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EACVI DOCUMENT

Multi-modality imaging in aortic stenosis: an EACVI clinical consensus document

Marc R. Dweck [1]*, Krithika Loganath[1], Rong Bing [1], Thomas A. Treibel[2,3], Gerry P. McCann [4,5], David E. Newby[1], Jonathon Leipsic[6], Chiara Fraccaro[7], Pasquale Paolisso [8,9], Bernard Cosyns[10], Gilbert Habib [11], João Cavalcante[12], Erwan Donal [13], Patrizio Lancellotti [14,15], Marie-Annick Clavel [16,17], Catherine M. Otto[18], and Phillipe Pibarot[16]

[1]Centre for Cardiovascular Science, University of Edinburgh, Chancellors Building, Little France Crescent, Edinburgh, EH16 4SB, UK; [2]Barts Heart Centre, Bart's Health NHS Trust, W Smithfield, EC1A 7BE, London, UK; [3]University College London Institute of Cardiovascular Science, 62 Huntley St, WC1E 6DD, London, UK; [4]Department of Cardiovascular Sciences, University of Leicester, University Rd, Leicester LE1 7RH, UK; [5]The NIHR Leicester Biomedical Research Centre, Glenfield Hospital, Groby Road, Leicester, LE3 9QP, UK; [6]Centre for Cardiovascular Innovation, St Paul's and Vancouver General Hospital, 1081 Burrard St Room 166, Vancouver, British Columbia V6Z 1Y6, Canada; [7]Department of Cardiac, Thoracic and Vascular Science and Public Health, Via Giustiniani, 2 - 35128, Padua, Italy; [8]Cardiovascular Center Aalst, OLV Clinic, Moorselbaan 164, 9300 Aalst, Belgium; [9]Department of Advanced Biomedical Sciences, University of Naples, Federico II, 80125 Naples, Italy; [10]Department of Cardiology, Universitair Ziekenhuis Brussel, Laarbeeklaan 101, 1090 Jette, Belgium; [11]Cardiology Department, Hôpital La Timone, 264 Rue Saint-Pierre, 13005 Marseille, France; [12]Allina Health Minneapolis Heart Institute, Abbott Northwestern Hospital, 800 E 28th St, Minneapolis, MN 55407, USA; [13]Cardiology and CIC, Université Rennes, 2 Rue Henri Le Guilloux, 35033 Rennes, France; [14]GIGA Cardiovascular Sciences, Department of Cardiology, University of Liège Hospital, CHU Sart Tilman, Liège, Belgium; [15]Gruppo Villa Maria Care and Research, Corso Giuseppe Garibaldi, 11, 48022 Lugo RA, Italy; [16]Institut Universitaire de Cardiologie et de Pneumologie de Québec/Québec Heart and Lung Institute, 2725 Ch Ste-Foy, Québec, QC G1V 4G5, Canada; [17]Faculté de Médecine—Département de Médecine, Université Laval, Ferdinand Vandry Pavillon, 1050 Av. de la Médecine, Québec City, Quebec G1V 0A6, Canada; and [18]Division of Cardiology, Department of Medicine, University of Washington School of Medicine, 4333 Brooklyn Ave NE Box 359458, Seattle, WA 98195-9458, USA

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In this EACVI clinical scientific update, we will explore the current use of multi-modality imaging in the diagnosis, risk stratification, and follow-up of patients with aortic stenosis, with a particular focus on recent developments and future directions. Echocardiography is and will likely remain the key method of diagnosis and surveillance of aortic stenosis providing detailed assessments of valve haemodynamics and the cardiac remodelling response. Computed tomography (CT) is already widely used in the planning of transcutaneous aortic valve implantation. We anticipate its increased use as an anatomical adjudicator to clarify disease severity in patients with discordant echocardiographic measurements. CT calcium scoring is currently used for this purpose; however, contrast CT techniques are emerging that allow identification of both calcific and fibrotic valve thickening. Additionally, improved assessments of myocardial decompensation with echocardiography, cardiac magnetic resonance, and CT will become more commonplace in our routine assessment of aortic stenosis. Underpinning all of this will be widespread application of artificial intelligence. In combination, we believe this new era of multi-modality imaging in aortic stenosis will improve the diagnosis, follow-up, and timing of intervention in aortic stenosis as well as potentially accelerate the development of the novel pharmacological treatments required for this disease.

Keywords aortic stenosis • cardiac magnetic resonance • cardiac computed tomography • echocardiography • positron emission tomography

Introduction

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

Non-invasive imaging, in combination with clinical assessment, has played a central role in the assessment and management of AS for many decades. In particular, echocardiography remains the reference standard; however, other imaging modalities are now increasingly being used, providing complementary information that is improving our understanding of the underlying biology and helping to guide clinical decision-making. This consensus document seeks to complement

* Corresponding author. E-mail: Marc.Dweck@ed.ac.uk

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the recent European Society of Cardiology guidelines,[2] providing added detail on the role of multi-modality AS imaging in current clinical practice as well as a focus on emerging applications and future developments.

Pathology

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

The myocardial remodelling response to AS varies between individuals and has an important influence on the development of symptoms, heart failure, and long-term prognosis. AS causes an increased afterload, triggering a hypertrophic remodelling response that restores wall stress and cardiac performance for many years in accordance with the law of Laplace.[7] Importantly, the degree of left ventricular hypertrophy is not well predicted by AS severity alone, being under the influence of multiple other factors including arterial hypertension, sex, and genetic polymorphisms.[8] Eventually, the hypertrophic response decompensates and patients transition to heart failure and the development of adverse clinical events. At the pathological level, this left ventricular decompensation relates to progressive diffuse myocardial fibrosis and myocyte cell death triggered by the hypertrophied myocardium outgrowing its blood supply.[9,10] Alongside increased end-diastolic pressures, capillary rarefaction, and arteriolar remodelling, these pathological changes characterize left ventricular decompensation and the transition to heart failure, resulting in increased myocardial stiffness, reduced contractility, and impaired cardiac function.

Finally, it is increasingly appreciated that AS and transthyretin amyloidosis (ATTR) commonly co-exist [e.g. 16% of transcatheter aortic valve implantation (TAVI) candidates,[11] most likely reflecting the increasing prevalence of the two conditions with advancing age[12,13]].

Echocardiography

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

Assessments of the aortic valve

Aortic valve morphology

Transthoracic echocardiography is able, in the majority of cases, to determine the valve phenotype (tricuspid, bicuspid, unicuspid, or other) according to Sievers classification (type 0: no raphe; type 1: one raphe; and type 2: two raphes) or a new classification recently proposed by an international group of experts.[14,15] Transoesophageal echocardiography (TOE), computed tomography (CT), or cardiac magnetic resonance (CMR) can be helpful to clarify aortic valve morphology when transthoracic echocardiography is not diagnostic.

Haemodynamic severity of AS

The main echocardiographic parameters to define AS severity are the peak aortic jet velocity, peak and mean transvalvular gradients, aortic valve area, and Doppler velocity index (DVI).[16] Aortic valve area can be indexed for body surface area to account for differences in height, particularly in those of shorter stature. It should be avoided in obese or very thin patients, when indexing to height may be superior. Based on these echocardiographic parameters, we can differentiate severe from non-severe AS (*Table 1*).

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

Discordant grading of AS severity at echocardiography

Up to 40% of patients with severe AS have an apparent discordance between the peak velocity/mean gradient and aortic valve area: most commonly where the aortic valve area indicates severe disease and the peak velocity or mean gradient suggest otherwise.[20] 'Discordant grading' includes three main categories: (i) 'classical' low-flow, low-gradient AS with stroke volume index <35 mL/m^2 and with reduced left ventricular ejection fraction (<50%); (ii) 'paradoxical' low-flow, low-gradient AS with stroke volume index <35 mL/m^2 but with preserved left ventricular ejection fraction (≥50%); and (iii) normal-flow, low-gradient AS with stroke volume index ≥35 mL/m^2 and preserved left ventricular ejection fraction (≥50%).

In cases of low-flow, low gradient AS with low ejection fraction, dobutamine stress echocardiography is recommended.[2,21] True severe AS is characterized by a fixed aortic valve area (≤1.0 cm^2) in the face of an increased flow rate. This will result in higher gradients and velocities across the stenotic valve (transaortic velocity ≥ 4 m/s and mean pressure gradient across the valve of >40 mmHg at any stage of dobutamine stress echocardiography). Another important parameter to assess is the change in stroke volume with dobutamine administration. An increase of stroke volume of <20% is a marker of reduced LV reserve and is associated with a worse prognosis and higher peri-operative

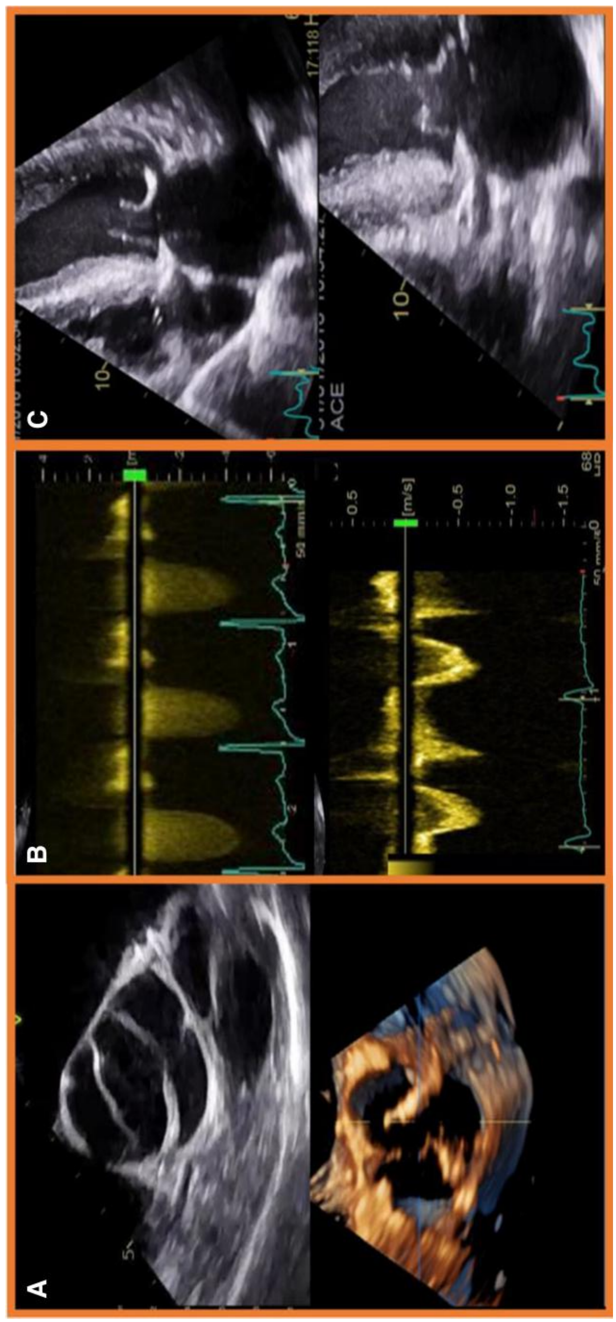

Figure 1 Valvular and myocardial assessments by echocardiography. Echocardiography has the ability to assess the valve morphology and haemodynamics as well as myocardial remodelling and function. (*A*) Bicuspid aortic valve (top) and 3D echocardiography assessment of a stenotic aortic valve (bottom). (*B*) Measurement of peak velocities through the valve (top) and LVOT (bottom). (*C*) Assessment of myocardial structure and function on cine imaging.

Table 1 Echocardiographic parameters of severe and very severe AS

	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	3.0–4.0	≥4.0	≥5.0
Mean gradient (mmHg)	<40	20–40	≥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

Patients may have discordant echocardiographic assessments where the above parameters do not agree on the true severity of AS. Most commonly, this is encountered in patients with an AVA < 1.0 cm^2 and a peak velocity of <4.0 m/s).
AVA, aortic valve area; AS, aortic stenosis.

risk.[22] This can help guide decision-making in these higher-risk patients, where TAVI would be preferrable to surgical aortic valve replacement (AVR). However, recent data assessing the performance of the above guideline measures against to the calculated projected aortic valve area (AVA_{proj}) from the True or Pseudo Severe Aortic Stenosis (TOPAS) study demonstrated that AVA_{proj} was superior to the AVA and haemodynamic measures at distinguishing true severe AS from pseudo-severe AS and at predicting mortality in medically managed patients.[23] A multimodality approach is useful in patients where clinical ambiguity remains.

Assessments of pressure recovery can also be useful, particularly in smaller patients with an ascending aorta diameter of less than 30 mm. Using pressure recovery to adjust the aortic valve area helps to reclassify patients with discordant echocardiography from severe to moderate AS with corresponding improvements in prognosis observed.[16,24] The final alternative that is being increasingly used in patients with discordant echocardiography and that is recommended in the European Society of Cardiology (ESC) guidelines is CT calcium scoring (section Computed tomography). *Figure 7* demonstrates a systematic approach to assessing these discordant patients (section Computed tomography).[25]

Assessment of the myocardium

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

Deterioration of left ventricular ejection fraction generally occurs late in the course of the disease and is often preceded by the development of left ventricular diastolic dysfunction. Indeed, left ventricular ejection fraction underestimates systolic dysfunction in the presence of concentric remodelling or hypertrophy and may thus lack sensitivity in patients with AS. Recent observational studies and UK National Institute for Health and Care Excellence (NICE) guidelines[24] suggest applying a higher cut-off ejection fraction (<55%) to improve its sensitivity in detecting subclinical left ventricular systolic dysfunction.

Quality and standardization of echocardiographic examination and reporting

Echocardiography should be performed in patients with AS, according to European Association of Cardiovascular Imaging expert advice for image acquisition and analysis.[25] A multi-parameter integrative approach should be used to grade the severity of AS and of concomitant aortic regurgitation if any. The echocardiography report should include the parameters outlined in *Table 2*.

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, or severe)	
AS **severity**	
Peak aortic jet velocity (V_{max})	
Mean gradient (mean PG)	
Aortic valve area	
DVI	
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, or 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	

AS, aortic stenosis; LV, left ventricular; EDVi, indexed end-diastolic volume; ESVi, indexed end-systolic volume.

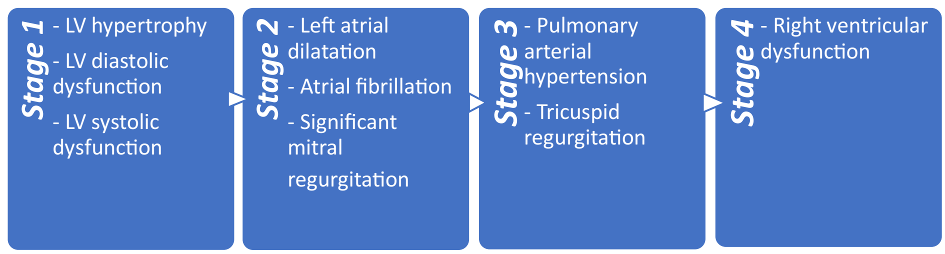

Figure 2 Integrated echocardiographic assessment of the cardiac chambers to aid in risk stratification in patients with AS.[33]

Developing techniques in the echocardiographic assessment of AS

Assessment of left ventricular function

Other echocardiographic techniques are emerging to provide more sensitive assessments of left ventricular function in AS. Speckle tracking echocardiography provides assessment of myocardial strain. In particular, global longitudinal strain appears to provide a more sensitive marker of systolic dysfunction than ejection fraction. A threshold of <15% is associated with AS patients who have a higher risk of adverse outcomes.[26]

The first phase of left ventricular ejection fraction (EF1) is the percentage change in left ventricular volume from end-diastole to peak aortic valve flow. This has recently been proposed for early identification of left ventricular dysfunction in AS, with a threshold of <25% being associated with an increased risk of adverse events.[27]

Diastolic dysfunction is another important and relatively well-established component of overall left ventricular function. Recent registry data demonstrated diastolic dysfunction of grade II and above in 42% of severe AS patients, with more severe diastolic dysfunction incrementally associated with cardiovascular mortality and hospitalizations.[28] Similarly, left atrial strain, another marker of left ventricular diastolic function, has demonstrated an association with increased hospitalization and mortality in patients with moderate to severe AS.[29]

Assessment of other cardiac chambers

Assessment of left atrial dilatation, pulmonary artery pressure, right ventricular dysfunction, and tricuspid regurgitation provides incremental information on the stage of disease and may have important prognostic implications in patients with AS.[30] On this basis, a classification for staging the extent of extra aortic valve cardiac damage and heart failure associated with AS has recently been proposed integrating progressive involvement of the chambers of the heart[31–33] (*Figure 2*).

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

Next steps

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

Computed tomography

CT calcium scoring

Discordant echocardiographic measurements are common and governed by complex interactions between the ventricle, the valve, and systemic arterial compliance.[34] 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 standardized 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%)[34,35] (*Figure 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.[2,36]

Aortic valve CT calcium scoring can be performed quickly with no iodinated contrast and a low dose of ionizing radiation (∼1 mSv).[37] 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.[38,39] As with any technique, there are limitations which include motion artefact 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 cases where echocardiographic measures are uncertain, borderline cases are often simply that—borderline—and a single value close to the established thresholds should be regarded within the broader clinical context.

CT angiography

CT angiography plays an important role in the workup of patients with AS being considered for TAVI. An accurate pre-TAVI CT assessment is pivotal not only in determining a patient's eligibility but also for precise procedure planning. Imaging is needed to assess the optimal access route and to accurately select the optimal size of the valve

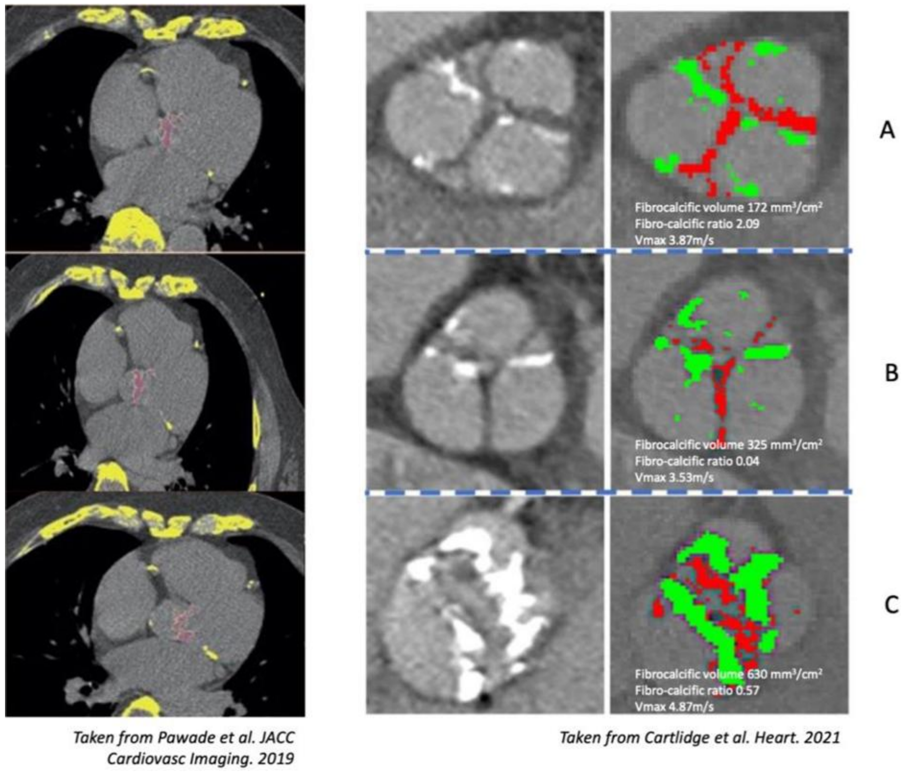

Figure 3 CT aortic valve calcium scoring. AS, aortic stenosis; AU, Agatston units; CT, computed tomography; ECV, extracellular volume; Vmax, peak velocity. Left panel: Non-contrast–enhanced cardiac CT images of a male patient with discordant aortic valve measurements on echocardiography. Areas in yellow are areas of calcium identified by the software (bone, coronary arteries, aortic valve, aorta, and mitral valve). Areas labelled in pink were manually selected for calculation of aortic valve calcification, which was scored at 2747 AU (severe AS). Middle and right panels (*A–C*): Contrast-enhanced CT of three patients identifying regions of valve fibrosis (red, also termed non-calcific leaflet thickening) and calcification (green) with calculated fibrocalcific volumes and ratios.

bioprosthesis. The latter is based on co-axial measurements of the annulus, a structure which is frequently underestimated by 2D echocardiography measurements due to its oval shape. The aim is to achieve appropriate anchoring and sealing of the device with the goal of mitigating paravalvular leakage whilst minimizing the risk of annular rupture.[40,41] Over recent years, cardiac CT has become the reference standard imaging modality for TAVI procedure planning. Specific acquisition requirements have become standardized, and image analysis is performed using dedicated semi-automated approaches[41,42] to assess coronary anatomy and select the optimum type and size of bioprostheses and access route, with high intra- and inter-observer reproducibility (*Figure 4*).[43–48] In selected cases, CT can also be used to provide useful information about coronary anatomy prior to intervention.

Developing applications

Contrast-enhanced CT angiography holds promise in refining anatomic assessments of AS severity, with advantages over non-contrast approaches. These include high spatial resolution and improved anatomical definition, which facilitates assessment of the valve in a uniform *en face* view and differentiation of valve pathology from that in adjacent structures. Importantly, both non-calcific and calcific leaflet thickening can be quantified, a major potential advantage over CT aortic valve calcium scoring (*Figure 3*). Various cohorts have attempted to derive thresholds and correct for variations in contrast load surrounding the valve.[49,50] Recent studies have demonstrated good inter-observer reproducibility and confirmed that valve fibrosis is more prominent in women than men.[51] Moreover, indexed fibrocalcific volumes have shown a close association with echocardiographic measures of valve haemodynamics.[34] Further work is now required to establish a rapid and generalizable methodology as well as identifying appropriate severity thresholds to guide clinical decision-making.

Contrast-enhanced CT can also provide advanced assessment of the myocardium, including the measurement of extracellular volume and global longitudinal strain. These demonstrate good agreement with CMR and echocardiographic measurements, respectively, may highlight dual pathology of AS and cardiac amyloidosis[52] and correlate with adverse outcomes.[53–55] Importantly, these myocardial CT approaches require delayed imaging or retrospective image acquisition across the full cardiac cycle, involving additional radiation exposure. More research is required to validate these emerging CT methods.

Cardiac magnetic resonance

The ability of CMR to characterize the aortic valve, the myocardium, and the aorta make it an attractive imaging modality in AS (*Figure 5*). The major limitations of CMR compared to echocardiography include its lack of portability, length of scan, and relative expense, although rapid image acquisition protocols have already improved the latter two issues.[56]

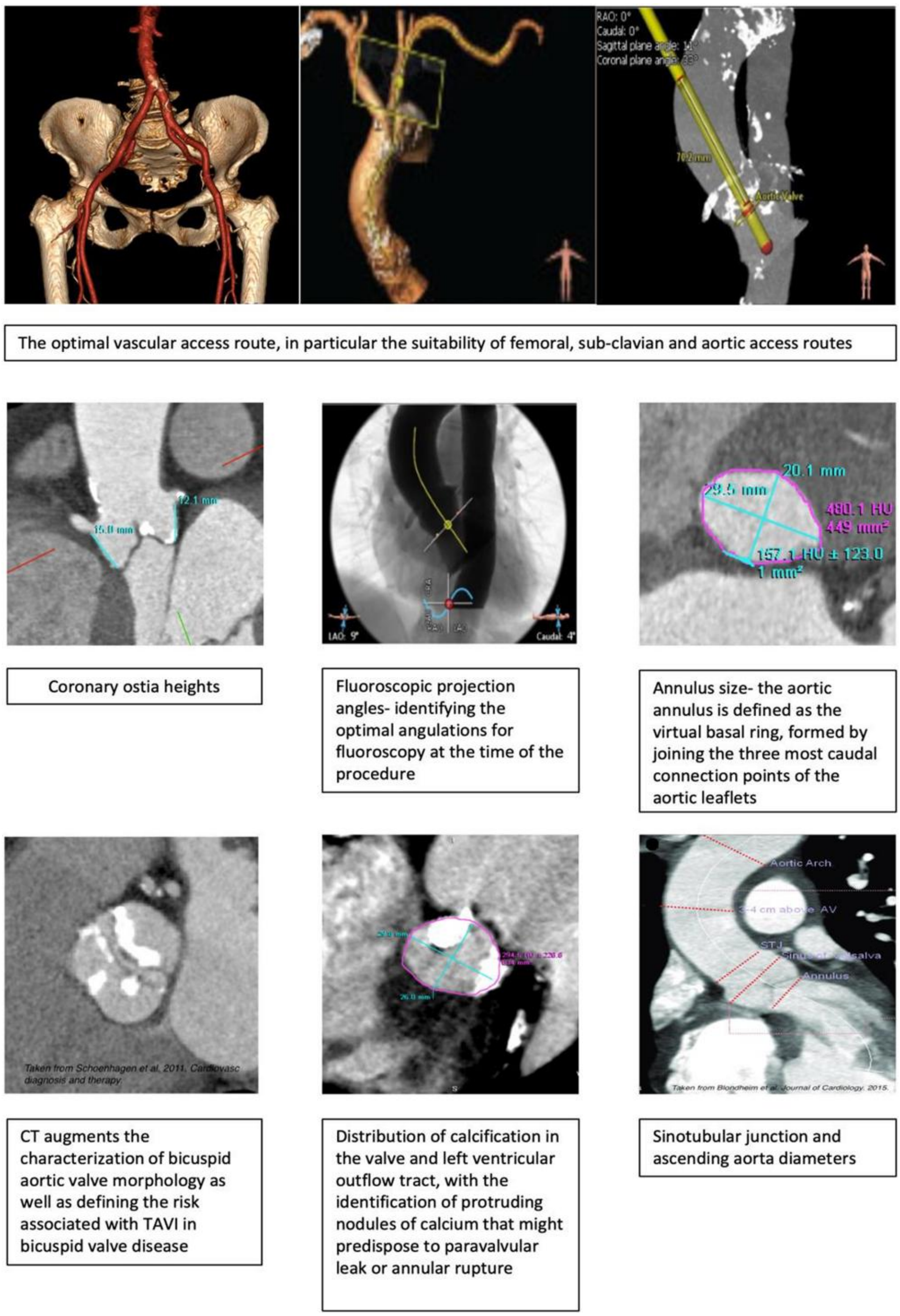

Figure 4 Parameters to measure on CT angiography. CT, computed tomography; TAVI, transcatheter aortic valve implantation.

Assessment of the aortic valve

CMR allows direct and multi-planar visualization of the aortic valve for accurate assessment of valve morphology (tricuspid or bicuspid subtypes).[57] CMR can help assess AS severity via direct planimetry of valve area[58] with good agreement with TOE. Importantly, both CMR and TOE planimetry measure the anatomic orifice area (i.e. maximum instantaneous valve area), which is different to the calculated aortic valve area derived from the continuity equation, the effective orifice area. This is important, because standard aortic valve area severity thresholds are based on the continuity equation and therefore not applicable to planimetered aortic valve area measurements, which are generally larger as they are not affected by the physical contraction of flow when blood passes through the stenotic orifice.[59]

AS severity can be assessed using phase-contrast velocity mapping that allows visualization and quantification of blood flow through the valve.[58] Velocities are used to assess AS severity similar to

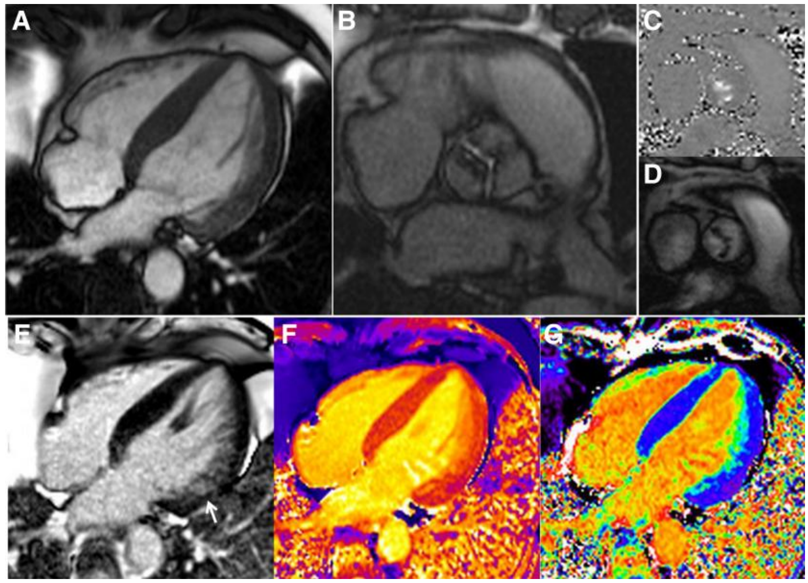

Figure 5 CMR imaging in the assessment of the aortic valve and myocardium. Patient with critical AS. Four-chamber balanced steady-state free precession (bSSFP) cine image (*A*) showing normal left ventricular cavity size with concentric hypertrophy. Short-axis bSSFP cine image (*B*) *en face* view of the aortic valve demonstrating fusion of the left and right coronary cusp and a planimetered aortic valve area of 0.6 cm^2. Phase-contrast imaging just above the aortic valve (*C* + *D*) demonstrating a peak velocity of nearly 5 m/s. Bright-blood LGE images demonstrating patchy, non-infarct scar in the lateral wall (*E*). A native T1 map (*F*) and ECV map (*G*) demonstrate no evidence of myocardial infiltration.

echocardiographic Doppler measurements and can also accurately quantify regurgitant volume, when present. Whilst CMR offers better jet alignment compared to echocardiography, however lower temporal and spatial resolution means CMR may underestimate the peak velocity.[60] These limitations mean that CMR is only used as a third-line imaging technique to assess AS severity after echocardiography and CT, although it can prove of particular value in patients with multi-valvular involvement.

Assessment of the aorta

CMR is an excellent clinical tool for the assessment and serial monitoring of the thoracic aorta. Like CT, it provides accurate diameter measurements but without radiation exposure, allowing the identification of aortic dilatation, aneurysm formation, and coarctation.[25]

TAVI planning and follow-up

CMR can be used as an alternative to CT for TAVI planning, in patients with an allergy to iodine-based contrast agents or severe renal impairment.[61] Post-TAVI, CMR provides accurate quantification of paravalvular regurgitation[62] and may be useful in those with uncertain regurgitation severity on echocardiography.

Assessment of the myocardium

CMR provides reference standard assessments of left ventricular structure (wall thickening, hypertrophy dilatation, and mass–volume ratio)[63] and function (ejection fraction and myocardial strain using feature-tracking) and should be used in cases where echocardiographic windows are poor and ventricular assessments uncertain.

Developing applications

Myocardial fibrosis

The unique strength of CMR is myocardial tissue characterization. Non-infarct patterns of late gadolinium enhancement (LGE) can be identified in patients with AS as a marker of focal replacement fibrosis, demonstrating a close association with increased collagen deposition and microscars on histology.[64] The prevalence of non-infarct LGE in severe AS ranges from 27 to 51%[65] and is associated with multiple other markers of left ventricular decompensation including impairment in systolic and diastolic function, the electrocardiogram (ECG) strain pattern, elevated serum biomarkers (e.g. B-type natriuretic peptide and cardiac troponin), reduced exercise capacity, and symptomatic status.[66] Once established, further LGE appears to accumulate rapidly over time[67] and to be irreversible following aortic valve replacement.[68] The myocardial scar burden that patients develop whilst waiting for aortic valve replacement therefore persists into the long-term, an important observation given that it also serves as a powerful independent predictor of long-term outcomes.[65] The ongoing EVOLVED randomized controlled trial is investigating whether prompt valve replacement in asymptomatic patients with severe AS and myocardial scarring improves patient outcomes[69] (Clinicaltrials.gov identifier: NCT03094143). Furthermore, distinct patterns of non-ischaemic LGE make it possible to identify concomitant pathology such as cardiac amyloidosis which is also associated with a higher risk of all-cause mortality.[70,71]

Beyond LGE, T1 mapping and extracellular volume fraction (ECV) quantification can identify extracellular matrix expansion: a surrogate for fibrosis (both replacement and diffuse interstitial fibrosis) or infiltration (e.g. amyloidosis).[72] Diffuse fibrosis increases with more severe AS and left ventricular hypertrophy.[67] Unlike the focal fibrosis detected by LGE, diffuse fibrosis is largely reversible after aortic valve replacement. Indeed, patients with more extensive diffuse fibrosis derive a larger benefit in symptoms and left ventricular function following aortic valve replacement.[73] Several recent large multi-centre studies of patients with severe AS imaged prior to aortic valve replacement demonstrated ECV% was associated with markers of left ventricular decompensation and both cardiovascular and all-cause mortality.[74,75]

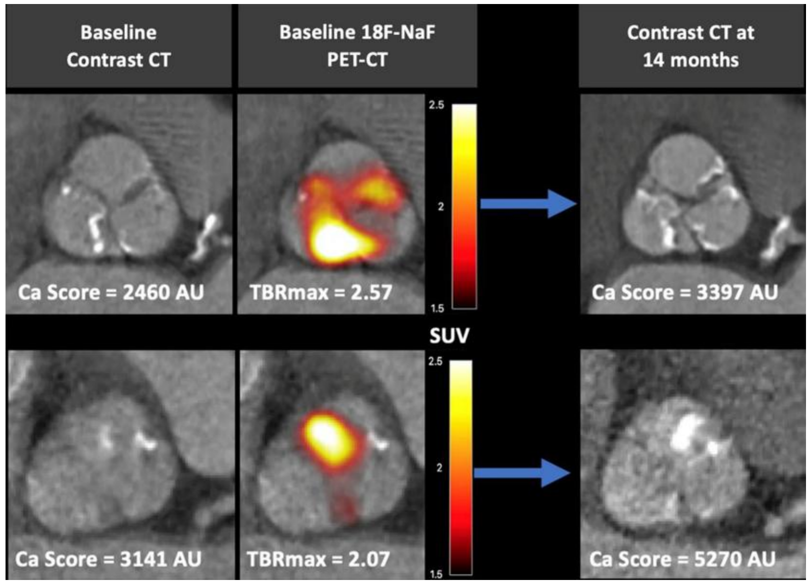

Figure 6 ^{18}F-sodium fluoride PET–CT for aortic valve calcification. AU, Agatston units; CT, computed tomography; PET–CT, positron emission tomography–computed tomography; TBR_{max}, maximum tissue-to-background ratio. Areas of red and yellow show ^{18}F-sodium fluoride uptake on the aortic valve. Areas of maximal uptake at baseline correspond to the development of visible calcification on CT at 14 months. Taken from Fletcher & Dweck. 2021. *Journal of Nuclear Cardiology*.

Myocardial perfusion

Stress CMR allows assessment of myocardial ischaemia and measurement of myocardial blood flow at rest and stress. The ratio of stress and rest myocardial blood flow, known as the myocardial perfusion reserve, represents the ability of the myocardium to increase blood flow during stress. In patients with AS, left ventricular hypertrophy, and unobstructed coronary arteries, perfusion CMR often demonstrates global subendocardial perfusion defects and reduction in myocardial perfusion reserve due to supply–demand mismatch and a relative reduction in capillary density.[76] Myocardial perfusion reserve is an independent predictor of exercise capacity[77] and symptom onset in asymptomatic patients with AS.[78] Automated quantification techniques producing absolute myocardial blood flow maps have recently overcome complex post-processing and may make this technique more accessible.[79]

Reverse left ventricular remodelling after aortic valve replacement

Reverse remodelling after aortic valve replacement is associated with early normalization in left ventricular function within 6 months[80] and 20–30% left ventricular mass regression in the first 6–12 months.[81,82] Mass decreases most in those with more left ventricular hypertrophy and no scar.[81] ECV quantification is able to discern cellular from matrix volume regression, although more research into this area is required.[68,75] *De novo* LGE is found in a fifth of patients, highlighting that new peri-operative myocardial injury may also contribute to prognosis.[83,84]

Other approaches

Other CMR tissue parameters under investigation that may emerge for clinical use are T2 mapping for inflammation,[85] CMR spectroscopy investigating myocardial energetics,[86] manganese-enhanced CMR as a marker of myocardial calcium handling,[87] and 4D flow to assess the complex flow patterns in the aorta that may contribute to aortopathy.[88]

Nuclear imaging

Bone scintigraphy and concomitant cardiac amyloid

Bone scintigraphy holds potential clinical value in the detection of concomitant cardiac amyloidosis in patient.[71,89] The most frequent type of amyloidosis in the AS population is ATTR. If clinical, ECG, or echocardiographic features of amyloidosis are identified, bone scintigraphy and light chain analysis in blood and urine should be performed to confirm the presence and type of concomitant amyloidosis [i.e. exclusion of light chain (AL) amyloidosis which requires different management to ATTR].[90] Although this may have prognostic or treatment implications, non-randomized data suggest that TAVI should not be withheld purely on the basis of concomitant cardiac amyloidosis, since outcomes in cohorts have been better following valve intervention compared to medical therapy alone.[89,91] Diagnostic algorithms typically include ^{99m}Tc-pyrophosphate (PYP), ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), or ^{99m}Tc-hydroxymethylene diphosphonate (HMDP) scintigraphy alongside other clinical, biomarker, and imaging investigations.[92]

Developing applications

Assessing disease activity with positron emission tomography

Molecular cardiac imaging with positron emission tomography (PET) remains largely investigational for cardiovascular applications but has a broad range of potential uses. Hybrid scanners permit combined assessments of disease activity provided by PET, with anatomical and functional information from CT or CMR. Radiotracers are injected

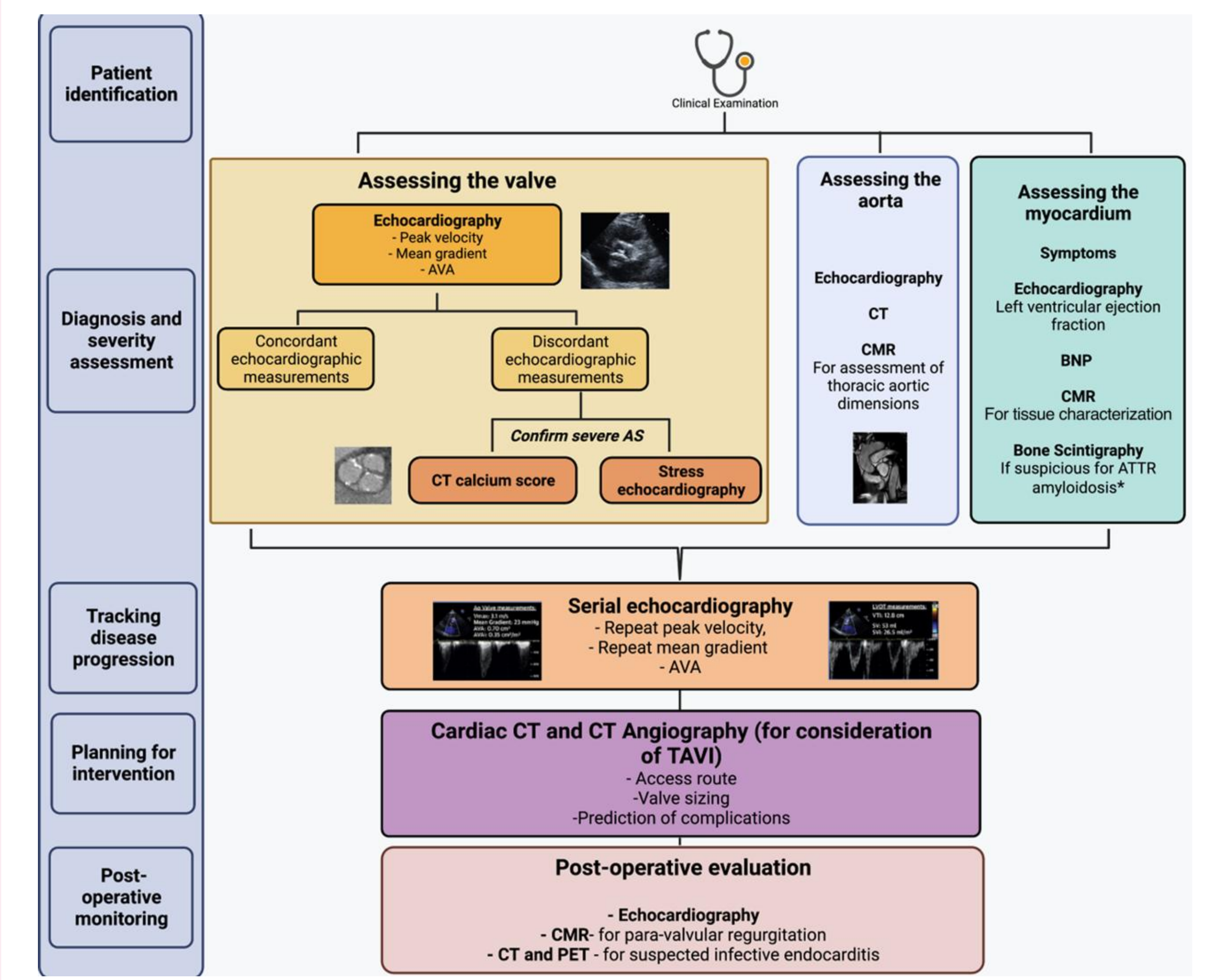

Figure 7 The current patient pathway in diagnosing and monitoring AS with the use of multi-modality imaging. AVA, aortic valve area; AS, aortic stenosis; ATTR, transthyretin; BNP, beta-natriuretic peptide; CMR, cardiac magnetic resonance; CT, computed tomography; LV, left ventricular; TAVI, transcatheter aortic valve implantation. *Features of amyloidosis including but not limited to features of heart failure, carpal tunnel syndrome, neuropathy, low-voltage QRS complex on ECG, left ventricular hypertrophy, left ventricular diastolic dysfunction, and granular speckling effect of myocardium on echocardiography. Figure created on Biorender.

intravenously and localize in areas where the disease process of interest is active. In principle, the activity of any pathological process can be investigated, subject to the availability of a relevant radiotracer. In practice, these studies have largely focused on assessment of valve calcification activity in AS using the tracer ^{18}F-fluoride. Such studies remain in the research arena but have provided important insights into the pathobiology underlying AS. Initial reports demonstrated that calcification is the predominant active pathological process in AS, particularly in patients with more advanced stenosis where inflammation activity assessed by ^{18}F-fluorodeoxyglucose was comparatively lower.[93] Subsequent studies have demonstrated that valve ^{18}F-fluoride activity can be measured with excellent repeatability[94] and provides powerful prediction of subsequent disease progression and the need for aortic valve replacement (*Figure 6*).[95,96] They have also helped highlight the role that lipoprotein(a) plays in both the initiation and propagation phases of AS, thereby identifying it as a potential treatment target.[97] Whilst the clinical role of ^{18}F-fluoride PET may be limited in AS (CT provides similar diagnostic and prognostic information at lower expense and radiation exposure), this technique is increasingly being used as an endpoint in clinical trials assessing the ability of potential novel treatments to reduce valve calcification activity.[98]

Integrating current clinical modalities

Echocardiography remains the mainstay of diagnosis and monitoring in patients with AS. It provides vital information on the valve and myocardium and is both widely available and cost-effective. In many patients, no further imaging is required. However, in certain patient groups, additional imaging approaches can improve patient assessment and should be given due consideration. An integrated approach, facilitated by a dedicated Heart Valve Team[99] is proposed in *Figure 7*.

In patients with discordant echocardiography, additional imaging using either CT calcium scoring or stress echocardiography in patients

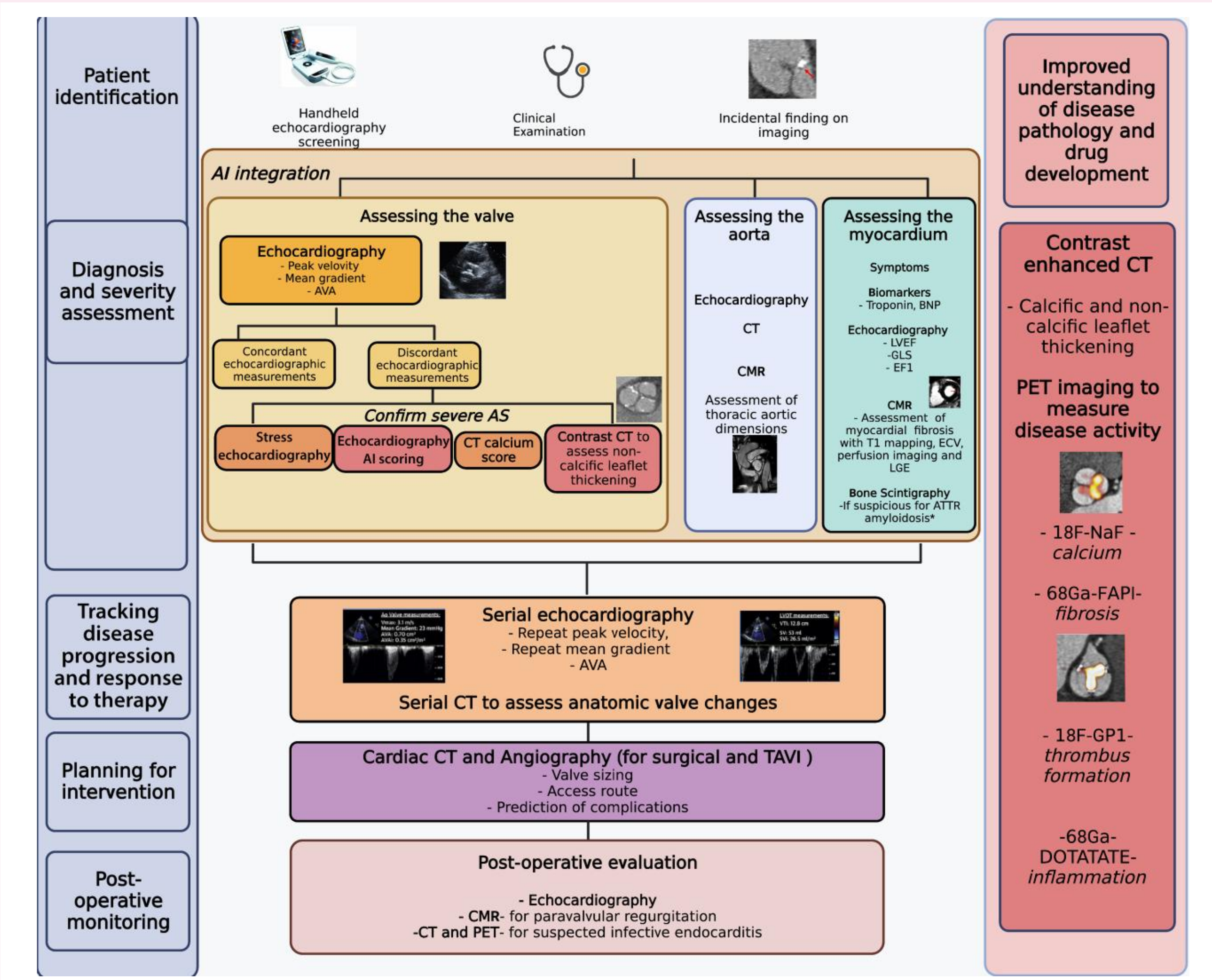

Figure 8 Potential future patient pathway in patients with AS. 18F-NaF, ^{18}F-sodium fluoride; 68Ga-FAPI, ^{68}Ga-labelled fibroblast activation protein inhibitor; AI, artificial intelligence; ATTR, transthyretin; AVA, aortic valve area; BNP, beta-natriuretic peptide; CMR, cardiac magnetic resonance; CT, computed tomography; ECV, extracellular volume; LGE, late gadolinium enhancement; LV, left ventricle; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; EF1, first-phase ejection fraction; PET, positron emission tomography; TAVI, transcatheter aortic valve implantation. *Features of amyloidosis including but not limited to features of heart failure, carpal tunnel syndrome, neuropathy, low-voltage QRS complex on ECG, left ventricular hypertrophy, left ventricular diastolic dysfunction, and granular speckling effect of myocardium on echocardiography. Figure created on Biorender.

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

The future of multi-modality imaging in AS

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

Initial diagnosis/screening

Early identification of patients with AS is important. Traditionally, AS is identified as an incidental finding upon stethoscope auscultation. However, this strategy is limited by the diagnostic accuracy of auscultation, particularly when performed by non-specialists, and also by the reduction in direct face-to-face patient contact observed since the emergence of COVID-19. Automated stethoscope technology may help with this issue, but novel imaging approaches also hold promise. The development of handheld echocardiography might facilitate screening programmes in the community to identify patients with AS, although the cost-effectiveness of such approaches would have to be carefully assessed.[100] With smartphone-associated imaging probes and artificial intelligence-directed imaging, self-directed patient echocardiography may also one day become a reality. The use of artificial intelligence to identify patients with AS on even simpler tests, such as the ECG, also holds promise.[101,102] A more immediate strategy would be the reporting of incidental aortic valve calcification identified on CT scans performed for other purposes, providing an opportunity to identify patients with calcific aortic valve disease that is frequently overlooked in current clinical practice.[103]

Improved pathological understanding

A major priority in AS is the development of an effective medical therapy. This will require an improved understanding of the underlying pathophysiology. Molecular imaging now allows us to investigate the activity of a range of pathological process underlying cardiovascular disease. In AS, future studies may inform the exact contribution of inflammation (^{8}F-fluorodeoxyglucose and ^{68}Ga-DOTATATE), calcification (^{18}F-fluoride), thrombus (^{18}F-GP1), and fibrosis (^{68}Ga-fibroblast activation protein inhibitor) activity at the different stages of the disease process and how their relative contributions vary between patient groups. Initial PET studies have already identified novel targets for therapy in AS and identified important sex differences, suggesting that these approaches may help accelerate the development of novel treatments as part of a precision medicine approach.

Valve and myocardial assessments

The anatomic assessment provided by CT may come to play a greater role in how we assess and track AS severity, particularly in patients with discordant echocardiography or suboptimal echo windows. As has been observed in coronary artery disease, there is a natural progression from non-contrast to contrast CT angiography, allowing more detailed assessment of fibrotic as well as calcific valve thickening. As novel medical therapies emerge targeting valve calcification or fibrosis, these contrast CT assessments may allow us to tailor optimal therapies for individual patients and provide an imaging technique able to track the effects of new therapies on anatomic disease progression in phase 2 clinical trials. This can then inform which therapies should proceed to phase 3 clinical endpoint trials.[104]

Advanced multi-modality myocardial assessments by echocardiography, CMR, and CT may also be increasingly used to track mild to moderate AS and the effects of AS on the myocardium and to identify more precisely when the left ventricle is starting to decompensate in the face of AS, thereby optimizing the timing of aortic valve replacement. Finally, the impact of artificial intelligence is likely to be felt in daily clinical practice across all the imaging modalities, optimizing and standardizing cardiac imaging.[74,105] *Figure 8* demonstrates a potential model for the future identification and management of patients with AS.

Conclusion

The diagnosis and management of AS continue to evolve and to improve, with many exciting imaging techniques in development. Echocardiography remains the most important imaging test, playing an indispensable role in the diagnosis and monitoring of patients with this condition and in clinical decision-making. However, other imaging modalities provide complementary information and are increasingly being used in complex patients where echocardiographic assessments are inconclusive or in the planning of TAVI procedures. A multidisciplinary approach with a Heart Valve Team is recommended by the latest ESC guidelines to ensure the appropriate use of multimodality imaging and to optimize the care provided to our AS patients.

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Data availability

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

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