes (52-54). Importantly these myocardial CT approaches
14 require delayed imaging or retrospective image acquisition across the full cardiac cycle,
15 involving additional radiation exposure. More research is required to validate these emerging
16 CT methods.

17 **5. CARDIAC MAGNETIC RESONANCE**

18
19 The ability of CMR to characterise the aortic valve, the myocardium and the aorta make it an
20 attractive imaging modality in AS (Fig. 5). The major limitations of CMR compared to
21 echocardiography include its lack of portability, length of scan and relative expense although
22 rapid image acquisition protocols have already improved the latter two issues (55).

23 **5.1 Assessment of the aortic valve**

24
25 CMR allows direct and multi-planar visualisation of the aortic valve for accurate assessment
26 of valve morphology (tricuspid or bicuspid subtypes) (56). CMR can help assess AS severity
27 via direct planimetry of valve area (57) with good agreement with TOE. Importantly, both CMR
28 and TOE planimetry measure the anatomic orifice area (i.e maximum instantaneous valve

1 area), which is different to the calculated aortic valve area derived from the continuity equation,
2 the effective orifice area. This is important, because standard aortic valve area severity
3 thresholds are based on the continuity equation and therefore not applicable to planimeted
4 aortic valve area measurements which are generally larger as they are not affected by the
5 physical contraction of flow when blood passes through the stenotic orifice (58).

6
7 AS severity can be assessed using phase-contrast velocity mapping which allows visualisation
8 and quantification of blood flow through the valve (57). Velocities are used to assess AS
9 severity similar to echocardiographic Doppler measurements and can also accurately quantify
10 regurgitant volume, when present. Whilst CMR offers better jet alignment compared to
11 echocardiography, however lower temporal and spatial resolution means CMR may
12 underestimate the peak velocity (59). These limitations mean that CMR is only used as a third-
13 line imaging technique to assess AS severity after echocardiography and CT, although it can
14 prove of particular value in patients with multivalvular involvement.

15 16 **5.2 Assessment of the aorta**

17 CMR is an excellent clinical tool for the assessment and serial monitoring of the thoracic aorta.
18 Like CT, it provides accurate diameter measurements but without radiation exposure, allowing
19 the identification of aortic dilatation, aneurysm formation and coarctation (24).

20 21 **5.3 Transcatheter aortic valve implantation planning and follow-up**

22 CMR can be used as an alternative to CT for TAVI-planning, in patients with an allergy to
23 iodine-based contrast agents or severe renal impairment (60). Post-TAVI, CMR provides
24 accurate quantification of paravalvular regurgitation (61) and may be useful in those with
25 uncertain regurgitation severity on echocardiography.

26
27

1 **5.4 Assessment of the Myocardium**

2 CMR provides reference standard assessments of left ventricular structure (wall thickening,
3 hypertrophy dilatation, mass-volume-ratio) (62) and function (ejection fraction and myocardial
4 strain using feature-tracking) and should be used in cases where echocardiographic windows
5 are poor and ventricular assessments uncertain.

7 **5.5 Developing applications**

8 *Myocardial fibrosis*

9 The unique strength of CMR is myocardial tissue characterisation. Non-infarct patterns of late
10 gadolinium enhancement (LGE) can be identified in patients with AS as a marker of focal
11 replacement fibrosis, demonstrating a close association with increased collagen deposition
12 and microscars on histology (63). The prevalence of non-infarct LGE in severe AS ranges
13 from 27% to 51% (64) and is associated with multiple other markers of left ventricular
14 decompensation including impairment in systolic and diastolic function, the ECG-strain
15 pattern, elevated serum biomarkers (e.g. B-type natriuretic peptide and cardiac troponin)
16 reduced exercise capacity and symptomatic status (65). Once established, further LGE
17 appears to accumulate rapidly over time (66) and to be irreversible following aortic valve
18 replacement (67). The myocardial scar burden that patients develop whilst waiting for aortic
19 valve replacement therefore persists into the long-term, an important observation given that it
20 also serves as a powerful independent predictor of long-term outcomes (64). The ongoing
21 EVOLVED randomised controlled trial is investigating whether prompt valve replacement in
22 asymptomatic patients with severe AS and myocardial scarring improves patient outcomes
23 (68) (Clinicaltrials.gov identifier: NCT03094143). Furthermore, distinct patterns of non-
24 ischaemic LGE make it possible to identify concomitant pathology such as cardiac amyloidosis
25 which is also associated with a higher risk of all-cause mortality (69, 70).

26
27 Beyond LGE, T1 mapping and extracellular volume fraction (ECV) quantification can identify
28 extracellular matrix expansion: a surrogate for fibrosis (both replacement and diffuse interstitial

1 fibrosis) or infiltration (e.g. amyloidosis) (71). Diffuse fibrosis increases with more severe AS
2 and left ventricular hypertrophy (66). Unlike the focal fibrosis detected by LGE, diffuse fibrosis
3 is largely reversible after aortic valve replacement. Indeed, patients with more extensive
4 diffuse fibrosis derive a larger benefit in symptoms and left ventricular function following aortic
5 valve replacement (72). Several recent large multicentre studies of patients with severe AS
6 imaged prior to aortic valve replacement, demonstrated ECV% was associated with markers
7 of left ventricular decompensation and both cardiovascular and all-cause mortality (73, 74).

8

9 *Myocardial perfusion*

10 Stress CMR allows assessment of myocardial ischaemia and measurement of myocardial
11 blood flow at rest and stress. The ratio of stress and rest myocardial blood flow, known as the
12 myocardial perfusion reserve, represents the ability of the myocardium to increase blood flow
13 during stress. In patients with AS, left ventricular hypertrophy and unobstructed coronary
14 arteries, perfusion CMR often demonstrates global subendocardial perfusion defects and
15 reduction in myocardial perfusion reserve due to supply-demand-mismatch and a relative
16 reduction in capillary density (75). Myocardial perfusion reserve is an independent predictor
17 of exercise capacity (76) and symptom onset in asymptomatic patients with AS (77).
18 Automated quantification techniques producing absolute myocardial blood flow maps have
19 recently overcome complex post-processing and may make this technique more accessible
20 (78).

21

22 *Reverse left ventricular remodelling after aortic valve replacement*

23 Reverse remodelling after aortic valve replacement is associated with early normalisation in
24 left ventricular function within 6 months (79) and 20-30% left ventricular mass regression in
25 the first 6 to 12 months (80, 81). Mass decreases most in those with more left ventricular
26 hypertrophy and no scar (80). ECV quantification is able to discern cellular from matrix volume
27 regression although more research into this area is required. (67, 74). De-novo LGE is found

1 in a fifth of patients, highlighting that new peri-operative myocardial injury may also contribute
2 to prognosis (82, 83).

3

4 *Other approaches*

5 Other CMR tissue parameters under investigation that may emerge for clinical use are T2
6 mapping for inflammation (84), CMR spectroscopy investigating myocardial energetics (85),
7 manganese-enhanced CMR as a marker of myocardial calcium handling (86) and 4-
8 dimensional flow to assess the complex flow patterns in the aorta that may contribute to
9 aortopathy (87).

10

11 **6. NUCLEAR IMAGING**

12

13 **6.1 Bone Scintigraphy and Concomitant Cardiac Amyloid**

14 Bone scintigraphy holds potential clinical value in the detection of concomitant cardiac
15 amyloidosis in patient (70, 88). The most frequent type of amyloidosis in the AS population is
16 ATTR. If clinical, electrocardiogram or echocardiographic features of amyloidosis are
17 identified, bone scintigraphy and light chain analysis in blood and urine should be performed
18 to confirm the presence and type of concomitant amyloidosis (i.e. exclusion of light chain [AL]
19 amyloidosis which requires different management to ATTR) (89). Although this may have
20 prognostic or treatment implications, non-randomised data suggest that TAVI should not be
21 withheld purely on the basis of concomitant cardiac amyloidosis, since outcomes in cohorts
22 have been better following valve intervention compared to medical therapy alone (88, 90).
23 Diagnostic algorithms typically include 99mTc-pyrophosphate (PYP), 99mTc-3,3-
24 diphosphono-1,2-propanodicarboxylic acid (DPD) or 99mTc-hydroxymethylene
25 diphosphonate (HMDP) scintigraphy alongside other clinical, biomarker and imaging
26 investigations (91).

27

28

1 **6.2 Developing Applications**

2 *Assessing Disease Activity with Positron Emission Tomography*

3 Molecular cardiac imaging with positron emission tomography (PET) remains largely
4 investigational for cardiovascular applications but has a broad range of potential uses. Hybrid
5 scanners permit combined assessments of disease activity provided by PET, with anatomical
6 and functional information from CT or CMR. Radiotracers are injected intravenously and
7 localise in areas where the disease process of interest is active. In principle, the activity of
8 any pathological process can be investigated, subject to the availability of a relevant
9 radiotracer. In practice these studies have largely focused on assessment of valve calcification
10 activity in AS using the tracer ^{18}F -fluoride. Such studies remain in the research arena but have
11 provided important insights into the pathobiology underlying AS. Initial reports demonstrated
12 that calcification is the predominant active pathological process in AS, particularly in patients
13 with more advanced stenosis where inflammation activity assessed by ^{18}F -
14 Fluorodeoxyglucose was comparatively lower (92). Subsequent studies have demonstrated
15 that valve ^{18}F -fluoride activity can be measured with excellent repeatability (93) and provides
16 powerful prediction of subsequent disease progression and the need for aortic valve
17 replacement (Fig.6) (94, 95). They have also helped highlight the role that lipoprotein(a) plays
18 in both the initiation and propagation phases of AS, thereby identifying it as a potential
19 treatment target (96). Whilst the clinical role of ^{18}F -fluoride PET may be limited in AS (CT
20 provides similar diagnostic and prognostic information at lower expense and radiation
21 exposure), this technique is increasingly being used as an endpoint in clinical trials assessing
22 the ability of potential novel treatments to reduce valve calcification activity (97).

23

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26

1 **7. INTEGRATING CURRENT CLINICAL MODALITIES**

2 Echocardiography remains the mainstay of diagnosis and monitoring in patients with AS. It
3 provides vital information on the valve and myocardium and is both widely available and cost-
4 effective. In many patients no further imaging is required. However, in certain patient groups
5 additional imaging approaches can improve patient assessment and should be given due
6 consideration. An integrated approach, facilitated by a dedicated Heart Valve Team is
7 proposed in Figure 7.

8

9 In patients with discordant echocardiography, additional imaging using either CT calcium
10 scoring or stress echocardiography in patients with a low flow state, helps clarify AS severity
11 and aids decision making. In patients with suspected aortopathy, CT or CMR should be used
12 to provide a comprehensive assessment of the thoracic aorta. In patients with suspected
13 concomitant amyloidosis, CMR or bone scintigraphy (both with exclusion of light chain
14 disease) is recommended in the latest ESC guidelines. Similarly in patients with left ventricular
15 systolic dysfunction, CMR can clarify whether the impairment is due to the valve disease (and
16 might therefore improve following aortic valve replacement) or other irreversible process
17 including myocardial infarction. This can help decision making around the need for valve
18 intervention. Finally in those patients being considered for valve intervention, CT angiography
19 is now routinely used to assess the suitability and access options for the majority of patients
20 prior to TAVI.

21

22 **8. THE FUTURE OF MULTIMODALITY IMAGING IN AS**

23 Novel multimodality imaging approaches provide the opportunity to phenotype patients with
24 AS in exquisite detail. The challenge will be to harness this powerful information in order to
25 improve patient assessment, treatment and outcomes in a cost-effective manner. There are
26 several areas where these new approaches may have an impact.

27

1 *Initial Diagnosis / Screening*

2 Early identification of patients with AS is important. Traditionally, AS is identified as an
3 incidental finding upon stethoscope auscultation. However, this strategy is limited by the
4 diagnostic accuracy of auscultation, particularly when performed by non-specialists, and also
5 by the reduction in direct face-to-face patient contact observed since the emergence of
6 COVID-19. Automated stethoscope technology may help with this issue, but novel imaging
7 approaches also hold promise. The development of handheld echocardiography might
8 facilitate screening programmes in the community to identify patients with AS, although the
9 cost-effectiveness of such approaches would have to be carefully assessed (98). With smart
10 phone-associated imaging probes and artificial intelligence-directed imaging, self-directed
11 patient echocardiography may also one day become a reality. The use of artificial intelligence
12 to identify patients with AS on even simpler tests, such as the ECG, also holds promise (99,
13 100). A more immediate strategy would be the reporting of incidental aortic valve calcification
14 identified on CT scans performed for other purposes, providing an opportunity to identify
15 patients with calcific aortic valve disease that is frequently overlooked in current clinical
16 practice (101).

17 *Improved Pathological Understanding*

18 A major priority in AS is the development of an effective medical therapy. This will require an
19 improved understanding of the underlying pathophysiology. Molecular imaging now allows us
20 to investigate the activity of a range of pathological process underlying cardiovascular disease.
21 In AS, future studies may inform the exact contribution of inflammation (^{18}F -
22 Fluorodeoxyglucose, ^{68}Ga -DOTATATE), calcification (^{18}F -fluoride), thrombus (^{18}F -GP1) and
23 fibrosis (^{68}Ga -fibroblast activation protein inhibitor) activity at the different stages of the
24 disease process and how their relative contributions vary between patient groups. Initial PET
25 studies have already identified novel targets for therapy in AS and identified important sex

1 differences, suggesting that these approaches may help accelerate the development of novel
2 treatments as part of a precision medicine approach.

3 *Valve and Myocardial Assessments*

4 The anatomic assessment provided by CT may come to play a greater role in how we assess
5 and track AS severity, particularly in patients with discordant echocardiography or suboptimal
6 echo windows. As has been observed in coronary artery disease, there is a natural
7 progression from non-contrast to contrast CT angiography, allowing more detailed
8 assessment of fibrotic as well as calcific valve thickening. As novel medical therapies emerge
9 targeting valve calcification or fibrosis these contrast CT assessments may allow us to tailor
10 optimal therapies for individual patients and provide an imaging technique able to track the
11 effects of new therapies on anatomic disease progression in phase 2 clinical trials. This can
12 then inform which therapies should proceed to phase 3 clinical end-point trials(102).

13 Advanced multi-modality myocardial assessments by echocardiography, CMR and CT may
14 also be increasingly used to track mild to moderate AS and the effects of AS on the
15 myocardium and to identify more precisely when the left ventricle is starting to decompensate
16 in the face of AS, thereby optimising the timing of aortic valve replacement. Finally, the impact
17 of artificial intelligence is likely to be felt in daily clinical practice across all the imaging
18 modalities, optimising and standardising cardiac imaging (73, 103). Figure 8 demonstrates a
19 potential model for the future identification and management of patients with AS.

20

21

22 **9. CONCLUSION**

23

24 The diagnosis and management of AS continues to evolve and to improve, with many exciting
25 imaging techniques in development. Echocardiography remains the most important imaging
26 test, playing an indispensable role in the diagnosis and monitoring of patients with this
27 condition and in clinical decision making. However, other imaging modalities provide

1 complementary information and are increasingly being used in complex patients where
2 echocardiographic assessments are inconclusive or in the planning of TAVI procedures. A
3 multidisciplinary approach with a Heart Valve Team is recommended by the latest ESC
4 guidelines to ensure the appropriate use of multimodality imaging and to optimise the care
5 provided to our AS patients.

7 **Data availability statement**

8
9 No new data were generated or analysed in support of this research.

10

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29

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 6

7 **FIGURES AND TABLES**

8

9 **Table 1: Echocardiographic parameters of severe and very severe aortic stenosis**

	Non-Severe AS	Discordant AS (with low flow defined as SVI < 35 ml/m ²)	Severe AS	Very severe AS
Peak jet velocity (m/s)	<4.0	3.0 to 4.0	≥ 4.0	≥ 5.0
Mean gradient (mmHg)	<40	20 to 40	≥ 40	≥ 60
AVA (cm ²)	>1.0	≤ 1.0	≤1.0	<0.6
Indexed AVA (cm ² /m ²)	>0.6	≤ 0.6	≤ 0.6	<0.4

10 AVA: aortic valve area; AS: Aortic stenosis. Patients may have discordant echocardiographic
 11 assessments where the above parameters do not agree on the true severity of AS. Most
 12 commonly this is encountered in patients with an AVA<1.0cm² and a peak velocity of
 13 <4.0m/s).

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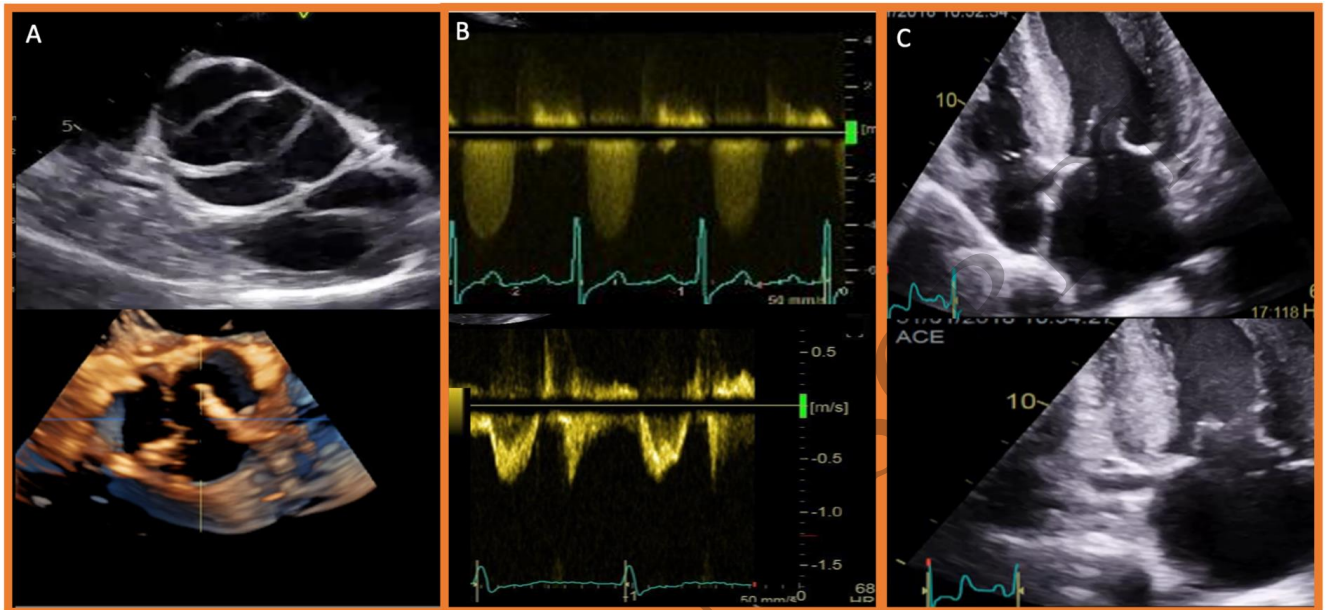
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1 **Figure 1: Valvular and myocardial assessments by echocardiography**

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5 Echocardiography has the ability to assess the valve morphology and haemodynamics as
6 well as myocardial remodelling and function. **A:** Bicuspid aortic valve (top) and 3-D
7 echocardiography assessment of a stenotic aortic valve (bottom). **B:** Measurement of peak
8 velocities through the valve (top) and left ventricular outflow tract (bottom) **C:** Assessment of
9 myocardial structure and function on cine imaging.

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1 **Table 2: Essential echocardiographic parameters to report in patients with AS**

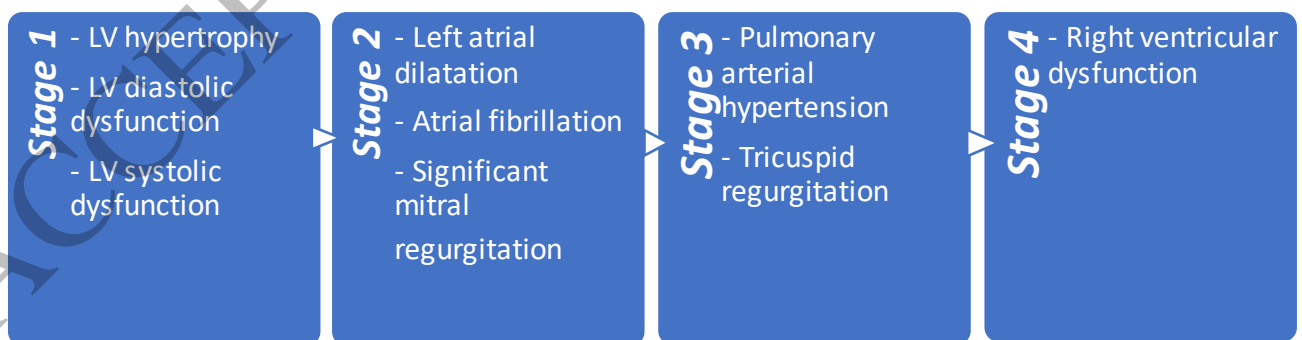
Aortic valve morphology	
Aortic valve phenotype	Bicuspid
	Trileaflet
Severity of valve calcification (mild, moderate, severe)	
Aortic stenosis severity	
Peak aortic jet velocity (Vmax)	
Mean gradient (Mean PG)	
Aortic valve area	
Doppler velocity index	
Grade of AS severity	Mild
	Moderate
	Severe
	Very severe
	Discordant (inconclusive on resting TTE)
Assessment of structure and function of the left ventricle and other cardiac structures	
LV volumes (EDVi and ESVi) and wall thickness measurements	
Qualitative LV hypertrophy assessment (mild, moderate severe)	
Degree of LV diastolic dysfunction	
LV ejection fraction (3D or 2D Biplane method)	
Stroke volume index (low flow < 35 ml/m ²)	
LV global longitudinal strain	

Other echocardiographic data	
Indexed left atrial volume	
Aorta dimensions	Sinus of Valsalva
	Sinotubular junction
	Ascending aorta
Estimated systolic pulmonary arterial pressure	
Degree of right ventricular dysfunction	
Severity of any valvular regurgitation or other valve lesions	

1 AS: aortic stenosis; LV :Left ventricular; EDVi: Indexed end-diastolic volume; ESVi: Indexed
 2 end-systolic volume;

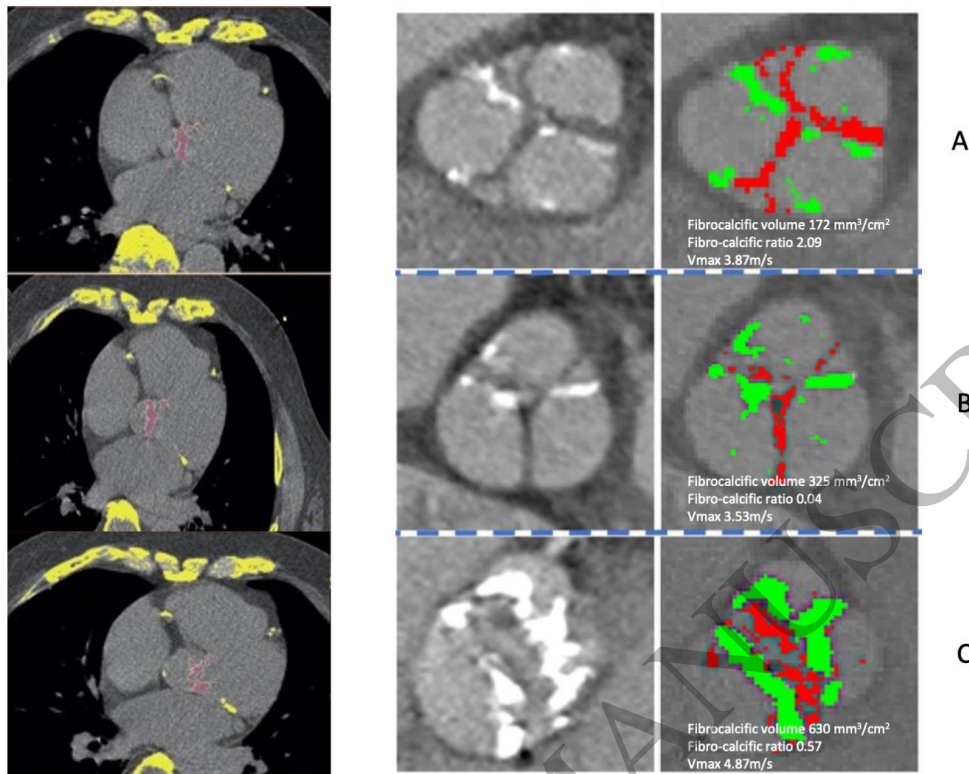
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Figure 2: Integrated echocardiographic assessment of the cardiac chambers to aid in risk stratification in patients with AS ([Généreux P, Eur Heart J. 2017](#))



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1 **Figure 3: Computed tomography aortic valve calcium scoring**



2 *Taken from Pawade et al. JACC Cardiovasc Imaging. 2019*

Taken from Cartlidge et al. Heart. 2021

3 AS: Aortic stenosis; AU: Agatston units; CT: Computed tomography; ECV: Extracellular
4 volume; Vmax: Peak velocity.

5 **Left panel:** Non-contrast enhanced cardiac computed tomography images of a male patient
6 with discordant aortic valve measurements on echocardiography. Areas in yellow are areas
7 of calcium identified by the software (bone, coronary arteries, aortic valve, aorta and mitral
8 valve). Areas labelled in pink were manually selected for calculation of aortic valve
9 calcification which was scored at 2,747 AU (severe aortic stenosis).

10 **Middle and right panels A-C:** Contrast-enhanced computed tomography of 3 patients
11 identifying regions of valve fibrosis (red, also termed non-calcific leaflet thickening) and
12 calcification (green) with calculated fibrocalcific volumes and ratios.

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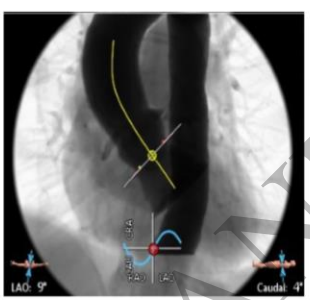
1 **Figure 4: Parameters to measure on computed tomography angiography**



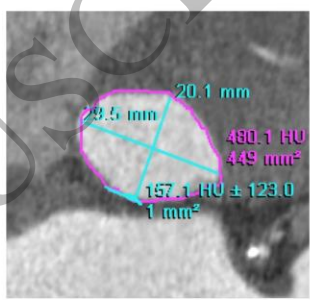
The optimal vascular access route, in particular the suitability of femoral, sub-clavian and aortic access routes



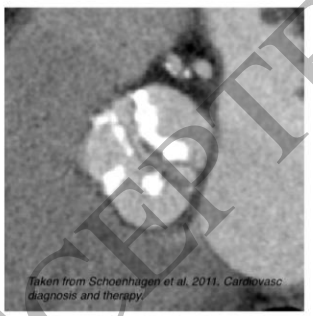
Coronary ostia heights



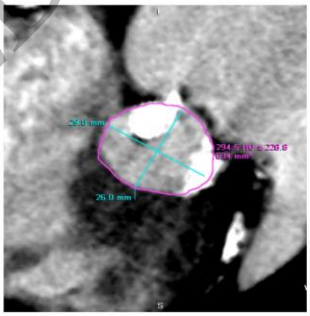
Fluoroscopic projection angles- identifying the optimal angulations for fluoroscopy at the time of the procedure



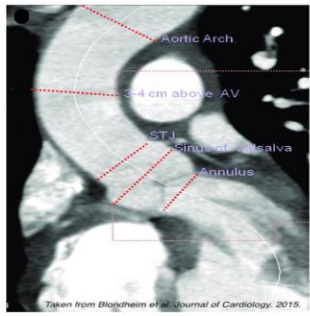
Annulus size- the aortic annulus is defined as the virtual basal ring, formed by joining the three most caudal connection points of the aortic leaflets



CT augments the characterisation of bicuspid aortic valve morphology as well as defining the risk associated with TAVI in bicuspid valve disease



Distribution of calcification in the valve and left ventricular outflow tract, with the identification of protruding nodules of calcium that might predispose to paravalvular leak or annular rupture

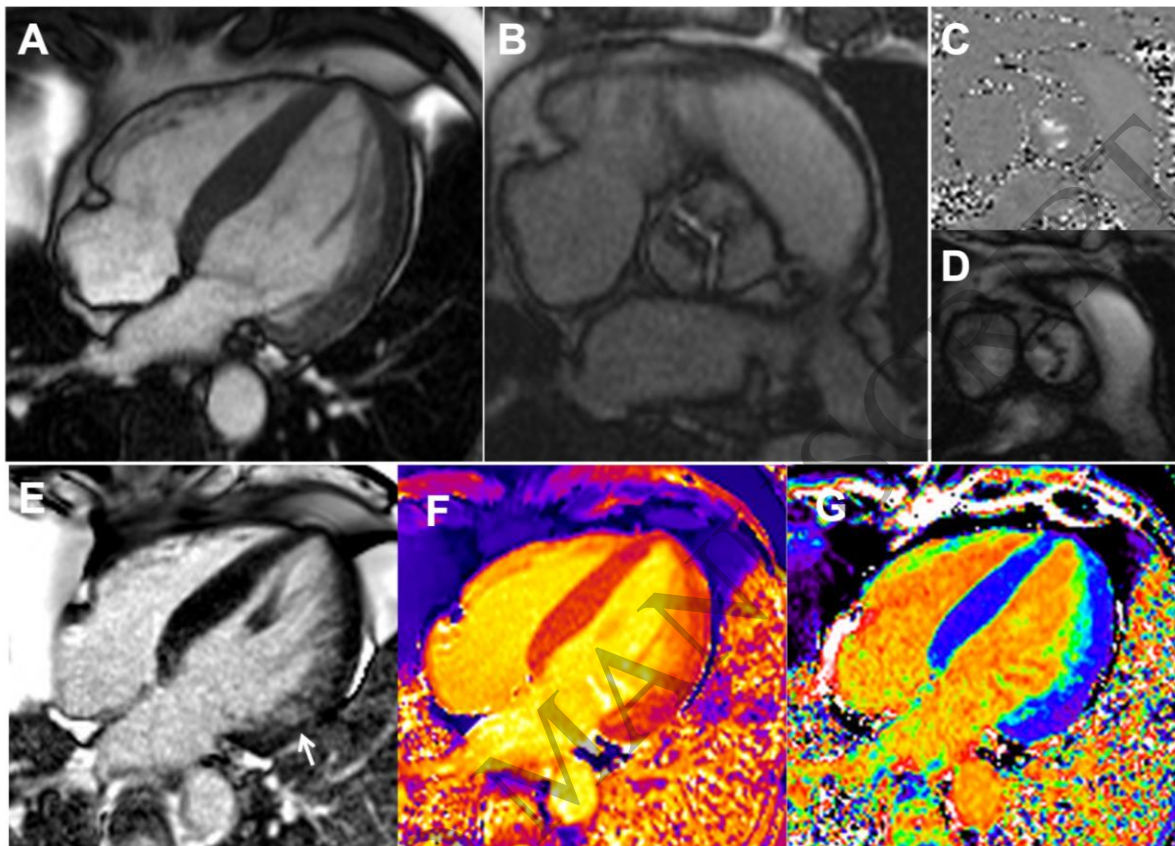


Sinotubular junction and ascending aorta diameters

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3 CT: Computed tomography; TAVI: Transcatheter aortic valve implantation

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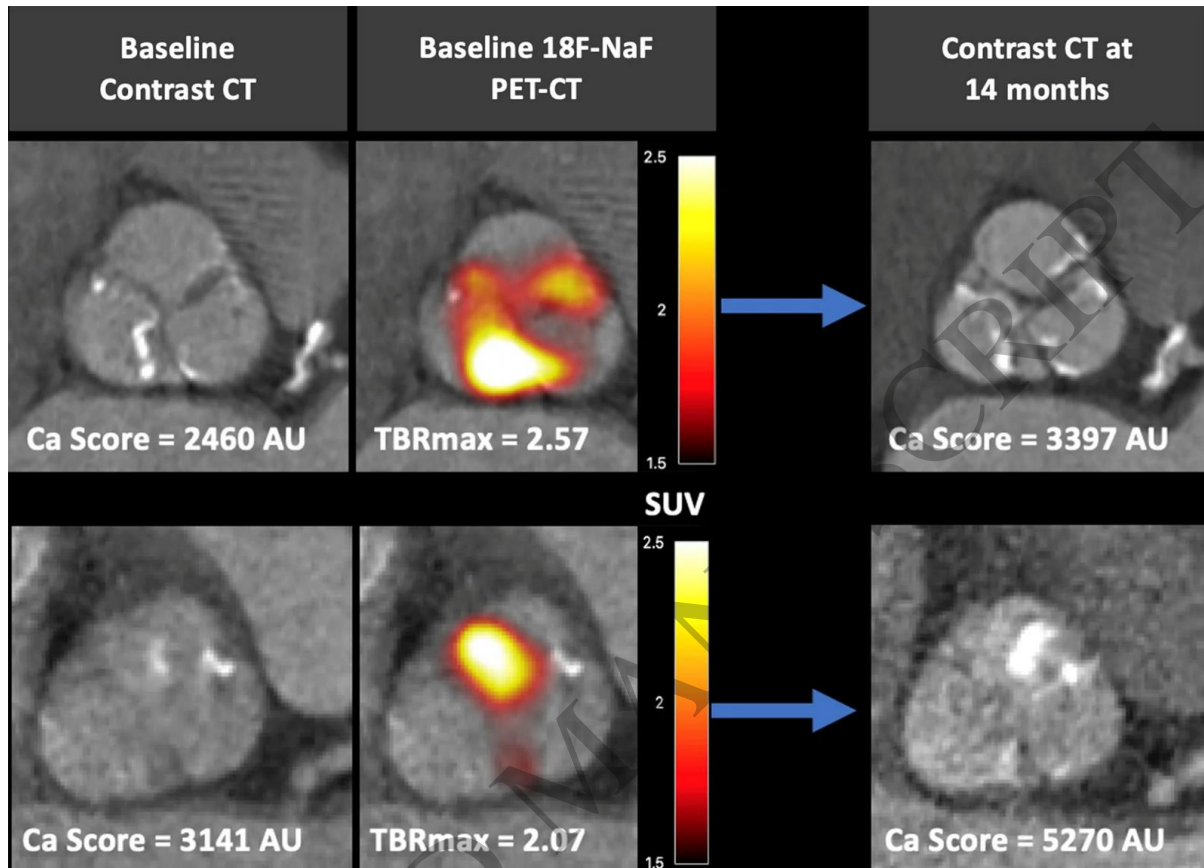
1 **Figure 5: Cardiac magnetic resonance imaging in the assessment of the aortic valve**
2 **and myocardium**



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4 Patient with critical aortic stenosis. 4-chamber bSSFP-cine image (A) showing normal left
5 ventricular cavity size with concentric hypertrophy. Short axis bSSFP-cine image (B) en-face
6 view of the aortic valve demonstrating fusion of the left and right coronary cusp and a
7 planimetered aortic valve area of 0.6cm². Phase-contrast imaging just above the aortic valve
8 (C+D) demonstrating a peak velocity of nearly 5 m/s. Bright blood late gadolinium
9 enhancement images demonstrating patchy, non-infarct scar in the lateral wall (E). A native
10 T1 map (F) and extracellular volume fraction map (G) demonstrate no evidence of
11 myocardial infiltration.

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1 **Figure 6: ^{18}F -sodium fluoride Positron emission tomography-computed tomography**
 2 **for aortic valve calcification**

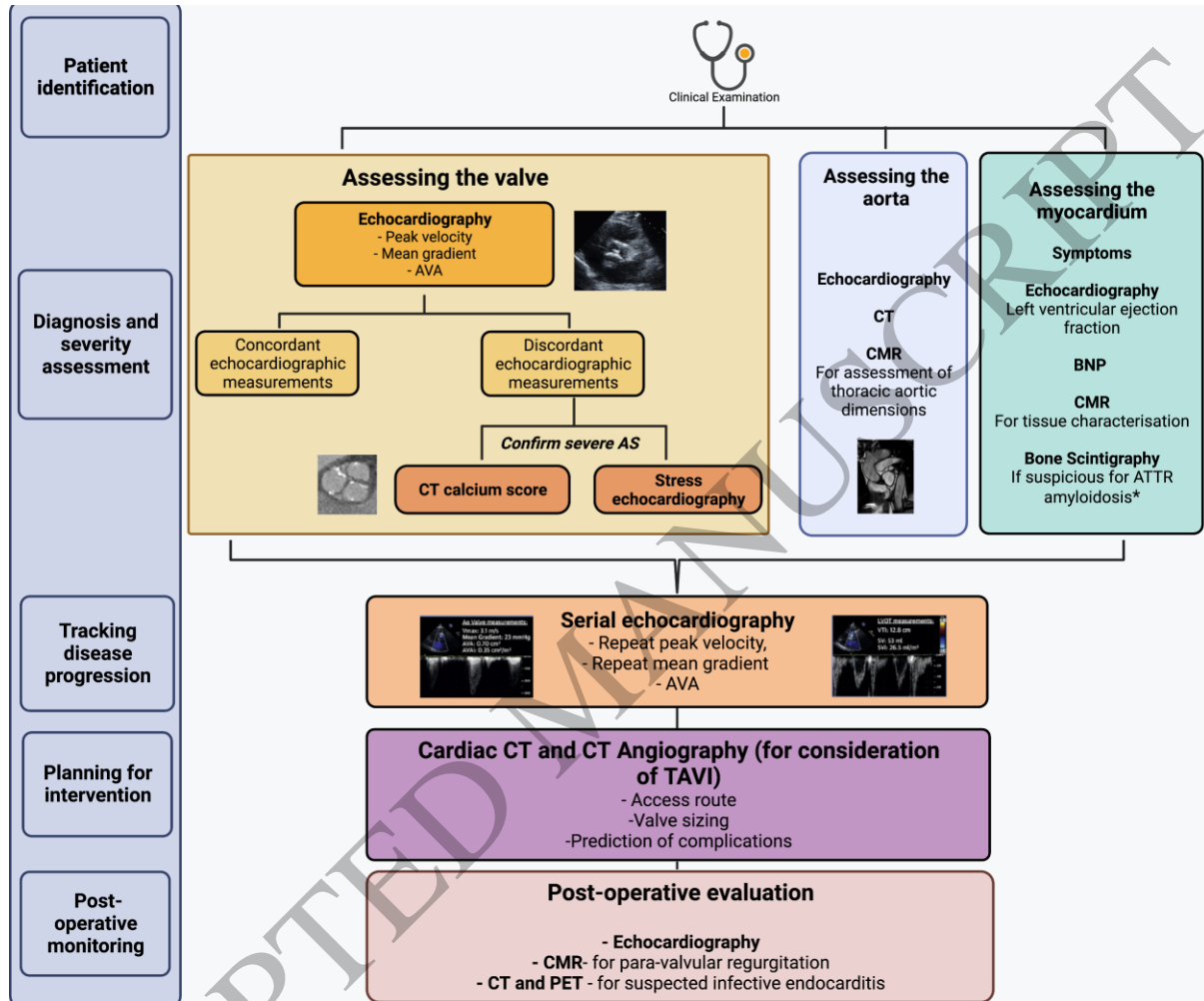


3
 4 AU: Agatston units; CT: Computed tomography; PET-CT: Positron emission tomography-
 5 Computed tomography; TBR_{max}: Maximum tissue-to-background ratio
 6 Areas of red and yellow show ^{18}F -sodium fluoride uptake on the aortic valve. Areas of
 7 maximal uptake at baseline correspond to the development of visible calcification on CT at
 8 14 months. Taken from Fletcher & Dweck. 2021. *Journal of Nuclear Cardiology*

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1 **Figure 7: The current patient pathway in diagnosing and monitoring AS with the use**
 2 **of multi-modality imaging**

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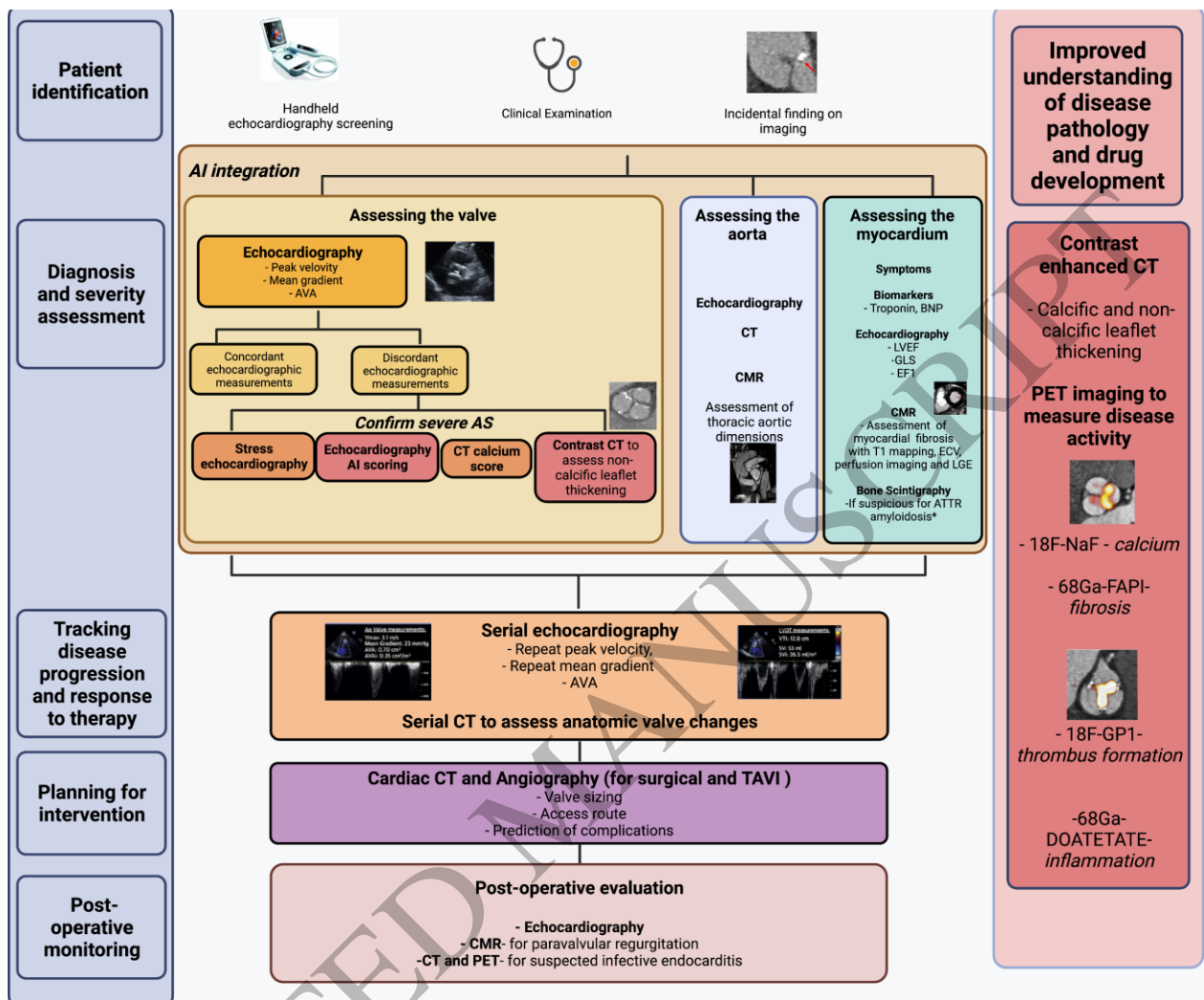
5 AVA: Aortic valve area; AS: aortic stenosis; ATTR: transthyretin; BNP: Beta-natriuretic
 6 peptide; CMR: Cardiac Magnetic resonance; CT: computed tomography; LV: Left ventricular;
 7 TAVI: Transcatheter aortic valve implantation. *Features of amyloidosis including but not
 8 limited to features of heart failure, carpal tunnel syndrome, neuropathy, low voltage QRS
 9 complex on electrocardiogram, left ventricular hypertrophy, left ventricular diastolic
 10 dysfunction, granular speckling effect of myocardium on echocardiography

11 *Figure created on Biorender*

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1 **Figure 8: Potential future patient pathway in patients with AS**



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3 18F-NaF: 18F- Sodium fluoride; 68Ga-FAPI: 68-Gallium labelled fibroblast activation protein
 4 inhibitor; AI: Artificial intelligence; ATTR: transthyretin; AVA: Aortic valve area; BNP: Beta-
 5 natriuretic peptide; CMR: Cardiac Magnetic resonance; CT: computed tomography; ECV:
 6 Extracellular volume; LGE: late gadolinium enhancement LV: Left ventricle; LVEF: Left
 7 ventricular ejection fraction; GLS: global longitudinal strain; EF1: first-phase ejection fraction;
 8 PET: Positron emission tomography; TAVI: Transcatheter aortic valve implantation.

9 *Features of amyloidosis including but not limited to features of heart failure, carpal tunnel
 10 syndrome, neuropathy, low voltage QRS complex on electrocardiogram, left ventricular
 11 hypertrophy, left ventricular diastolic dysfunction, granular speckling effect of myocardium on
 12 echocardiography. *Figure created on Biorender.*

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