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Role of multimodality cardiac imaging in the management of patients with hypertrophic cardiomyopathy in 2025. A Clinical Consensus Statement of the European Association of Cardiovascular Imaging (EACVI) of the ESC

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Abbreviations

- ^{123}I-MIBG: ^{123}I-metaiodobenzylguanidine
- ASE: American Society of Echocardiography
- AI: Artificial Intelligence
- AF: Atrial fibrillation
- CCT: Cardiac computed tomography
- CMI: Cardiac myosin inhibitors
- ECG: Electrocardiogram

- EACVI: European Association of Cardiovascular Imaging
- ESC: European Society of Cardiology
- FAPI: Fibroblast activation protein inhibitor
- GLS: Global longitudinal strain
- HF: Heart failure
- HCM: Hypertrophic cardiomyopathy
- ICD: Implantable cardioverter-defibrillator
- IVS: Interventricular septum
- LGE: Late gadolinium enhancement
- LA: Left atrial
- LV: Left ventricular
- LVMCO: Left ventricular mid cavity obstruction
- LVEF: LV ejection fraction
- LVOT: LV outflow tract
- LVOTO: LV outflow tract obstruction
- MWT: Maximum wall thickness
- MR: Mitral regurgitation

- MMI: Multimodality imaging

- PET: Positron emission tomography

- SPECT: Single photon-emission computed tomography

- SCD: Sudden cardiac death

- SAM: Systolic anterior motion

- TOE: Transoesophageal echocardiography

- TTE: Transthoracic echocardiography

Abstract

After the 2014 European Society of Cardiology (ESC) guidelines on hypertrophic cardiomyopathy (HCM) were published, the European Association of Cardiovascular Imaging (EACVI) of the ESC developed the 2015 EACVI consensus paper on multimodality imaging (MMI) in HCM, providing in-depth knowledge on the role of imaging in this disease. Since then, new evidence on HCM diagnosis, management and patient prognosis has accumulated, and the role of MMI has further expanded. Now that the 2023 ESC guidelines on cardiomyopathies have been published, a new EACVI document on MMI in HCM is needed, providing state-of-the-art, in-depth knowledge of imaging in HCM. The scope of this document is to focus on the role of the different imaging techniques in HCM in a logical, didactic and comprehensive way using a multimodality approach. We provide our vision for future directions on MMI in HCM.

1. Introduction

The 2023 European Society of Cardiology (ESC) guidelines for the management of cardiomyopathies 1 emphasize the key roles for multimodality imaging (MMI) in the management of patients with hypertrophic cardiomyopathy (HCM). In this complementary document, we provide more detailed guidance regarding how modern imaging techniques contribute to (re)evaluating hypertrophied heart muscle in suspected and known HCM Graphical abstract. A clinical perspective on the role of imaging in this disease includes several key needs where imaging can add increasing value:

(1) Diagnosis. This refers to the detection of the morphological and functional features of HCM. Conventionally, the key diagnostic feature of HCM is left ventricular (LV) maximum wall thickness (MWT) of sufficient magnitude that is unexplained by loading conditions. Limitations in current diagnostic definitions of HCM based on MWT are increasingly recognized, and more sophisticated, often multimodal, assessments may be needed. Though the classical imaging definition of hypertrophy relates to increased LV mass (and not on wall thickness), we have decided in this document (in accordance with the current definition of HCM) to keep the definition of LV hypertrophy in HCM based on wall thickness.

(2) Symptoms. This refers to detecting and characterizing the pathophysiological mechanisms responsible for symptoms in HCM. Systolic and diastolic dysfunction and mitral regurgitation (MR) are frequent contributors to symptoms, and the importance of LV outflow tract (LVOT) obstruction (LVOTO) as a mechanism for symptomatic limitations in HCM is well-established. Abnormal myocardial perfusion represents a frequently under-appreciated cause of symptoms in HCM.

(3) Prognosis. This principally refers to the detection and characterization of features associated with increased risks of ventricular arrhythmia and sudden cardiac death (SCD), atrial fibrillation (AF), thromboembolic disease, and progressive heart failure (HF).

(4) Screening. At its most challenging, this refers to the discrimination between very mild myocardial disorders and normal hearts.

A decade after our last European Association of Cardiovascular Imaging expert consensus on this topic 2, we observe significant advances in our understanding of HCM (Box 1, Box 2).

The established role of echocardiography remains robust as the first imaging modality in HCM patients (Box 3), but many modern developments result from the application of cardiovascular magnetic resonance (CMR) (Box 4).

2.Context matters: Imaging in hypertrophic cardiomyopathy

2.1. The natural history of HCM

HCM generally has a benign course, with most patients remaining asymptomatic. Occasionally, HCM is diagnosed incidentally in older individuals presenting with mild phenotypic expressions. However, in a small subset of patients, significant clinical events occur. The disease, in the 50% of patients with monogenic HCM, shows variability in clinical and phenotypic penetrance and expressivity at all stages: from pure variant carriers (genotype positive (G+), no phenotype (P-)) to non-hypertrophic, early-phenotype stage, progressing through more classical phenotypes, and eventually advancing to adverse remodelling and overt dysfunction stages ("end stage" or "burn-out" HCM) in a minority 3 (Figure 1).

While SCD is the most catastrophic outcome, LVOTO, AF and HF with preserved ejection fraction (HFpEF), alone or in combination, are significant contributors to disease burden. According to a prospective follow-up study from the ESC-EORP

Cardiomyopathy Registry, the annual incidence of major adverse cardiovascular events encompassing any cardiovascular death or heart disease-related urgent hospital admission 4 in HCM was relatively low, at 5.3%. Specifically, annual incidence was 4.1% for major arrhythmic events, 1.2% for HF, and 1.8% for cardiovascular death. The long-term risk of adverse events was greater in patients diagnosed at a younger age and in those known to carry disease-causing sarcomere variants 5. Although the incidence of SCD decreases with age, the risks of HF and AF increase, peaking in mid-to-late adulthood. Finally, there is evidence that identifying high-risk patients and undertaking subsequent therapeutic interventions can save many lives; one study suggests that contemporary therapies reduce HCM-related annual mortality 6.

2.1.1. Early, non-hypertrophic phenotypes

Some G+ patients show mild functional and morphological abnormalities without LV wall thickening (Table 1) 7-12. These findings have only been described in small echo and CMR studies; none are disease-specific or consistently detected in G+/P- individuals but are often associated with abnormal electrocardiograms. Moreover, none are reliably linked to the development of LV wall thickening or to disease outcomes. Their presence has lower specificity in the elderly because of ageing and coexisting diseases.

The positive predictive value of these mild abnormalities is low (as they may never develop criterion magnitude of LV wall thickness), and their negative predictive value is also low (because their absence does not exclude later progression in LV wall thickness) 7-12.

2.1.2 Classical phenotypes

The extension and distribution of LV wall thickening are highly variable in HCM and may affect one to all LV segments. The prospective multicentre HCM Registry 13 describes several principal morphological subtypes: localized basal septal hypertrophy, reverse curvature septal hypertrophy, apical HCM, concentric HCM and mid-cavity obstruction with apical aneurysm.

2.1.3. Advanced LV remodelling and overt dysfunction

This phenotype is thought to result from consecutive bursts of symptomatic or asymptomatic microvascular ischaemia resulting in abnormal global longitudinal strain (GLS) and replacement fibrosis (LGE) 2. Overt dysfunction identifies a high-risk subgroup with increased mortality due to SCD, progressive HF, and AF 15.

Stereotypically, two extreme phenotypes are described: severe systolic dysfunction with a (relatively) dilated LV and (relatively) thin and fibrotic LV walls; and, more frequently, a restrictive type where a small LV cavity and advanced diastolic dysfunction are associated with high LV filling pressures and mild systolic dysfunction, often with little or no abnormal LGE (Figure2) 14. In reality, features of these HCM phenotypes are not mutually exclusive, and frequently co-exist in the same patient.

2.2. Modifiers of hypertrophic cardiomyopathy phenotypes

The phenotypic expression of HCM is highly variable and influenced by genetic, environmental, and haemodynamic factors. Phenotypic heterogeneity is frequently evident in patients with the same disease-causing variants, even when they are first-degree relatives 16,17. This variability in clinical presentation and disease severity is regulated by modifier genes and by a variety of factors such as sex, obesity,

hypertension, physical activity, pregnancy and COVID-19 (Table 2). To this end, personalized LV MWT thresholds for HCM diagnosis have been proposed 18,19.

2.2.1. Sex differences

Male patients are typically overrepresented in HCM cohorts and exhibit more pronounced LV wall thickening compared to females 20-26. Conversely, females are more likely to have a causative sarcomere variant, exhibit obstructive phenotypes and present with worse diastolic dysfunction compared to men 20-26. Women often have smaller hearts when corrected for body surface area and, as such, require a greater degree of MWT to meet the diagnostic criteria of at least 15 mm MWT 20-26. Consequently, HCM in females may be underdiagnosed and/or detected later in the disease process.

This, in turn, may lead to a higher prevalence of HF and AF at the time of presentation 20-26. Individualised MWT thresholds based on demographic and other patient variables 18 may improve the diagnostic precision of imaging diagnostics.

2.2.2. Obesity

As for other cardiovascular disorders, interactions between obesity and HCM can exacerbate both disorders. A sedentary lifestyle due to exertional intolerance and/or iatrogenic exercise proscription contributes to weight gain. Additionally, the obese state may exacerbate the severity of HCM 27- 33. Excess weight is associated with increased LV wall thickness and LV mass, LV and LA enlargement, impaired diastolic function and a higher likelihood of LVOT obstruction 33-36. Obese HCM patients have a higher risk of developing HF, AF, obstructive sleep apnoea, and are often more symptomatic 33-36. Obesity may exacerbate HCM phenotypes through a variety of

mechanisms including elevated cardiac workload, metabolic dysfunction, microvascular dysfunction, and hypertension 27-37. Repeat cardiac imaging following weight loss may provide evidence of weight-mediated contribution to LV hypertrophy. Consequent to increased risks of premature coronary disease, MMI strategies may also need to evaluate coronary anatomy.

2.2.3. Hypertension

The interaction between hypertensive heart disease and HCM often presents diagnostic challenges 38-40. Whilst the presence of multiple myocardial crypts, elongated mitral valve leaflets and asymmetric septal or apical LV hypertrophy may help to distinguish the two entities, several other CMR-derived findings initially considered promising as discriminants have proven less helpful at an individual-patient level. These features, including non-ischaemic LGE, increased native T1 values, and increased extracellular volume fraction, are found in both HCM and hypertensive heart disease 41-43. Hypertension in HCM patients contributes to greater magnitude LV wall thickness, showing a predilection towards mid-ventricular and apical distributions, and higher provocable LVOTO 44. Despite these differences in phenotype, hypertension does not seem to affect HCM-related mortality 44. Repeat cardiac imaging following sustained control of hypertension (3 months or more) may provide evidence of blood pressure-mediated contribution to LV hypertrophy.

2.2.4. Athletes

The cardiac phenotype of the athlete's heart can (2% of Caucasians, up to 18% of black athletes) mimic HCM, showing increased LV wall thickness in the grey zone (13-15mm) due to the demands of intensive training 45,46.

Reliable differentiation between the two entities and accurate risk stratification in athletes with HCM are of utmost importance, considering the potential prognostic consequences of competitive and/or endurance sports as well as the negative implications of exercise proscription and/or disqualification from competition. Among others, the type, duration and frequency of sport activity, ethnicity, sex, age, somatometric characteristics of the athletes, the effect of detraining, and the use of anabolic drugs may play a significant role in the differential diagnosis, with those participating in endurance sports having the most prominent changes 46.

Imaging techniques may be useful to separate physiological adaptation from pathological changes (Table 3) 47-56. Historical recommendations have generally restricted competitive sports participation for individuals with HCM. However, emerging evidence (including multimodality imaging data) suggests that selected patients with mild HCM and low-risk profiles may safely engage in more intense exercise with strict follow-up and after a shared decision process 46-56.

2.2.5. Pregnancy

Pregnancy induces significant physiological changes that can alter the HCM phenotype. The increase in blood volume and cardiac output leads to an expansion of LV size, helping to mitigate LVOTO, particularly during the first and second trimesters 57. However, for HCM patients with HF or severe LVOTO, the increased workload can worsen symptoms and raise the risk of arrhythmias and HF, especially during labour 58-60. Despite these risks, most women with HCM tolerate pregnancy well, with favourable maternal and foetal outcomes for those under close observation 61.

2.2.6. COVID-19

HCM patients are generally considered at higher risk for severe COVID-19 62, 63, and the increased expression of angiotensin-converting enzyme 2 receptors in patients with HCM may partially contribute to this heightened vulnerability 64. Additionally, factors such as age, baseline New York Heart Association functional class, systolic dysfunction and LVOTO significantly increase the risk of mortality in these individuals 65-66.

3. Routine imaging assessment in known or suspected hypertrophic cardiomyopathy

3.1 Hypertrophy and maximal wall thickness

Accurate measurement of left ventricular MWT is a key step in the diagnosis of HCM; conventionally, measures ≥15 mm are considered diagnostic in adults in the absence of other causes of increased wall thickness. In individuals with a positive family history of HCM or in carriers of a disease-causing variant, a diagnostic threshold of ≥13 mm is considered appropriate1. Furthermore, MWT is a key component in stratification for HCM-related SCD1,2. In HCM, LV hypertrophy is almost always regional or asymmetric; notably, despite elevated MWT, global LV mass (as a raw measure or indexed) is often in the normal range unless the regional hypertrophy is particularly marked or if the hypertrophy is more global.

Echocardiography is the primary imaging modality used to assess LV wall thickness. MWT is measured with 2D (bidimensional) echocardiography at end-diastole in the

parasternal long- or, preferably, short-axis views. Care should be taken to image all LV wall segments completely (Figure 3).

The administration of LV opacification contrast agents helps to provide more accurate measurements of MWT, and may be needed when acoustic windows are poor, and to accurately detect apical disease (e.g. hypertrophy, apical aneurysm +/- thrombus). The identification of asymmetric septal hypertrophy, defined as a septal/posterior wall thickness ratio of >1.3 in normotensive patients (or >1.5 in patients with arterial hypertension), may be used to describe the distribution of LV wall thickening, but is not considered diagnostic as a single variable. Table 4 shows common measurement errors and proposed solutions.

CMR imaging offers complementary information (Figure 3). CMR imaging can aid in detecting regional wall thickening in segments/walls that are difficult to assess with transthoracic echo (TTE), such as the anterolateral wall and the apex, and other changes in the architecture of the LV and/or mitral valve apparatus. Table 4. Furthermore, CMR can provide an accurate assessment of global LV mass and can better identify concomitant right ventricular (RV) hypertrophy, a finding that may have diagnostic implications. The shape of the hypertrophied interventricular septum can be classified as reversed curve, neutral, sigmoidal, apical or mixed, with the reversed curve shape most associated with a positive genetic test 67.

MWT can be measured using cardiac computed tomography (CCT) when echo is of insufficient quality and CMR unavailable or contraindicated.

3.2. Tissue characterization

In HCM patients, late gadolinium enhancement (LGE, a surrogate marker for macroscopic myocardial fibrosis) is progressive, and is present in 65% of patients. LGE is most likely to be absent in young patients and in those with mild hypertrophy 68, 69. By CMR, two major distribution patterns of late gadolinium enhancement (LGE) are seen: 1) intramural or epicardial LGE, more frequently seen in the hypertrophied segments, which corresponds to replacement fibrosis; and/or in the RV insertion points LGE, which corresponds to interstitial fibrosis and/ or myocyte disarray (Figure 4) 70. The location of LGE may be useful in the diagnosis of specific aetiologies; accordingly, Fabry disease should be suspected if sub-epicardial or transmural LGE is detected in inferior or lateral LV segments70. 2) Subendocardial LGE that may not correspond to a coronary vascular distribution has been observed in some patients with HCM 71. It is hypothesized to be related to a 'microvascular' cause of recurrent myocardial ischaemia, leading to myocardial fibrosis and LGE.

Though the pathophysiological consequences of the different types of LGE and their independent prognostic role are still debated 71-73, LGE is associated with adverse outcome in HCM patients74.

Extensive LGE (in % of LV mass) is associated with an increase in SCD risk and LV systolic impairment. A meta-analysis of eight studies with 3808 patients suggests that the presence of LGE is associated with a 2.3-fold increased risk of SCD/SCD equivalents and a 2.1-fold increase in all-cause mortality75. Accordingly, it has been suggested that the addition of LGE to the current AHA/ACC SCD algorithm or the ESC's

HCM-SCD risk model improves stratification of patients who are otherwise considered low or intermediate risk76.

However, the selection bias of some retrospective studies still limits LGE's value as a robust and independent SCD risk factor. The ESC guidelines suggest first estimating SCD risk using the HCM-SCD Risk calculator. For patients in low or intermediate risk categories, the presence of extensive LGE (≥15%)1 can be used when indications for primary-prevention ICDs are being discussed with patients/guardians. However, for a number of technical reasons, the accurate quantification of LGE in HCM remains challenging.

Though LGE-CMR has been considered the gold standard for non-invasive assessment of fibrosis, it underestimates the severity and distribution of myocardial fibrosis (especially the diffuse interstitial type) 77. In addition, LGE does not always represent myocardial fibrosis (e.g. immediately following myocardial infarction), and should be considered as a surrogate marker of fibrosis.

New methods for myocardial tissue characterization include T1 mapping, a tool that allows direct signal quantification on a standardized scale for each myocardial voxel. T1 mapping overcomes some of the limitations associated with LGE's and permits an estimate of the extracellular volume fraction. The diagnostic and prognostic utility of T1 mapping (and also of T2 mapping, increased in some patients) in HCM remains a subject of intense research interest 78-81 (Figure 4).

The capacity of CMR to assess areas of macroscopic myocardial scar, regions with diffuse fibrotic interstitial expansion, interstitial oedema, cellular oedema, iron deposition, accumulation of amyloid protein, and intramyocardial fat, among others,

provides useful information in the diagnosis and in the differential diagnosis with phenocopies.

3.3. Systolic function

LV ejection fraction (LVEF) serves as a suboptimal measure of systolic function in patients with LV hypertrophy 82. LVEF often appears normal or supranormal in patients with HCM due to increased circumferential contractility, even at later stages of the disease. Additionally, due to the small dimensions of the LV cavity, these patients often have a decreased stroke volume and cardiac output (Figure 4). LV longitudinal function is often abnormal, even at the initial stages of the disease; this can be detected by reduced longitudinal strain 83,84 using speckle-tracking echo (STE) or feature-tracking CMR 85. The assessment of global longitudinal strain (GLS) is important in HCM. It may be useful in the early diagnosis of disease (early phenotypes may show abnormal GLS) and in the detection of early systolic dysfunction. Moreover, GLS may play a role in risk stratification (more abnormal GLS associated with worse clinical outcomes) and in the prediction of evolution to overt dysfunction stages with severe systolic dysfunction 83,84. The role of GLS as an independent risk factor for SCD is still in debate 83-85. It may also prove useful in the assessment of the effects of different therapeutic modalities in this disease 83-85.

Due to the relatively late development of impairment of LVEF in progressive HCM disease (and to the typically high EF characteristic of early stages), findings of systolic dysfunction with LVEF <50% or adverse LV remodelling with ventricular cavity enlargement are considered representative of advanced impairment of systolic function.

Further deterioration with scar-related wall thinning may represent end-stage ("burnout") HCM with increased risks for heart failure related death and of lethal ventricular tachyarrhythmias.

Myocardial work, as assessed by echocardiography, is a new research tool for assessing myocardial function. As it incorporates afterload (blood pressure), it is less load-dependent than myocardial strain and has been increasingly used in non-obstructive and apical HCM 86. In these patients, this tool reports reduced myocardial work index, constructive work and cardiac efficiency, and increased wasted work 86 (Figure 5). The potential clinical applications of myocardial work in HCM include the assessment of disease severity, risk stratification, prognostication, differential diagnosis with phenocopies, such as amyloidosis, and evaluation of the effectiveness of therapeutic interventions. In obstructive forms, afterload quantification is more challenging because blood pressure alone does not include the afterload component due to intraventricular obstruction. Accordingly, current research focuses on quantification and a proposed formula for afterload is: systolic blood pressure + [max LVOTO gradient + mean LVOT gradient)/2]87.

3.4. Diastolic function

Some patients with non-obstructive HCM develop heart failure symptoms despite preserved LV ejection fraction, and this is often attributed abnormal diastolic function. Diastolic dysfunction in HCM patients may result from impaired or delayed LV relaxation and/or reduced chamber compliance (increased stiffness). In some cases, abnormal atrial contractile function contributes to impaired ventricular filling. Echo is the standard approach to diagnose and identify abnormally elevated LV filling pressures. According

to the European Association of Cardiovascular Imaging 2,88 (EACVI)/American Society of Echocardiography (ASE) recommendations, the integrated four-criteria approach to assessing high LV filling pressures in HCM is as follows: 1. E/e′ ≥ 10; 2. Time difference between the duration of atrial reverse wave of the pulmonary venous flow Ar and the duration of the transmitral A wave (Ar-A) ≥ 30 ms; 3. LA volume index ≥34ml/m^2; 4. Systolic pulmonary artery pressure >35 mmHg 1, Figure 6. Atrial strain, particularly left atrial (LA) reservoir strain, seems to be useful in the assessment of diastolic function in HCM and may be beneficial when the four-criteria approach is inconclusive 89, 90. A diastolic stress test with exercise echo may be used to clarify symptoms of dyspnoea and exercise intolerance. The inability to increase stroke volume (due to lack of diastolic reserve during exercise) results from the small and stiff ventricle's incapacity to accommodate the increased venous return from exercising muscles. In some patients, this limitation may only become apparent during exercise 91- 93.

CMR's value in providing complementary information with techniques such as transmitral and pulmonary venous velocities, LV and LA strain, and T1/ECV mapping is increasingly recognized 29.

3.5. Mitral valve

Primary mitral valve abnormalities, including of the subvalvular apparatus, are common in patients with HCM 1,2, and can contribute to developing systolic anterior motion (SAM) of the mitral valve, leading to dynamic LV outflow tract obstruction.

Remarkably, more than half of HCM patients have abnormal mitral leaflets, and more than one quarter have abnormal chordae and papillary muscles (PM) 1,2. These abnormalities include leaflet elongation with abnormal leaflet length (> 3.5mm) with excessive tissue, dysplasia and prolapse, and chordal elongation, laxity and hypermobility. In some patients, leaflets and chordae length are increased in absolute terms (length exceeding age, sex, and body size matched controls by 2 SDs), as a primary phenotypic expression of the disease; in other patients, leaflets and chordae are normal sized but are too large relative to the small LV cavity and LVOT size, also contributing to obstruction. 1,2

PM abnormalities include hypertrophy, bifidity, anterior/apical displacement, and direct insertion into the anterior mitral valve leaflet. 1,2

The imaging report should include a precise description of these variations, as they may determine the options available for septal reduction therapy (Figure 7).

Because the anterior leaflet is usually longer than the posterior leaflet, an interleaflet gap often occurs during mitral SAM, resulting in a posteriorly directed jet of SAM-related mitral MR. 94,95 Organic mitral valve disease should be excluded if the MR jet is anterior and/or central. 94,95

3.6. Intraventricular obstruction

Obstruction in HCM may occur at the LVOT (LVOTO) or at the mid-LV cavity (LVMCO), and echo is the first-line technique to assess it 2. The imaging report should provide the description, mechanism, magnitude and anatomical level of obstruction. LVOTO is defined by the presence of a peak gradient higher than 30 mmHg at rest; after provocation, a peak gradient > 50 mmHg is defined as clinically significant. LVOTO at

rest is present in about one-third of symptomatic HCM patients. In another third, LVOTO only develops after provocative manoeuvres. The most widely accepted explanation for LVOTO is the presence of interventricular septal (IVS) wall thickening with narrowing of the LVOT with Venturi effect (creating a low-pressure zone in the narrowed LVOT which can draw the mitral valve leaflets towards the septum, contributing to obstruction) in addition to dragging forces pushing the mitral valve anteriorly (SAM), towards the interventricular septum. Mitral valve abnormalities contribute to developing SAM and LVOTO. According to loading conditions and contractility status, LVOTO at rest and following provocation can appear to vary spontaneously 1,2. Three-dimensional echocardiography may also provide incremental information on the pathophysiology of obstruction1,2.

LVOTO usually causes aortic valve mid-systolic partial closure and mitral SAM with septal contact, posteriorly directed MR and turbulent colour Doppler flow in the LVOT. The severity of obstruction is quantified with continuous wave Doppler (CWD), from the apical 5-chamber view. The typical morphological appearance of the Doppler envelope in LVOTO is a ‘dagger-shaped’ and late-peaking curve during systole (Figure 8, Figure 9). Care should be taken to avoid contamination of the LVOTO velocity with the MR jet, particularly during exercise echo; the MR jet’s velocity will result in a significant overestimation of the magnitude of LVOTO gradient. The exclusion of fixed causes of LVOTO is mandatory (subaortic membrane, valvular and supravalvular stenosis); notably, these can co-exist with dynamic SAM-related LVOTO.

The assessment should be performed under resting conditions, ideally after food ingestion, when gradients become higher 96. If no obstruction is detected at rest,

bedside provocative manoeuvres (Valsalva, standing) should be performed. If clinical suspicion of obstruction remains despite negative bedside provocative manoeuvres (i.e. fails to induce LVOTO of at least 50 mmHg), an exercise echo is indicated. In asymptomatic patients, an exercise echo may also be considered when an LVOT gradient is relevant to lifestyle advice and decisions on medical treatment (Figure 10). 1,2 Accordingly, the exercise echo using treadmill or bicycle exercise is important in detecting labile or inducible obstruction in HCM. The assessment should be taken at baseline, during exercise and at the beginning of the recovery period, when preload abruptly decreases, increasing LVOTO 2. Exercise echo can be combined with ergospirometry and is feasible, safe, and physiological (mimicking real-life load conditions), allowing the clinical integration of assessments of obstruction, exercise tolerance, symptoms, blood pressure, and arrhythmia.

Additionally, exercise echo-provocable gradients can be helpful in clinical practice to support the diagnosis of HCM in individuals with a familial history of HCM and doubtful/borderline but non-diagnostic resting echo1,2.

Dobutamine as a provocative test is not indicated as it may induce non-physiological LVOT obstruction even in normal hearts. 1,2

LVMCO is less frequent than LVOTO. LVMCO occurs during LV ejection due to partial or complete systolic obliteration that divides the LV cavity into basal and apical portions. Hyperdynamic radial contractility and a focal narrowing of the LV cavity (often due to papillary muscle hypertrophy/displacement) form a constricting muscular ring at the point of the dynamic cavity division. High intracavitary pressure gradients can form across the mid-cavity obstruction, and an apical LV aneurysm may develop and

progressively enlarge. Larger LV apical aneurysms with scars are associated with increased risks of HF, ventricular arrhythmia and thromboembolic events 1,2.

In the presence of LVMCO, the LV chamber is typically 'hourglass-shaped' and apical aneurysms are common. Echo colour Doppler often shows aliasing in the sequestered apical area and a paradoxical early diastolic gradient directed from apex-to-base is often seen 97. Contrast echo may also be important in these patients to improve visualization of apical aneurysms, and longitudinal strain with STE is often abnormal in the apical segments (Figure 11, Figure 12).

In contrast to LVOTO, LVMCO can be associated with a complete cessation of flow across the obstructive component; accordingly, Doppler-derived assessments may severely underestimate the magnitude of the obstructive gradient. In such cases, a characteristic 'lobster-claw' envelope 98 often evident on Doppler interrogation of the apical LV. Invasive approaches to measure intracavitary pressures are needed if accurate estimates of LVMCO magnitude are needed1,2.

When an LV aneurysm is present, CMR sub-endocardial or transmural LGE is often detected in the walls of the aneurysmal apex, and LV thrombus may be seen on early and LGE. Stress perfusion imaging often demonstrates profound perfusion defects that are localized to the obliterating muscular neck of the LV aneurysm 99.

Sustained monomorphic VT is rare in HCM, and its detection should raise suspicions of an apical LV aneurysm with a fibrotic aneurysmal neck comprising a substrate for reentry 1,2.

3.7. Beyond the LV: the left atrium and the right ventricle

LA remodelling in HCM includes dilatation and dysfunction (Figure 13). As measured by echo an LA antero-posterior dimension (LA-AP)> 45mm, an LA volume index of 37ml/m^2, and a LA reservoir strain <23% have been associated with new-onset AF, with success and recurrence after electrical cardioversion and/or after ablation, and with outcomes 90. LA diameter is a component of the ESC HCM risk calculator. LA strain analysis by CMR is also predictive of adverse clinical events 100.

The RV MWT should also be measured, as it may be increased as part of the disease or phenocopy spectrum or a consequence of pulmonary hypertension. Normal RV MWT is 5 mm in subcostal or parasternal long-axis views at end-diastole, at the level of the tricuspid chordae. Including epicardial fat in the measurement of the RV-free MWT is a common cause of false RV hypertrophy on echocardiography, not on CMR. The presence of RV hypertrophy was independently related to the presence of ventricular arrhythmias 101.

4. Advanced imaging techniques not required in every baseline assessment

4.1. Ischaemia imaging techniques

Patients with HCM are susceptible to myocardial ischaemia, even in the absence of epicardial coronary artery disease, as a reduction in coronary vasodilator reserve in hypertrophied and non-hypertrophied LV segments is commonly seen 102-104. This microvascular dysfunction is multifactorial, including reduced capillary density, vascular remodelling with arteriolar medial hypertrophy and intimal hyperplasia, fibrosis, microstructural changes and myocyte disarray, extravascular compression due to LV

wall thickening, myocardial bridging, diastolic dysfunction, delayed myocardial relaxation, and LVOTO105,106.

HCM patients with identified sarcomere variants have more severe microvascular dysfunction than G- patients. 107,108 Microvascular dysfunction may also be seen in G+ individuals without LV wall thickening 108, constituting an early, non-hypertrophic phenotype biomarker.

Once obstructive epicardial coronary artery disease is excluded by an anatomical test, ideally CCT 2, microvascular dysfunction can be assessed by functional imaging (Echo, CMR, or positron emission tomography (PET)) or invasive microvascular measurements 109.

By Echo, the coronary flow velocity reserve may be assessed after adenosine-induced hyperaemia when image quality is sufficient. Coronary flow velocities are measured in the left anterior descending artery and the posterior descending artery at rest and during hyperaemia. Coronary flow velocity reserve is calculated as the hyperaemic to rest peak diastolic flow velocities ratio. HCM patients, particularly those with LVOTO, may have higher diastolic coronary flow velocities at rest and lower coronary flow velocity reserve after adenosine, showing that vasodilatory reserve is almost completely exhausted in basal conditions 110. Impaired coronary flow velocity reserve is associated with worse biventricular systolic performance and functional capacity assessed by peak VO_2 111.

CMR perfusion imaging using vasodilator pharmacological stress, most commonly with intravenous regadenoson or adenosine, also evaluates ischaemia (Figure 14). Stress myocardial blood flow is lower in the most hypertrophied and fibrotic segments, but

myocardial segments without LV hypertrophy or LGE may also have impaired perfusion 112,113. Furthermore, apical perfusion defects are universally present in apical HCM at all stages of disease 114. In HCM patients, ischaemia correlates with tissue abnormalities detected by parametric mapping and LV systolic function assessed by strain and myocardial work 115.

PET determines the absolute quantitative myocardial blood flow at rest and during hyperaemic vasodilation with subsequent myocardial flow reserve derivation 116. Studies using PET in HCM patients demonstrated that severe microvascular dysfunction is a long-term predictor of LV remodelling and systolic dysfunction, clinical deterioration and death 117,118.

4.2. Emerging techniques: When and how to image metabolism, microstructure, myocardial receptors and innervation

Although still limited to research applications and expert centres, molecular imaging to explore metabolism or biological pathways offers exciting perspectives that will require clinical validation in managing HCM. Most progress in this field has been made with PET and CMR or hybrid PET-CMR imaging.

^{31}P-nuclear MR spectroscopy has demonstrated and quantified the decline in the ratio of myocardial phosphocreatine (precursor of adenosine triphosphate) to adenosine triphosphate that accompanies LV wall thickening in HCM patients with or without variants in sarcomere protein genes, regardless of the degree of LV wall thickening and the presence of LVOTO 119-121. The hypothesis of a pathophysiological role for

energy deficiency in the progression of HCM has prompted several unsuccessful therapeutic trials 122 despite encouraging preliminary results on functional capacity123.

Cardiac MR diffusion tensor imaging is emerging as a technique to assess myocardial microstructure 124. Initial studies demonstrate the potential clinical utility in differentiating types of hypertrophy125, identifying early abnormalities in G+P- HCM patients 126 and detecting myocardial microstructural changes potentially predictive of arrhythmias 127.

Cardiac nuclear imaging, with its ability to image different biological pathways using different radiotracers, plays an essential role in molecular imaging. The concept is based on coupling a tracer specific to a metabolic target and a radioelement for imaging it (Table 5).

As described with the ^{31}P-nuclear magnetic resonance spectroscopy, abnormalities in energy metabolism have a vital role in the pathophysiology of HCM. The myocardium metabolizes various substrates, among which free fatty acids and glucose are the primary energy sources. In HCM, structural abnormalities within the myocardium can lead to a switch from free fatty acid to carbohydrate metabolism. Various nuclear tracers can be used to explore these metabolic changes. ^{18}F-fluorodeoxyglucose and ^{11}C-acetate PET imaging can assess myocardial carbohydrate 128 and oxidative 129 metabolism. Fatty-acid imaging using ^{123}I-betamethyl-p-iodophenylpentadecanoic acid single photon-emission computed tomography (SPECT) is one of the most sensitive techniques to assess metabolic changes induced by microvascular dysfunction in HCM 130,131.

Another aspect of molecular imaging made possible by cardiac nuclear imaging is the exploration of myocardial sympathetic innervation. The changes in sympathetic tone accompanying HCM result in impaired neurotransmitter reuptake, leading to increased local myocardial catecholamine levels despite normal plasmatic catecholamine concentrations. In terms of imaging, this local increase in catecholamine levels leads to a decrease in the density of sympathetic nervous system receptors, which correlates with disease progression and can be explored by hydrophilic beta-adrenoceptor antagonist ^{11}C-(S)-CGP-12177 labelled with carbon-11 [(S)-^{11}C]CGP-12177] 132 or ^{11}C-hydroxyephedrine PET imaging 133, or ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) SPECT imaging 134,135. In clinical practice, cardiac sympathetic nerve activity assessed by ^{123}I-MIBG-SPECT imaging in HCM is associated with reduced exercise reserve 136 and increased risk of malignant arrhythmias137.

The latest advances in HCM molecular imaging are made in exploring fibroblast activation within the myocardium using ^{18}F and ^{68}Ga -labelled fibroblast activation protein inhibitor (FAPI) PET imaging, which could help assess the role of these cells in the pathogenesis of HCM and help stratify a patient's arrhythmic risk138,139.

5. Imaging beyond diagnosis of the index case

5.1. Family screening

All first-degree relatives of patients with HCM should be offered screening 1,140,141. Asymptomatic first-degree relatives of an HCM patient in whom a pathogenic or likely pathogenic genetic variant has been identified, can be offered predictive genetic testing, with electrocardiography (ECG) and cardiac imaging undertaken if they carry the

disease-causing variant. If the HCM proband has a negative genetic test (or if it is refused or unavailable), clinical screening (ECG and imaging) of first-degree relatives should be offered 1,34, 140.

Echo is the first-line imaging method to screen family members of patients with HCM 2,141. CMR should be considered in technically challenging and inconclusive echocardiograms, as well as in patients with abnormal ECG findings and an apparently normal echo142,143. A lower cut-off value of LV MWT (13 mm) is diagnostic in family members of patients with HCM or carriers of pathogenic variants144 -146. When recognized, early non-hypertrophic phenotypes may warrant shorter screening intervals.

5.2 Risk stratification and prognosis

The European and North American guidelines recommend using several imaging parameters to estimate the risk for SCD in HCM, helping determine indications for primary-prevention implantable cardioverter-defibrillator (ICD) therapy 1,12 Both echo and CMR should be performed during the initial evaluation and follow-up.

The 2023 ESC guidelines in cardiomyopathies recommend the HCM Risk-SCD model for patients aged ≥16 years and the HCM Risk-Kids tool for children and adolescents <16 years to guide the implantation of a primary prevention ICD 1 . Both ESC calculators include MWT (usually derived from TTE or CMR), maximum LA-AP and peak LVOT gradient.

In patients in the low and intermediate HCM Risk-SCD risk category (estimated 5-year risk of SCD <6%), additional imaging parameters may be used as risk modifiers in shared decision-making about primary prevention ICD implantation: extensive LGE (≥15%) on CMR, presence of apical aneurysm with fibrosis and LV systolic dysfunction (LVEF <50%) (Table 6, Figure 15**).**

The North American guidelines recognize the importance of individual risk factors in a binary way12. A MWT ≥30 mm in any segment, the presence of LV apical aneurysm with fibrosis and an LVEF <50% are considered major risk factors warranting prophylactic ICD implantation. The presence of extensive LGE may serve as an additional risk marker, albeit with a lower class of recommendation (Table 6; Figure 15).

The ESC risk estimate calculators can be used as an additional tool during shared decision-making to help patients better understand the magnitude of their risk. While most centres in Europe follow ESC guidelines and use a 5-year HCM Risk-SCD score to guide ICD therapy, other centres use risk assessment strategies based on individual risk factors 147.

A few unresolved issues remain with the currently recommended imaging parameters for the SCD risk stratification. No consensus has been reached regarding the optimal method to quantify LGE on CMR. While 4 and 5 standard deviation techniques yield the

closest approximation to the extent of total myocardial fibrosis measured by the histopathological standard of reference 6, most studies employed a 6 standard deviation technique 148, 149, showing best agreement with visual assessment of LGE in patients with HCM 150. Furthermore, a meta-analysis 151 of 11 studies with 5500 patients suggested a lower LGE threshold (10% of LV mass) to be optimal in risk stratification of HCM patients. In patients with an apical aneurysm, it was recently suggested 152 that the aneurysm's size was the primary determinant of prognosis, and a threshold size ≥2 cm was proposed as an indication for a primary prevention ICD. Moreover, additional imaging biomarkers have shown an association with arrhythmic adverse events, such as Echo-derived GLS 153 -155, CMR feature tracking strain 156, and T1 mapping157; however, their role as predictors to guide SCD therapy needs to be further elucidated. SCD in G+, P- individuals is rare, and risk stratification of SCD can be omitted in patients without manifest disease.158

5.3. Treatment monitoring

MMI plays an important role in monitoring the treatment of patients with LVOTO. Novel cardiac myosin inhibitors (CMIs) are advised according to the 2023 ESC guidelines in cardiomyopathies as a second-line medical therapy in this group of patients 1. Since CMIs act by reducing actin-myosin cross-bridge formation and LV contractility, close

monitoring of LV systolic function is mandated during drug administration, dose titration, and maintenance treatment. In trials, LVEF ≥55% and LVEF ≥60% were a prerequisite for initiating treatment with the CMIs mavacamten and aficamten, respectively159,160. A fall in LVEF <50% requires temporary or permanent discontinuation of the CMI. Echo is the most suitable imaging technique for treatment monitoring, but CMR can be used if echocardiography is not feasible. Additionally, CMR enables a comprehensive assessment of LA and LV remodelling resulting from CMIs161,162.

Patients with LVOTO who remain symptomatic despite optimal medical treatment or who do not tolerate medical therapy are candidates for septal reduction therapies, either surgical myectomy (+/- concomitant mitral valve surgery) or alcohol septal ablation (Figure 16, Figure 17). Transoesophageal echocardiography (TOE), CMR and CCT provide detailed anatomical and pathophysiological information on the mechanism of LVOT obstruction and influence the choice of procedure 1, 2. Further details can be found in our 2015 EACVI HCM position statement 2. Periprocedural monitoring is mandatory during cardiac surgery (with TOE) and alcohol septal ablation (with TTE or TOE). An improved procedure outcome has been demonstrated when myocardial contrast echo is used to select optimum septal vessel(s) for alcohol septal ablation134. For patients who have undergone septal reduction therapies, TTE within 1-3 months after the procedure according to the European 1 and within 3 to 6 months according to the American guidelines 12 is recommended to evaluate the procedural results, particularly the evidence of septal thinning and LVOT gradient decrease. CMR may also

be performed after the procedure to assess the extent of scar and precise MWT measurements.

Management of symptomatic HCM patients with other clinical profiles focuses on the prevention of SCD and on the treatment of AF, HFpEF and HFrEF. The role of imaging to monitor treatment of these patients should follow appropriate guidelines163-166.

5.4. Follow-up

Patients with HCM require lifelong follow-up with imaging to detect changes in the degree of LV wall thickening, myocardial function, dynamic LVOTO and other factors that influence clinical management, including re-stratification for SCD risk. The frequency of monitoring is determined by patient age and the severity of the disease, including symptoms and the potential for a meaningful change in risk status (regarding AF, HF and SCD) over time.

In patients with HCM who have no change in clinical status or events, repeat TTE is recommended by the 2023 ESC guidelines in cardiomyopathies every 1 to 2 years 1. In patients who remain clinically stable after multiple evaluations, the follow-up interval may be extended. In contrast, in patients who experience a change in clinical status or a new clinical event, TTE should be performed sooner. Repeat CMR also is advised every 2-5 years, or more frequently in patients with progressive disease, particularly for SCD risk stratification, patients with borderline AF risk and understanding the cause of symptoms1. In individuals who are G+, P-, repeat screening is advised (Echo +/- CMR) according to the 2023 ESC guidelines in cardiomyopathies .

The ESC guidelines 1 state that these individuals should be screened with ECG and echo from childhood to old age, every 1–3 years before 60 years, and after 60 years old every 3–5 years. The North American guidelines recommend follow-up every 1-2 years in children and adolescents and every 3-5 years in adults, at least until 50 years of age12.

6. Imaging diagnosis of HCM phenocopies

Echo and CMR have important roles in the differential diagnosis of different hypertrophic diseases (Figure 18) and specific red flags pointing to specific phenocopies are known.167

Several genetic or acquired diseases can mimic HCM 168. The most common HCM phenocopies include hypertensive cardiomyopathy, athlete's heart, cardiac amyloidosis, Anderson-Fabry disease and Danon disease. More recently, reports describe the potential for intraventricular obstruction in Takotsubo syndrome 169, 170.

In hypertensive heart disease, concentric LV remodelling or hypertrophy (usually with MWT below 16 mm) is seen, with preserved LVEF until the late stages. Speckle tracking echo reveals an early reduction of GLS, with an initial compensatory torsion improvement and increased myocardial work-derived global work index171. A variable degree of diastolic dysfunction may be associated with abnormal LA strain and increased LV filling pressures. Aortic root, ascending aorta dilatation, and aortic valve calcifications are also common. CMR is not routinely advised in hypertensive patients. However, LGE may be present in these patients, correlating with the degree of diastolic dysfunction and associated with normal or mildly increased myocardial T1 172.

Athlete's heart hypertrophy in the grey zone is usually combined with a balanced dilatation of all cardiac chambers and normal or supranormal diastolic function and normal or low normal LVEF. CMR shows no LGE in most athletes, although it can be observed in the (inferior) RV insertion points, where it is associated with normal or low T1 and ECV values 173,174.

In cardiac amyloidosis (Figure 19), the echo assessment shows-elevated LV filling pressures, biatrial dilatation and progressively normal-to-abnormal systolic function. GLS is often characterized by the preservation of apical longitudinal deformation compared to the mid- and basal segments (so-called "apical sparing"). Whilst this has been considered a pathognomonic finding in cardiac amyloidosis for a long time, the specificity and sensitivity of apical sparing, calculated as the ratio of longitudinal strain in apical/basal + mid LV segments 175 may not be as high as previously thought, as in patients with other causes of LV hypertrophy and even in some control subjects the apical sparing phenomenon can be present. A LVEF/GLS ratio > 4.1 seems to be a more accurate screening tool for CA 175.

In these patients, the interatrial septum and mitral and aortic valve leaflets are frequently thickened, and a small pericardial effusion can occur. LGE-CMR often shows a diffuse subendocardial pattern, though transmural LGE, more suggestive of transthyretin amyloidosis, can also be found 175. A significant increase of myocardial T1 suggests cardiac amyloidosis. Bone scintigraphy and SPECT with ^{99}mTc-labeled radiotracers, among other tracers 176, have high specificity and sensitivity for diagnosing transthyretin amyloidosis.

In Anderson-Fabry disease, there are no pathognomonic echocardiographic findings, but concentric LV hypertrophy, also involving papillary muscles, RV hypertrophy and preserved EF, are common imaging presentations. Speckle tracking echo analysis reveals a selective reduction of regional longitudinal strain in the basal inferolateral wall, where LGE is often present on CMR (Figure 20). Contrary to cardiac amyloidosis, myocardial T1 is diffusely decreased but may appear pseudonormal in inferolateral areas of LGE177,178. In the inflammatory stages of the disease, T2 values on maps are increased179.

In Danon's disease, LV hypertrophy is usually striking and concentric, often involving the RV free wall. However, female patients can present with dilated cardiomyopathy later in life compared to males because of different inactivation patterns of the X-chromosome180. Extensive LGE consistently sparing the mid-septum is a specific CMR pattern of Danon's disease181.

7. Future directions. The management and understanding of HCM have significantly advanced with the integration of MMI. Future directions in this evolving field are oriented towards technological advances and a deeper clinical understanding of the disease. This section outlines anticipated future directions that might revolutionize the imaging-informed management of HCM.

7.1. Genotype-imaging phenotype correlations Improvements in imaging across modalities such as echo and CMR are expected to allow for more detailed visualization of myocardial architecture, fibrosis and tissue characterization. Though HCM is often a genetic disorder, evidence correlating imaging phenotypes, disease severity, and

genotypes is largely inconclusive. Whilst G+ patients have a more severe phenotype 182,183 with more severe LV wall thickening and a greater myocardial scar burden and increased T1 than G- patients, robust correlations between specific gene variants and phenotypes remain elusive (Figure 21). A late disease penetrance in *MYBPC3* compared to *MYH7* 184 was identified in some studies, but not confirmed in others185,186. Lower MWT but greater arrhythmic risk were observed in *TNNT2*, only in early studies; a restrictive physiology in *TNNI3* 187 needs confirmation; multiple sarcomere variants were associated with a worse prognosis in some cohorts188 but not reported in others 189. Despite these contradictory results, the spread of CMR tissue characterization is generating growing interest in the correlation between imaging findings and genotype, such as a possible role of CMR as a gatekeeper for genetic tests and its role as a prognosticator for G+ P-individuals to predict progression into the classical disease phenotype.

7.2. Artificial intelligence in imaging of HCM Artificial Intelligence (AI) and machine learning algorithms are already enhancing the automation and accuracy of image analysis. This approach promises more efficient and consistent quantification of key HCM parameters such as LV wall thickness distribution and MWT measurements 190 fibrosis extent, and ventricular function. AI is becoming more widespread in CV imaging, including when applied to radiomics, the emerging research field using quantitative features extracted from medical images that are not visible to the human eye 191 -194. LGE-radiomics was recently demonstrated to provide incremental prognostic value to the current SCD risk prediction models in HCM 195. In parallel, safety concerns about the spreading use of gadolinium-based contrast agents (considering the patient´s young

age and serial CMR evaluations required) led investigators to use radiomics to try to extract information on myocardial scar from non-contrast MR sequences. Several demonstrated the possibility of using AI morphological and functional radiomic features to identify HCM patients without scar as a screening tool for gadolinium administration 196,197. A groundbreaking study demonstrates the potential to replace LGE with virtual native enhancement in HCM198.

Though all these studies witness that AI is promising to revolutionize HCM imaging, aiming to improve diagnosis, characterization, and prognosis of HCM, a word of caution is needed. As with any emerging research tool, additional work in large and high-quality datasets is still needed to refine its technical performance 199 and clinical usefulness in the HCM population before widespread dissemination.

7.3. New diagnostic criteria for HCM Despite significant advancements in this field, the recently published European and North American guidelines on HCM 1, 12 proposed diagnostic criteria largely unchanged over the past decades. However, recent evidence suggests that the “one size fits all” criteria for the diagnosis of HCM (the 15 mm criteria) should be complemented in the future by fine-tuned criteria, considering wall thickness indexed to factors such as body habitus, age, sex or race 53. Apical HCM represents one of the most challenging forms to diagnose, as wall thickness in this region rarely exceeds 15mm even in established cases. Since the early 2000s, several studies highlighted the limitations of conventional criteria, introducing the concept of relative hypertrophy and of the apex-to-base ratio to diagnose apical HCM, describing the association of loss of apical tapering) and of a reduced apical angle with other

pathological features (T wave inversion on ECG, apical obliteration, apical aneurysm, and scarring on CMR) 199-204.

A new approach promises to revolutionize the current HCM criteria. In healthy volunteers, LV wall thickness was measured in short axis in each of the 16 LV segments and indexed to body surface area. The limit of normal was defined by mean ±3 SD. This group showed that apical thickness is dependent on body surface area but not on age and sex and defined the upper limit of the normality in apical segments to be 5.2-5.6 mm/m^2 205, 206.This approach will be extended to other LV segments, considering the influence of body surface area, sex and race on MWT (Figure 22) 18. These new criteria may significantly improve diagnostic accuracy compared to previously proposed criteria, but further work is required to see if the new criteria prove overly sensitive and whether they result in improvements in the clinical management of HCM206.

Myocardial shear wave imaging by echocardiography utilizing ultra-high frame rates, might also have a potential future role in evaluating the myocardial stiffness in HCM, but the technique needs more studies to understand its full potential 207.

7.4. Imaging registries and biobank in HCM

In cardiomyopathies, the spread of multicentre registries containing imaging, genetic and clinical data gained fundamental importance in promoting research initiatives.

The Sarcomeric Human Cardiomyopathy Registry is an international consortium of several world-leading centres that maintain longitudinal databases with phenotypic, genetic, and clinical outcomes data on patients with HCM and their families 13.

The UK Biobank is a population-based, prospective cohort study that enrolled 500,000 individuals aged 40 to 69 years, containing data collection on genotyping, clinical features and multimodal imaging. Despite not being an HCM disease cohort, UK Biobank has produced new insights relevant to this disease 208,209.

Collaborative, multi-centre research efforts are essential to validate emerging imaging biomarkers and technologies. Longitudinal studies tracking the natural progression of HCM using MMI can provide invaluable insights into disease mechanisms and predictors of adverse outcomes.

Integrating data from wearable devices monitoring physical activity, heart rate, and arrhythmias with imaging findings could offer a more holistic view of the disease's impact on patient lifestyle and health, possibly guiding therapeutic decisions.

8. Conclusion

The future of MMI in HCM is promising, with expected advancements poised to significantly enhance our ability to diagnose, monitor, and treat this complex condition. Continued innovation, along with collaborative research efforts, will be essential in realizing the full potential of these emerging technologies and filling current gaps in evidence (Box 5).

Data Availability Statement

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

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LEGENDS

GRAPHICAL ABSTRACT LEGEND

Legend- This figure summarizes the key roles of echocardiography (Echo), cardiac magnetic resonance (CMR), computed tomography (CT), and nuclear imaging in the assessment and management of hypertrophic cardiomyopathy (HCM). Key HCM characteristics that should be assessed in all patients with a working diagnosis of HCM are featured on the right side, with illustrative examples from echocardiography and CMR. The colour coding transitions from lilac to magenta, indicating features that

may be characterized by both Echo and CMR (providing complementary or overlapping information). Magenta highlights tissue characterization, which is primarily described using CMR, whereas lilac is used for diastolic function, reflecting its primary assessment via echocardiography in clinical routine.

Abbreviations

Ar: Atrial reversal (in pulmonary vein flow); ASA: Alcohol septal ablation; CMR: Cardiac magnetic resonance; CT: Computed tomography; CWD: Continuous-wave Doppler; ECV: Extracellular volume; E/e′: Ratio of early transmitral flow velocity (E) to early diastolic mitral annular velocity (e'); Echo: Echocardiography; GLS: Global longitudinal strain; HCM: Hypertrophic cardiomyopathy; LAVI: Left atrial volume index; LGE: Late gadolinium enhancement; LV: Left ventricle; LVEF: Left ventricular ejection fraction; LVOTO: Left ventricular outflow tract obstruction; LVMCO: Left ventricular mid-cavity obstruction; MR: Mitral regurgitation; MWT: Maximum wall thickness; SAM: Systolic anterior motion; T1: T1 mapping value depicting longitudinal relaxation time "

FIGURE LEGENDS

Figure 1: The natural history of hypertrophic cardiomyopathy. Morphological and functional abnormalities in the different disease stages. ECV- extracellular volume; LGE-late gadolinium enhancement; LV-left ventricle; LVOTO-left ventricular outflow tract obstruction

Figure 2: Hypertrophic cardiomyopathy, overt dysfunction stage, restrictive type. **Top**: Reduced systolic function A- Tissue Doppler imaging of the mitral annulus with low s'; B-low LVEF and GLS. **Bottom:** C-non dilated hypertrophic LV and atrial and annular dilatation with secondary mitral and tricuspid regurgitation. D- severely depressed left atrial reservoir strain function (S_R 10%).

Figure 3: LV wall thickness measurement in hypertrophic cardiomyopathy. Complementary roles of echocardiography and cardiac magnetic resonance. The Maximal wall thickness is ideally measured with 2D (bidimensional) echocardiography at end-diastole in the parasternal long- or, preferably, short-axis views. A- Bidimensional echocardiography (arrows show the limits of the interventricular septum) B- Cardiac

magnetic resonance provides a more precise measurement (red arrow shows the limits of the anterior interventricular septum).

C- Bidimensional echocardiography: inclusion of RV structures (white arrow) should be avoided. The limits of the interventricular septum are depicted (yellow arrows).

D- Even in the current era of high-definition 2D linear measurements, in the real- world, M-mode may still play a role in some HCM patients, because of the high temporal resolution of this modality. Additionally, in some patients with sub-optimal acoustic windows, M-mode, though not the first option, may still be important, but the assessment needs expertise. M-mode echocardiography: inclusion of mitral and tricuspid chordae should be avoided (white arrows). The correct limits of the interventricular septum are depicted (yellow arrows) without LV and RV chordae.

Figure 4: CMR tissue characterization in hypertrophic cardiomyopathy.

A- Intramural late gadolinium enhancement (red arrow) and late gadolinium enhancement at the level of the RV/LV insertion points (yellow arrows). B- Native T1 mapping (E) showing prolonged T1 values. C- Increased extracellular volume (ECV) D- CMR subendocardial late gadolinium enhancement (arrows) in 4 chambers. E- CMR subendocardial late gadolinium enhancement in 2 chambers. F-CMR subendocardial late gadolinium enhancement in short axis.

Figure 5: Systolic function in non-obstructive hypertrophic cardiomyopathy, echocardiographic assessment. A-Preserved Simpson´s biplane LVEF 56%. B-Low indexed stroke volume, 30 ml/m^2. C- Abnormal GLS- 8%, and increased mechanical dispersion, 183 msec. D, E, F- Myocardial work assessment (blood pressure 140/100 mmHg). D- reduced myocardial work efficiency (68%). E- Abnormal myocardial work index (688 mmHg%) F- Reduced constructive work (1313 mmHg%) and increased wasted work (600 mmHg%)

Figure 6: Diastolic function in non-obstructive hypertrophic cardiomyopathy, echocardiographic assessment. All the parameters suggest increased LV filling pressures. **A- Triphasic mitral inflow pattern, with E/A>1 with L wave (arrow). B-**

Tissue Doppler imaging of the lateral mitral annulus with low e' (6 cm/s) and E/e'= 20. C- LAVI >34ml/$m^{2.}$ D- Prolonged pulmonary vein Ar duration (more than 30 ms of the transmitral A duration). E- Tricuspid regurgitation velocity > 2.8m/s). F- decreased left atrial strain during the reservoir phase (S_R), 11%

Figure 7: CMR cine still images showcasing different aspects of the mitral valve apparatus in hypertrophic cardiomyopathy. A, B, C, D: Apical displacement and hypertrophy of the posteromedial papillary muscle, contributing (A, B, C-yellow arrows) or not (D-green arrow) to LV mid-cavity obstruction. E-False tendon with insertion in the basal anterior wall (blue arrow). F-Bifid papillary muscles (red arrow). G- basal short – axis, no papillary muscles are seen. H , I, J, K, L- Multiple, "all around" papillary muscles, some of them hypertrophic (white arrows)

Figure 8: Echocardiography showing left ventricular outflow tract obstruction at rest in hypertrophic cardiomyopathy. A- Asymmetric septal hypertrophy with maximal wall thickness of 19 mm and mild to moderate hypertrophy of the remaining segments. B-Colour aliasing in the LV outflow tract and systolic anterior motion (SAM)-related, posterior and lateral mitral regurgitation with colour Doppler. C-M-mode complete SAM touching the interventricular septum in mid systole (arrow). D-SAM of the mitral valve in apical 3 chamber view. E- SAM-related mitral regurgitation with lateral and posterior jet. F- Typical "dagger-shaped" morphology of the left ventricular outflow tract Doppler envelope demonstrating obstruction.

Figure 9: Multimodality imaging of left ventricle outflow tract (LVOT) obstruction in hypertrophic cardiomyopathy. A-End-diastolic and B-end-systolic frame in the apical 3-chamber view on echo showing septal hypertrophy and systolic anterior motion (SAM) of the mitral valve. C-Colour Doppler in systole shows turbulent flow in the LVOT without any concomitant mitral valve regurgitation. D-CW Doppler at rest shows only a mild increase in velocity of 2.4 m/s (peak gradient 23 mmHg); D'- However, at Valsalva, there is a clear dagger-shaped pattern with a late systolic peak and a maximum velocity of 5.5 m/s (gradient 121 mmHg). E - 3-chamber view in diastole with cardiac CT. Cardiac CT is usually only indicated to assess morphology and function when CMR is contraindicated,

but this patient had concomitant CT for exclusion of epicardial coronary artery disease . F-Diastolic 3-chamber cine image with CMR showing the hypertrophy of the septum. G-During systole the SAM of the mitral valve was also visible with flow artefacts in the LVOT during systole (white arrow).

Figure 10: Hypertrophic cardiomyopathy and provocative manoeuvres in the assessment of left ventricular outflow tract obstruction (LVOTO). From left to right: A-Rest, B-Food ingestion, C- Standing D- Valsalva and E-exercise. Manoeuvres B, C, D and E may detect labile obstruction. Please see text for details.

Figure 11: Left ventricle mid-cavity obstruction with an apical aneurysm on echocardiography and CMR. A-End-diastolic and B-end-systolic frame in the apical 4 chamber view showing an 'hourglass-shaped' chamber. C-Colour Doppler in diastole and D- In systole, depicting the mid-ventricular velocity increase. E-CW Doppler with both systolic gradient (S) and early diastolic flow (EDF) up to 3.5 m/s (gradient 49 mmHg). "Paradoxical" EDF is often seen in patients with an apical aneurysm.

In the same patient, CMR was performed, showing the development of the aneurysm and late gadolinium enhancement (LGE) over time. The first CMR, 5 years ago, showed F-apical hypertrophy without aneurysm, and G- A spot of LGE (white arrow). A recent CMR shows H, I- an apical aneurysm on the cine images, and J- progression of LGE (J, white arrow). Note also the regional hypertrophy of the right ventricle apex. Based on these findings, an implantable cardioverter-defibrillator was inserted (see ICD lead in the right ventricle on echo images).

Figure 12-Multimodality imaging in left ventricle mid-cavity obstruction with an apical aneurysm (yellow arrows). A. Bidimensional echocardiography B. LV cavity opacification with contrast echocardiography; C. Cardiac Magnetic Resonance; D, E Computed tomography of the heart. F. Invasive ventriculography

Figure 13: Left atrium (LA) remodelling (morphologic and functional measurements) assessment in HCM: **Top:** Echocardiography: A- LA-AP (LA antero-posterior dimension), B- LAVI (LA volume indexed); C-LA strain . **Bottom:** Cardiac Magnetic Resonance, D, E-

LA volume during LV systole and diastole. F- linear dimensions, ejection fraction and strain.

Figure 14: 53-year-old male, with non-obstructive hypertrophic cardiomyopathy and exercise chest pain. Coronary angiogram documented the absence of epicardial coronary artery disease.

Top row-short-axis, from left to right A-basal, B-medial and C apical levels. No perfusion defects at rest.

Bottom row, short-axis, from left to right D-basal, E-medial and F-apical levels. Note the subendocardial circumferential perfusion defect on stress, in E-medial and F-apical segments (yellow arrows) not corresponding to any coronary artery distribution, typical of microvascular dysfunction.

Figure 15: Imaging parameters to estimate risk for sudden cardiac death. Echocardiography and cardiovascular magnetic resonance both play a key role in risk stratification. A-Maximum left ventricular wall thickness (MWT) in the basal anterior left ventricular (LV) segment. B- Left atrial (LA) diameter, measured in the parasternal long axis view. C-left ventricular outflow tract (LVOT) obstruction with peak LVOT gradient using pulsed wave Doppler echocardiography in the apical three chamber view. D-Reduced left ventricular ejection fraction (LVEF 49%). E-Left ventricular apical aneurysm in a patient with mid-LV cavity obstruction (arrow points at thrombus in the aneurysm); F-Extensive, yet subtle, late gadolinium enhancement (seen in hypertrophied apical segments, septum and LV lateral wall, as depicted by yellow arrowheads).

Figure 16 Important points to remember in the assessment of different treatment modalities in hypertrophic cardiomyopathy: cardiac myosin inhibitors, alcohol septal ablation and surgical myectomy

ECV- Extracellular volume; GLS- Global longitudinal strain; GCS – Global circumferential strain; LA – Left atrium; LAVI – Left atrium volume indexed; LGE – Late gadolinium enhancement; LVEF- Left ventricular ejection fraction; LVMI – Left ventricular mass index;

LVOT –Left ventricular outflow tract; MR- Mitral regurgitation; SAM- Systolic anterior motion; VSD- Ventricular septal defect

Figure 17: Imaging for treatment monitoring in hypertrophic cardiomyopathy (HCM) patients. **Top two rows**: pre- and post-myectomy in combination with mitral valve repair. End-diastolic and end-systolic 3 chamber cine CMR image. Left ventricular outflow tract (LVOT) obstruction with systolic anterior motion of the mitral valve and mitral regurgitation are clearly demonstrated prior to myectomy. **Third row**: a HCM patient following alcohol septal ablation with relative wall thinning of the basal septum that colocalizes with LGE on the short axis image. No residual LVOT obstruction at echocardiography. **Last row**: An HCM patient treated pharmacologically. The baseline LVOT gradient of 104 mmHg fell to 18 mmHg following treatment with a cardiac myosin inhibitor (CMI).

Figure 18: Left ventricular hypertrophy phenocopies and hypertrophic cardiomyopathy (HCM). **Top panel**: Speckle tracking echocardiography bull´s eye pattern: from left to right: a-HCM with asymmetrical septal hypertrophy. b) Apical HCM. C) Fabry disease and d) cardiac amyloidosis. **Middle panel**: Cine CMR still images. **Bottom panel**: Late gadolinium enhancement (LGE) images. A- Athlete's heart-mild hypertrophy accompanied by mild biventricular dilation in a master endurance athlete, no significant fibrosis; B-Cardiac sarcoidosis-biventricular dilation, asymmetry secondary to the septal wall thickening and lateral wall thinning. LGE in the subendocardial basal septum and subepicardial in the lateral wall. Fibrosis involving the RV; C- Hypertensive heart disease-concentric hypertrophy with no significant asymmetry. LGE in a "hazy/cloudy" pattern across all segments; D-Hypertrophic cardiomyopathy- asymmetric hypertrophy with LGE more prominent in the hypertrophied segments; E-Cardiac amyloidosis-asymmetric hypertrophy of the basal and mid septum and lateral wall, subendocardial enhancement in almost all LV segments including the RV, which appear also hypertrophied. Abnormal "nulling" of the myocardium.

Figure 19: Multimodality imaging of a case of amyloidosis. Echocardiography – on the 3 and 4 chamber views, the increased wall thickness and valvular thickening can be appreciated together with the sparkling appearance of the myocardium; the mitral annular

DTI shows reduced velocities, and the relative apical sparing pattern is noted with speckle tracking echocardiography. On cardiac magnetic resonance (CMR) septal wall thickness is increased, both on 4 chamber and short axis. Native T1 maps show very prolonged T1 values of the myocardium, up to 1245 ms (normal reference range 965±35 ms at 1.5T). On post-contrast acquisitions, the LGE pattern is typical for amyloid with diffuse enhancement, which is most evident subendocardially, is circumferential but relatevly sparing of apical segments, and is also detected in thickened atrial walls. A pattern similar to the LGE, can be seen on post-contrast ECV maps with increased ECV up to 50%. (DPD) SPECT-CT: marked cardiac tracer uptake on 3D SPECT/CT fusion image compatible with a diagnosis of cardiac amyloidosis.

Figure 20: Tissue characterization in a patient with LV hypertrophy diagnosed with Fabry disease during the 'inflammatory' phase. Basal mid and apical SAX views; A- Cine CMR still images show asymmetrical septal hypertrophy with a maximum wall thickness of 25mm. B- T1 maps demonstrate myocardial regions with low values (blue identifies lower values). C- T2 maps show areas with elevated values (yellow identifies the higher values). D- ECV mapping shows areas with higher values (green identifies higher values) E- LGE sequence shows patchy and, in some areas, dense and almost transmural late gadolinium enhancement especially in the lateral wall and in the true apex and apical segments. F- Stress (with adenosine) quantitative perfusion maps exhibit globally low myocardial perfusion, with subendocardial regions where stress-induced perfusion is particularly depressed (yellow demonstrates good perfusion, blue low perfusion, and black identifies myocardial regions with no detectable perfusion).

Figure 21: Genotype-phenotype correlations in hypertrophic cardiomyopathy (HCM). CMR images of a 33-year-old patient with a pathogenic variant in myosin binding protein C3 (*MYBPC3*). The typical phenotypic findings associated with this genotype are: A- high maximal wall thickness, 28 mm in medium antero-septal wall in long axis (LAX) and B- short axis (SAX) cine images; C- increased T1 mapping in SAX sequence, D-Intramural LGE in LAX sequence. E- intramural LGE in SAX sequence F- increased ECV SAX sequence

Figure 22. The current definition of HCM based on the 15mm cut-off of wall thickness may be improved according to the concept of "one size does not fit all". Accordingly, the normal range of wall thickness of each one of the 17 LV segments should be defined and take into account age, sex, body surface area and race. Top Row: while patient A and C have wall thickness above 15mm, patient B and D do not reach the "magic diagnostic number" of 15mm.

TABLES AND BOXES

Box 1: What's new

1. Strengthened role of MMI in HCM

2. Advances in echocardiography (GLS, myocardial work, LA strain, diastolic stress test)

3. Advances in CMR (T1, ECV, interstitial fibrosis)

4. Advances in CCT and nuclear imaging

5. New and/or developed topics/sections

- Key role of provocative manoeuvres including food ingestion for the diagnosis of labile HCM
-Comprehensive description of mid-cavity LV obstruction
-Modifiers of the hypertrophic phenotype (sex, obesity, hypertension, pregnancy, Covid-19)
-Update on ischaemia, metabolism, microstructure, myocardial receptors and innervation
-Update on phenocopies, including athletes´ hearts
- Genotype-imaging phenotype correlations
- Artificial intelligence in imaging of HCM
- Proposal of novel diagnostic criteria
- Role of imaging registries and biobanks

BOX 2: EACVI expert consensus key points on MMI in HCM

1. An MMI approach is encouraged in HCM patients, with the goal of selecting the right test for the right patient at the right time.

2. The established role of echocardiography remains robust as the first imaging modality in HCM patients, but many modern developments result from the use of cardiovascular magnetic resonance.
3. Cardiac CT and nuclear imaging techniques have more limited indications in this disease and are only indicated in specific clinical situations.
4. Proposals for novel diagnostic criteria are logical and conceptually attractive but need robust clinical validation.

BOX 3: What an echo report in HCM should include

1. Left ventricle

–Wall thickness
Involved segments and maximal thickness (use contrast echo if needed);
Assess asymmetric septal hypertrophy and septal morphology (reverse curvature, neutral, and sigmoid), concentric, midventricular, and apical variants, including apical aneurysm
–Left ventricle cavity size
–Systolic function: EF, indexed stroke volume, GLS; use consider s′ (TDI)
–Diastolic function
E/e′, Ar-A, LA volume index, sPAP

–Intraventricular obstruction
Mechanism, provocable vs. fixed obstruction
Level of obstruction (LV outflow tract, LV mid cavity)
Presence and severity at rest and under provocative manoeuvres—Valsalva, standing (obstructive, provocable/labile obstructive or non-obstructive HCM)

2. Right Ventricle
Exclude hypertrophy and intraventricular obstruction

2. Left atrium
LA remodelling- LA volume indexed, LA reservoir strain

3. Mitral valve findings
Mitral SAM (present/absent); characterization (septal contact and duration)
Leaflets, chordae and PM abnormalities
Exclude concurrent organic disease
Presence, mechanism, and severity of MR

4. Sudden cardiac death risk stratification

Maximal wall thickness

LA-anteroposterior dimension

LV outflow tract gradient (rest, Valsalva)

Also assess LV systolic dysfunction, LV apical aneurysm, LGE % of LV mass

Legend

Ar-A- time difference between the retrograde A wave duration in the pulmonar venous flow and the A wave duration in the transmitral inflow

EF- ejection fraction; GLS-Global longitudinal strain; LA-left atrium; LGE-late gadolinium enhancement

LV-Left ventricle; sPAP, systolic pulmonary artery pressure; PM-papillary muscle

SAM, systolic anterior motion of the mitral valve; TDI -Tissue Doppler imaging;

BOX 4: What a CMR report in HCM should include

1. Left ventricle volumes, mass, and ejection fraction
2. Location, type, distribution of hypertrophy (septum, apex, midventricular, concentric, focal, intermediate, diffuse); maximal wall thickness; maximal and minimal wall thickness in each SAX level
3. The presence mitral SAM +/- septal contact. Presence or absence of systolic cavity obliteration & its location. LVOT and/or mid-cavity obstruction. Provide peak velocity/gradient under resting conditions, supine position and breathhold
4. LGE presence/absence, pattern (RV insertion points, intramural, subendocardial) and extent (%)
5. T1 mapping, ECV
6. Evidence of MR and likely mechanism (e.g. SAM-related or otherwise)
7. Mitral valve apparatus (leaflets, chordae, papillary muscles). Description and its relation to obstruction /MR
8. The presence of architectural anomalies associated with HCH, including location and number of LV crypts, anomalous papillary muscle/ chordal anatomy, prominent trabeculation.

Legend

ECV-extracellular volume; LVOT- LV outflow tract obstruction; MR- Mitral regurgitation; SAX- Short axis

BOX 5: Gaps in evidence

- Advanced echo techniques, such as myocardial deformation methods, are promising but lack robust validation (e.g. GLS and EMD as an independent risk factor for SCD)

- Advanced CMR techniques, such as T1 mapping, T2 mapping and extracellular volume, are promising but lack strong validation.
- A universally accepted standardized method for myocardial fibrosis quantification is still lacking

- Artificial intelligence is a potentially powerful tool, but needs further studies for routine introduction in clinical practice

- The proposal for future new diagnostic criteria (normalized for body surface area, gender and ethnicity) is logical and conceptually attractive, but needs robust validation to prove its clinical impact

- The impact of morphological and functional abnormalities in early non-hypertrophic phenotypes to predict disease progression is missing

- The role of microvascular ischaemia in symptom limitation, sudden cardiac death risk, and in the evolution of myocardial injury leading to scarring and/or systolic dysfunction needs clarification

Table 1: Morphological and functional abnormalities of early, non-hypertrophic phenotypes

Morphological abnormalities	Functional abnormalities
Mitral valve apparatus	Provocable LVOT obstruction
Mild LA dilatation	Abnormal longitudinal function
Small size LV cavity	Abnormal apical rotation/torsion
Abnormal septal curvature	Low regional peak systolic circumferential strain/peak diastolic strain rate
Late gadolinium enhancement	Impaired energy metabolism
Myocardial crypts	.....
False tendons	....
Increased trabecular complexity	.....
Increased T1 map values	.....

Legend: LA-left atrium; LV-left ventricle; LVOTO-left ventricular outflow tract obstruction;

Table 2: Impact of key modifiers on imaging characteristics and clinical risks in HCM

Modifier	Myocardial mass	Chamber size	LVOT obstruction	Risk of arrhythmia	Risk of heart failure	Risk of mortality
Female sex	=/+	-	+	+	+	+
Obesity	+	+	+	+	+	+
Hypertension	+	=	+	=	=	=
Athletics	+	+	=	=	=	=
Pregnancy	=	+	-/+ *	=/+ *	=/+ *	=
COVID-19, other agents	=	=	=	+	+	+

Table legend: LVOT-left ventricular outflow tract

+ : Increases or exacerbates the characteristic/risk; **–** : Decreases or mitigates the characteristic/risk; **=** : No significant effect noted; * : 1st and 2nd trimester/ 3rd trimester

Table 3 Athletes' heart vs HCM

HCM	MMI criteria to distinguish HCM form athlete´s heart in the grey zone	Athlete´s heart
+	Atypical patterns of LVH	-
+/-	LVH regression after deconditioning	+
+	Small LV cavity (<45mm)	-
-	Large LV cavity (> 55mm)	+
+	Mitral valve apparatus abnormalities	-
+	Dynamic obstruction	-
+	MR> mild	-
+	Abnormal diastolic dysfunction	-
+	Abnormal longitudinal systolic dysfunction (TDI, GLS)	-
+	Abnormal electromechanical dispersion	-
+	Delayed LV untwist	-
+	Increased LV wall thickness to volume ratio	-
+	Late gadolinium enhancement	-
+	Increased T1	-

Legend

GLS- Global longitudinal strain; LVH-LV hypertrophy; MR -mitral regurgitation; TDI-Tissue Doppler imaging

Table 4: Barriers to HCM diagnosis: Errors in measurements

Type of error	Solution
Suboptimal acoustic window	contrast, 3D, CMR
Difficult echo segments (lateral, antero-lateral, apex)	contrast, 3D, CMR
Incorrect measurements	end diastolic measurements, 2D, PS-LAX or PS-SAX (mitral, PM, apical)
Foreshortened or oblique sections	Avoid with experience
Measurements in apical views (constraints of lateral resolution)	Avoid with experience

Inclusion of RV elements (subvalvular tricuspid valve apparatus, moderator band, crista supraventricularis, RV trabeculations,...)	Avoid with experience
Inclusion of LV elements (Subvalvular mitral apparatus, including chordae, false tendons parallel to the IVS)	Avoid with experience

Legend: CMR-cardiac magnetic resonance; LV-left ventricle; PM-papillary muscles; PS-LAX parasternal -long axis view; PS-SAX-parasternal short axis view; RV-right ventricular;2D- two dimensional echo; 3D-three dimensional echo

Table 5. Radiotracers used for HCM exploration

Full name	Abbreviation	Radioelement	Scan	Molecular target explored
15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid	BMIPP	iodine-123	SPECT	Fatty acid metabolism
Fluorodeoxyglucose	FDG	fluorine-18	PET	Carbohydrate metabolism
Acetate	-	carbon-11	PET	Oxygen consumption
(S)-CGP-12177	-	carbon-11	PET	Beta-adrenoceptor density
Hydroxyephedrine	HED	carbon-11	PET	Sympathetic nerve activity
Metaiodobenzylguanidine	MIBG	iodine-123	SPECT	Sympathetic nerve activity
Fibroblast activation protein	FAPI	gallium-68	PET	Fibroblast activity
Fibroblast activation protein	FAPI	fluorine-18	PET	Fibroblast activity

Figure legend: PET-positron emission tomography; SPECT- single photon-emission computed tomography

Table 6: Imaging parameters to estimate risk for sudden cardiac death in European 1 **and North American guidelines** 12

Parameter	Cut-off value	Cutoff value
Maximum LV wall thickness	Continuous variable[a]	≥30 mm (≥28 mm[b])
Left atrial diameter[c]	Continuous variable[a]	/

LVOT gradient[d]	Continuous variable[a]	/
LV systolic dysfunction	LVEF <50%[e]	LVEF <50%
LV apical aneurysm[f]	Presence[e]	Presence
LGE on CMR	Extensive LGE (≥15% of LV mass)[e]	Extensive LGE (≥15% of LV mass)[g]

Legend: CMR, cardiac magnetic resonance;; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract.

[a]Included in the HCM Risk-SCD calculator and HCM Risk-Kids calculator.

[b]In individual patients at the discretion of the treating cardiologist.

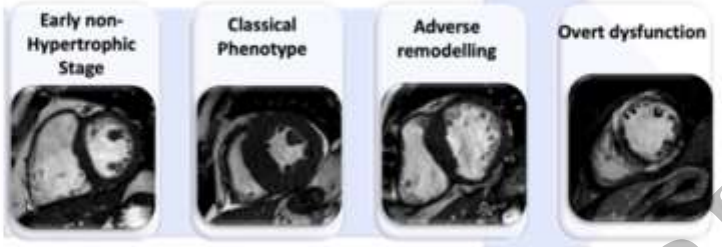
[c]Determined by M-mode or 2D echocardiography in the parasternal long axis view.

[d]Determined at rest and with Valsalva provocation, irrespective of concurrent medical treatment, using pulsed and continuous wave Doppler from the apical three and five chamber views.

[e]A risk modifier that may be used in shared decision-making about prophylactic ICD implantation in patients in the low to intermediate HCM Risk-SCD risk category[f]

Defined as a discrete thin-walled dyskinetic or akinetic segment with transmural scar or LGE of the most distal portion of the LV chamber

[g]Either quantified or estimated by visual inspection.



LV thickness	< 15 mm	≥ 15 mm	≥ 15 mm; Areas of LV thinning	≥ 15 mm; Aneurism
LV mass	= / ↑	↑	↑	↑
LVEF	= / ↑	= / ↑	= / ↓	< 50%
LV strain	= / ↓	↓	↓	↓
LV size	= / ↓	↓	↑	↑
Diastolic funcion	= /increased E/e'	Diastolic dysfunction	moderate to severe diastolic dysfunction	Severe dysfunciton
LVOT obstruction	Absent	Common	reduction of LVOT obstruction	Loss of LVOT obstruction
Mitral valve leaflet length	= / ↑	= / ↑	= / ↑	= / ↑
LGE	Absent	Common	Common; >15% LV mass	Common; >15% LV mass
Native T1 and ECV	= / ↑	↑	↑	↑
Microvascular obstruction	Absent/present	Common	Moderate to severe	Severe

Figure 1
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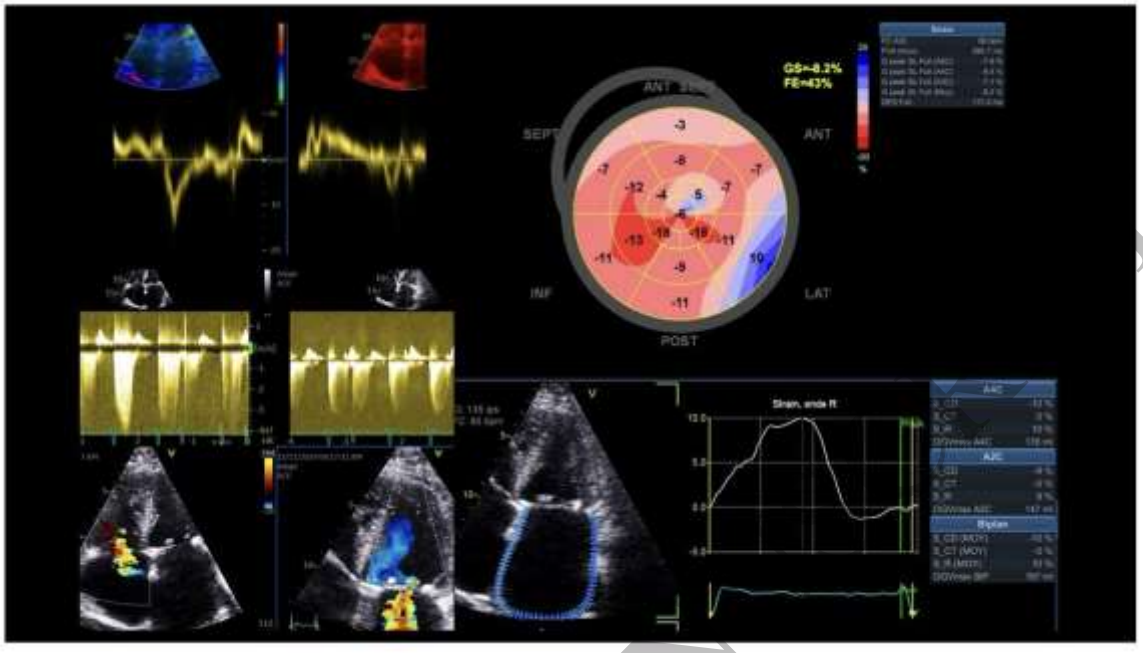

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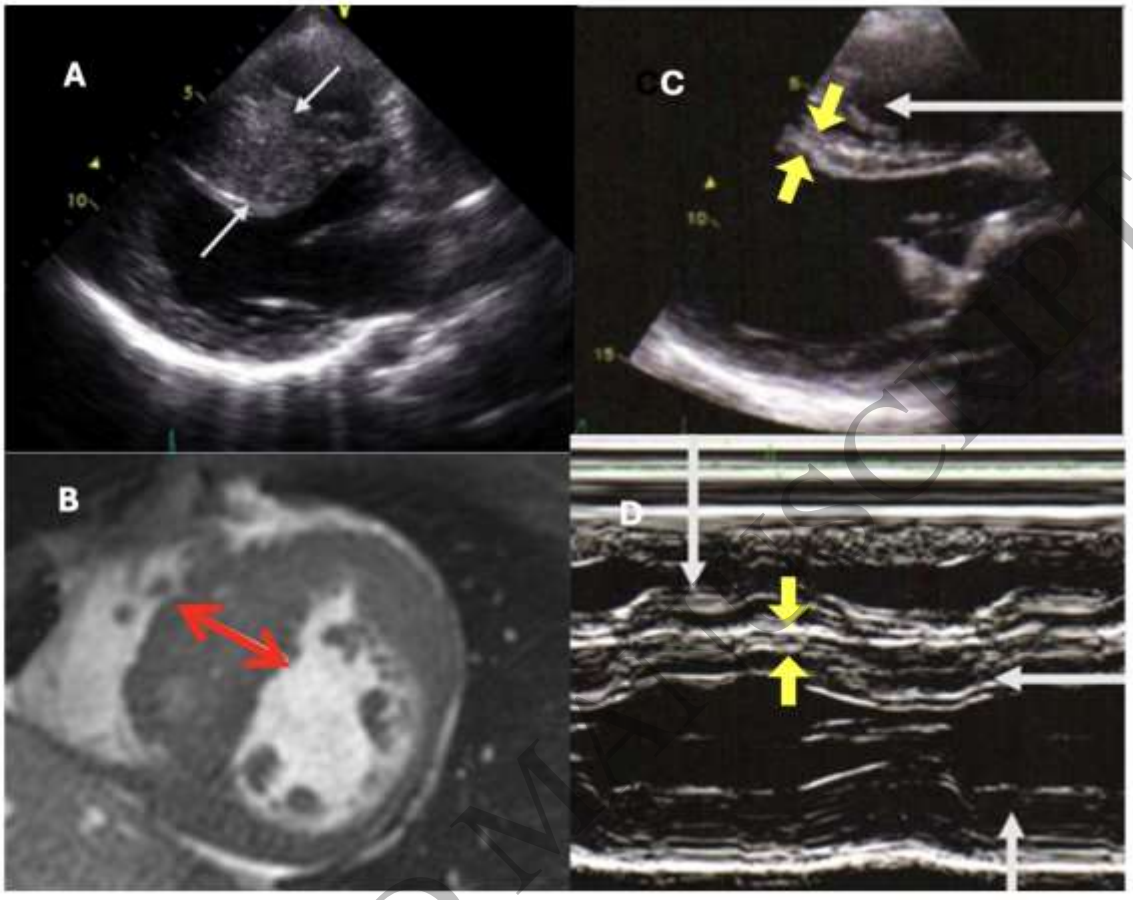

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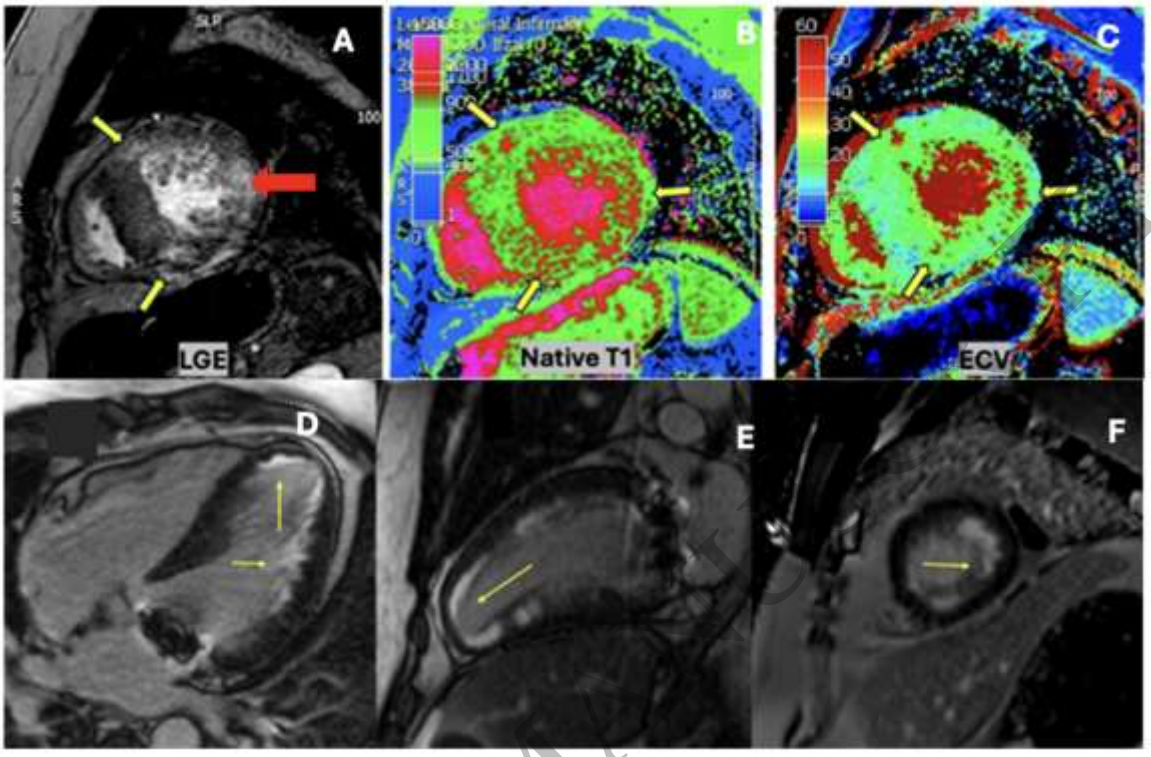

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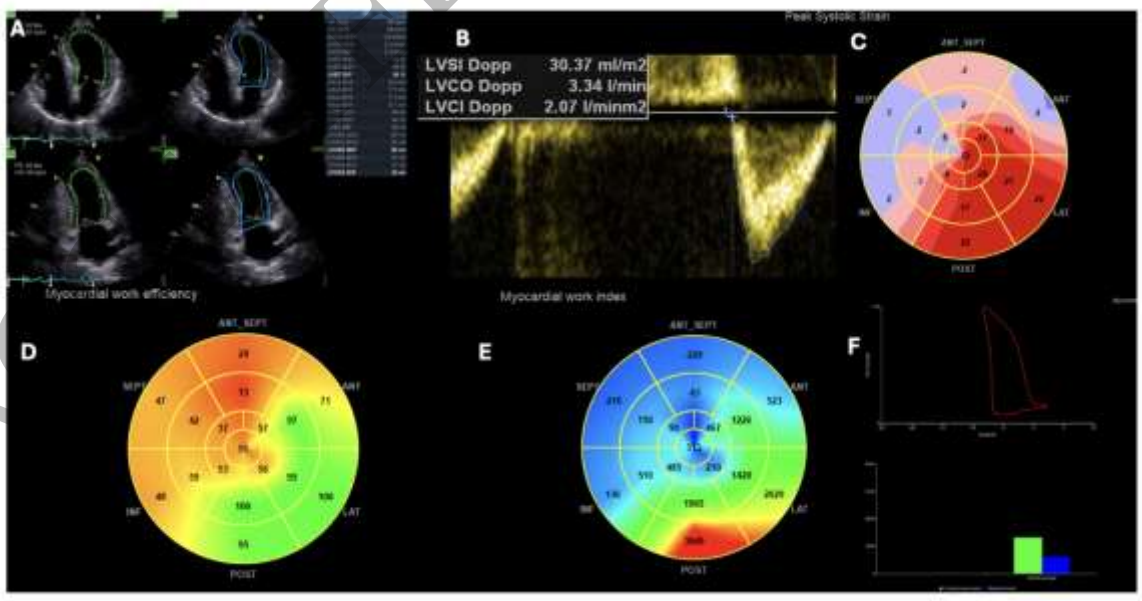

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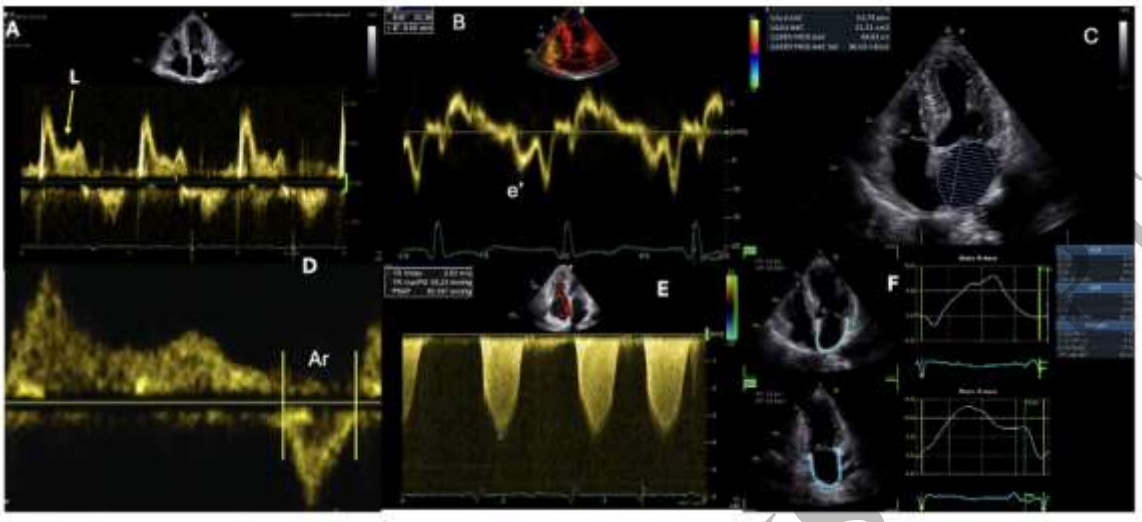

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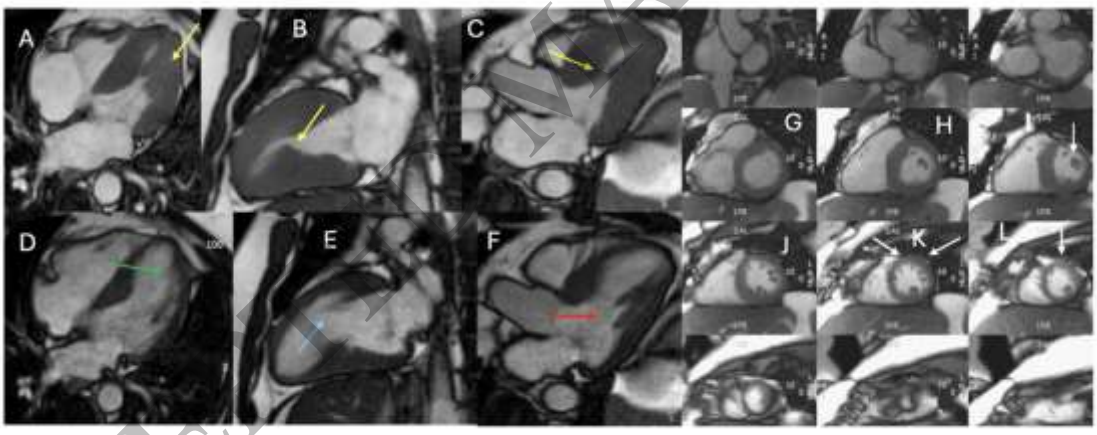

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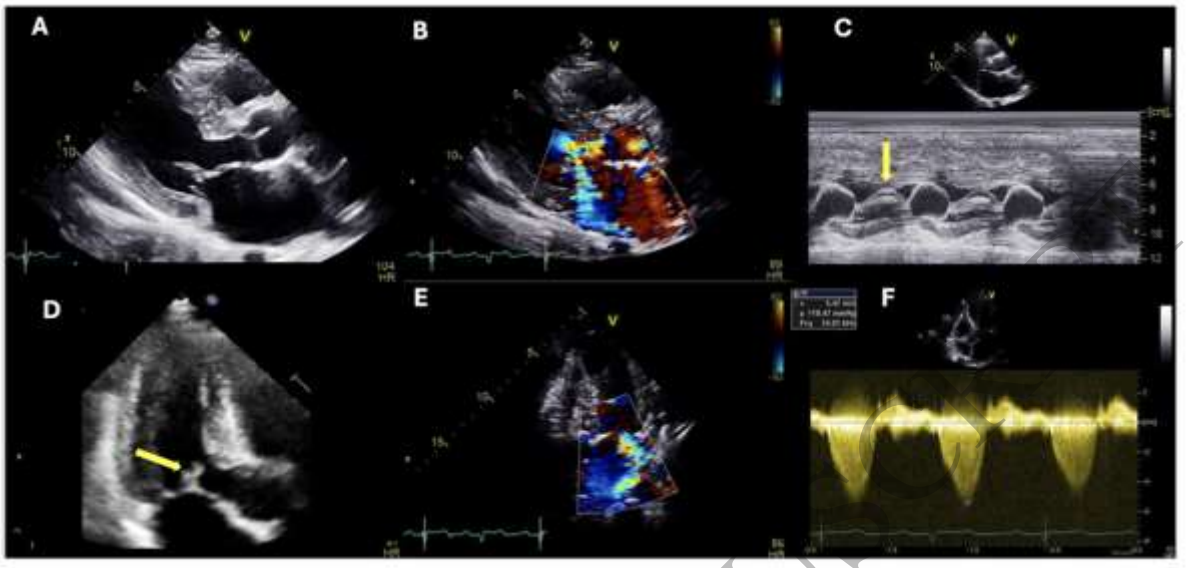

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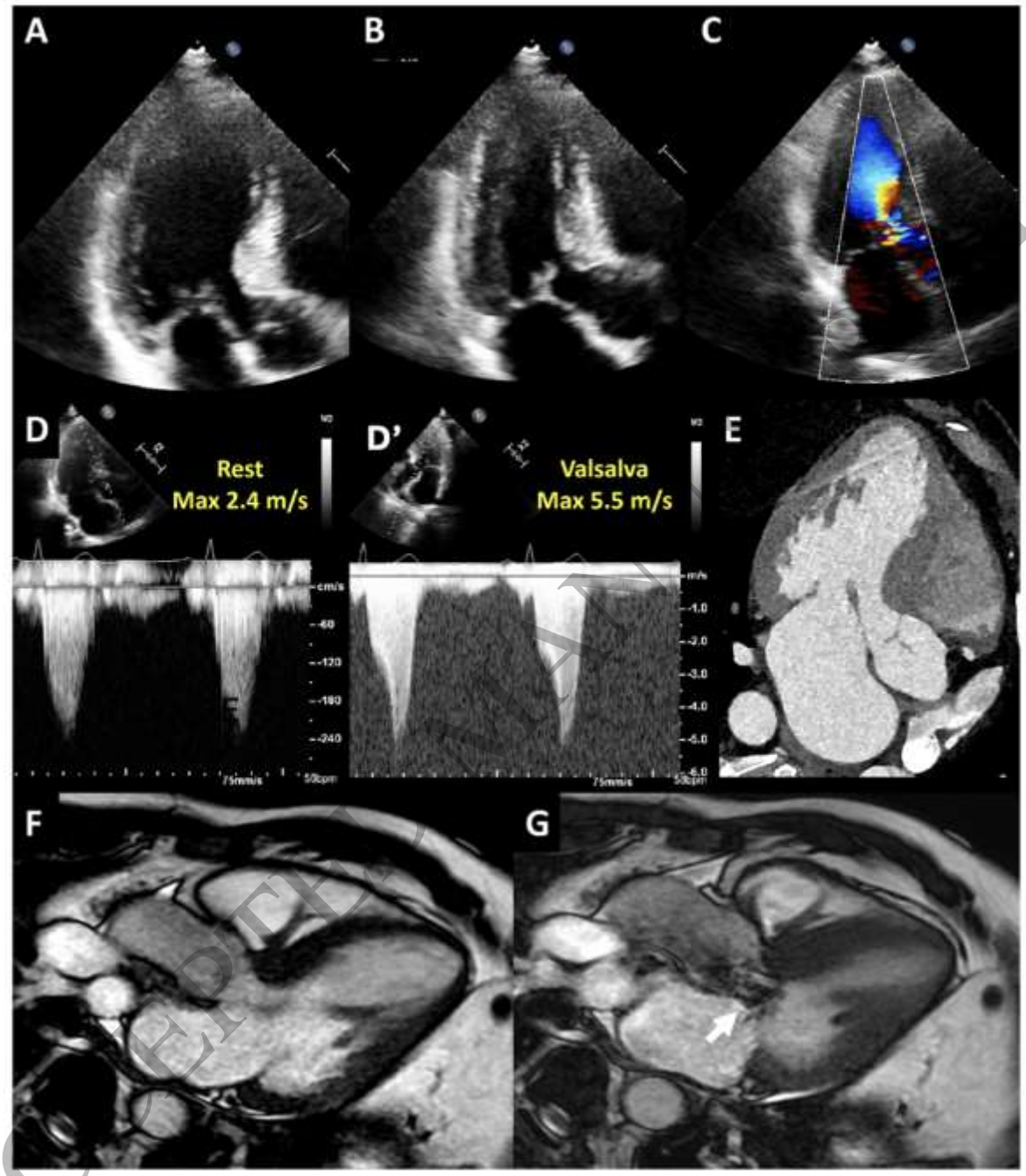

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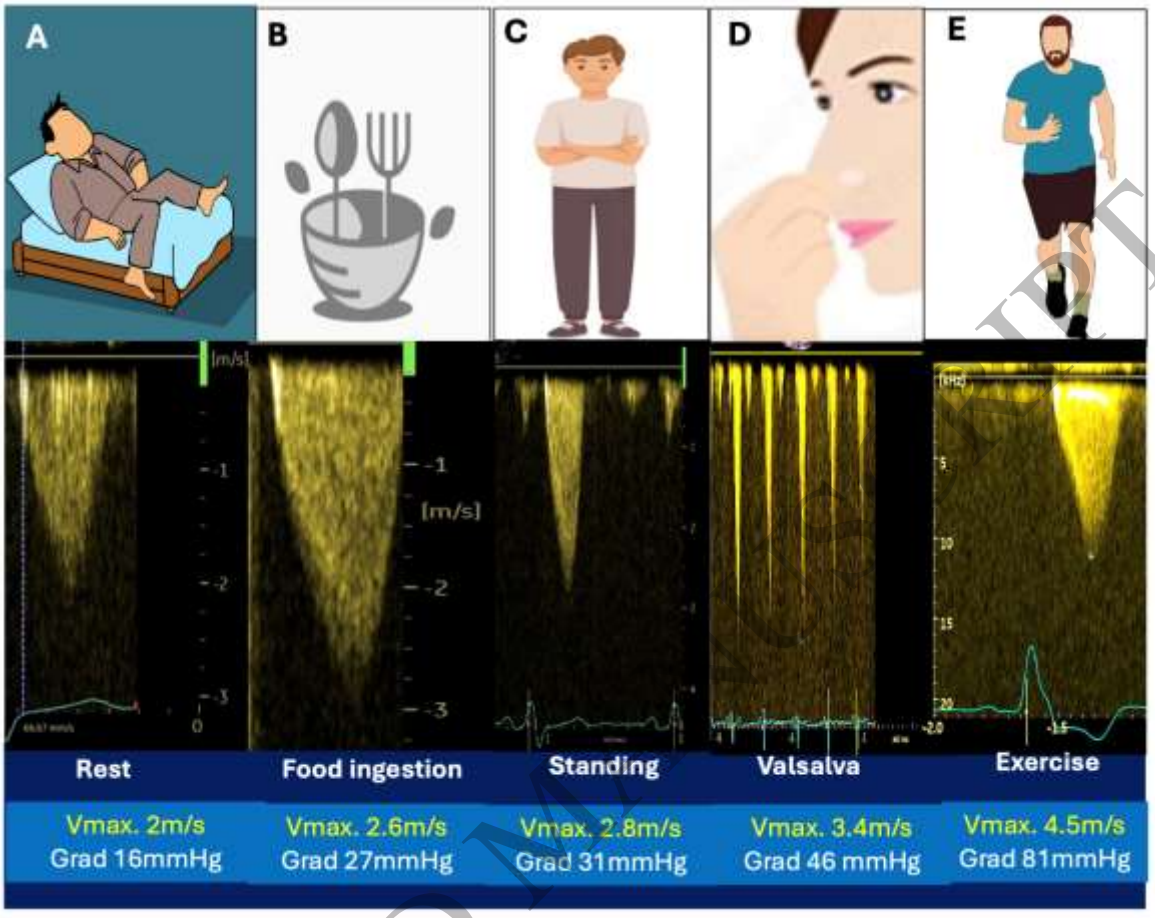

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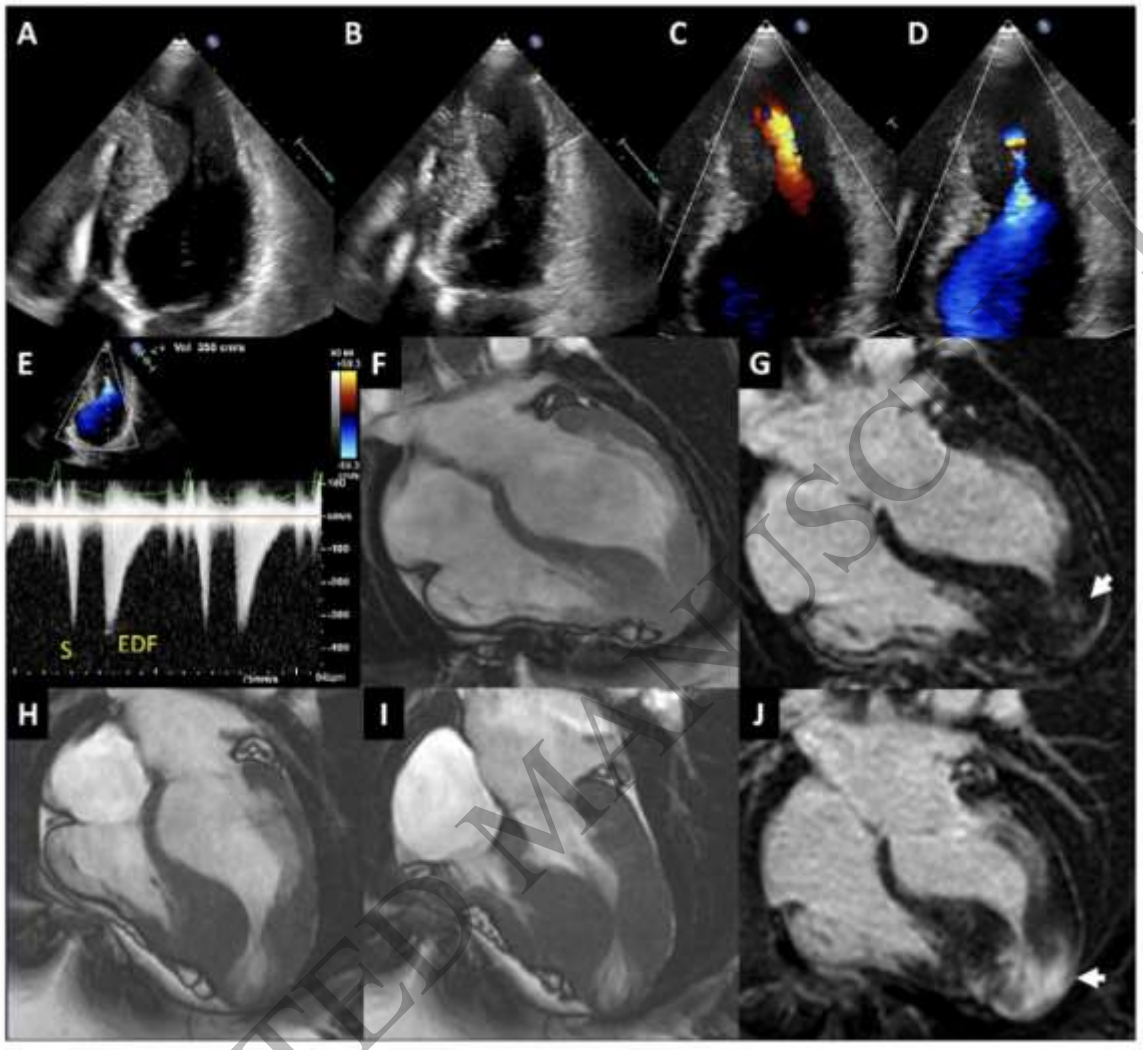

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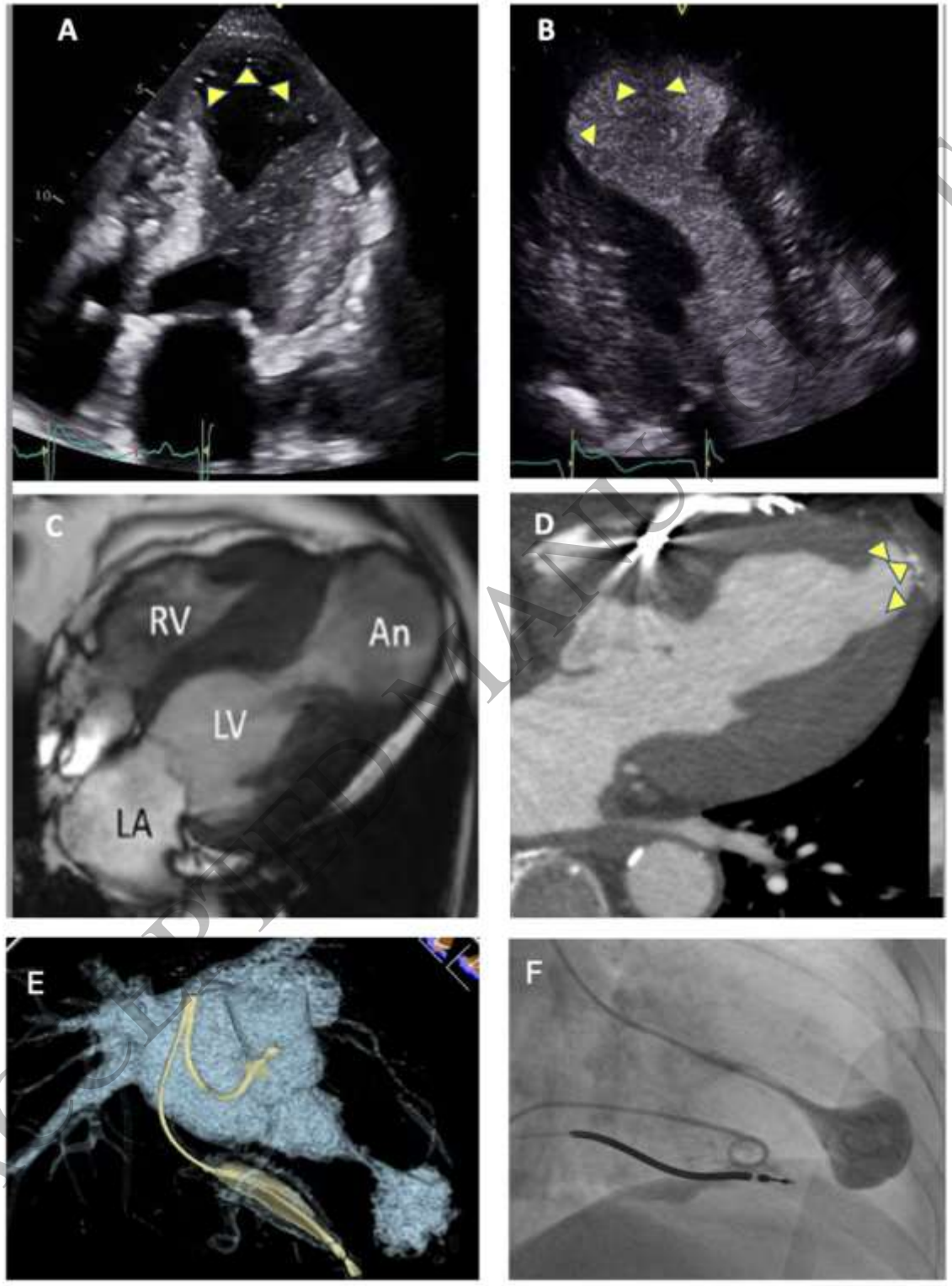

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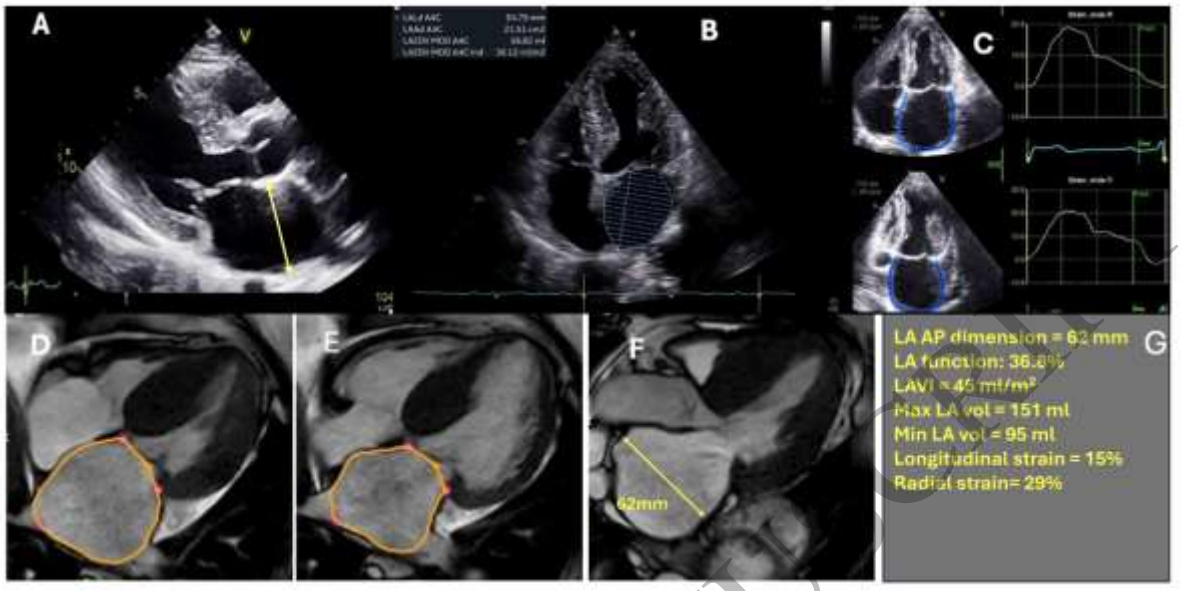

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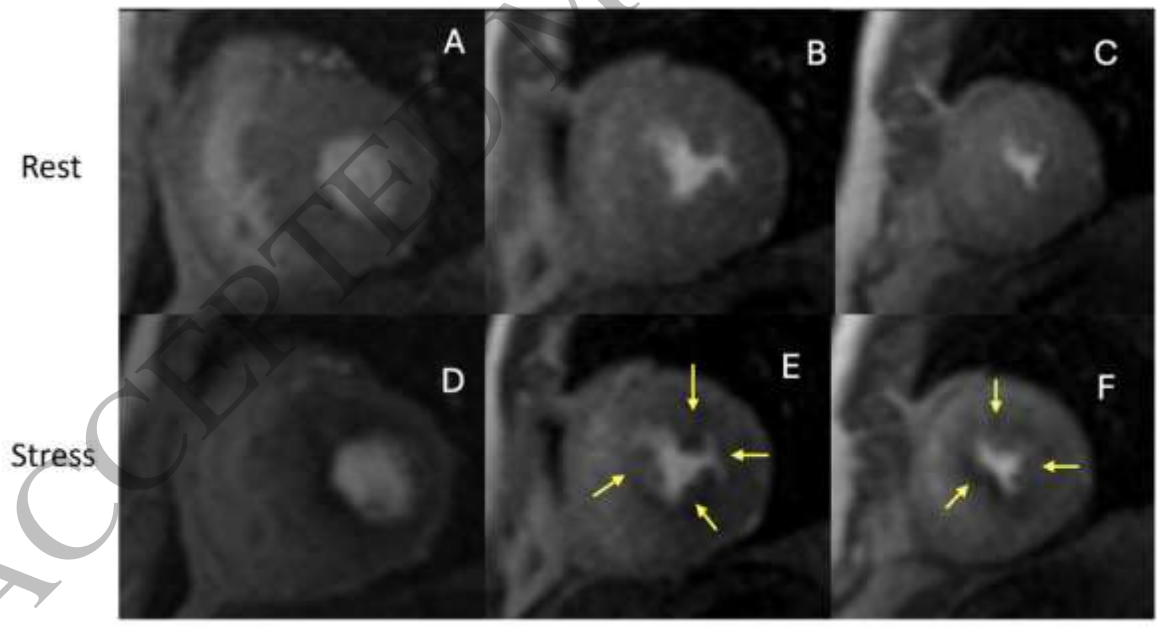

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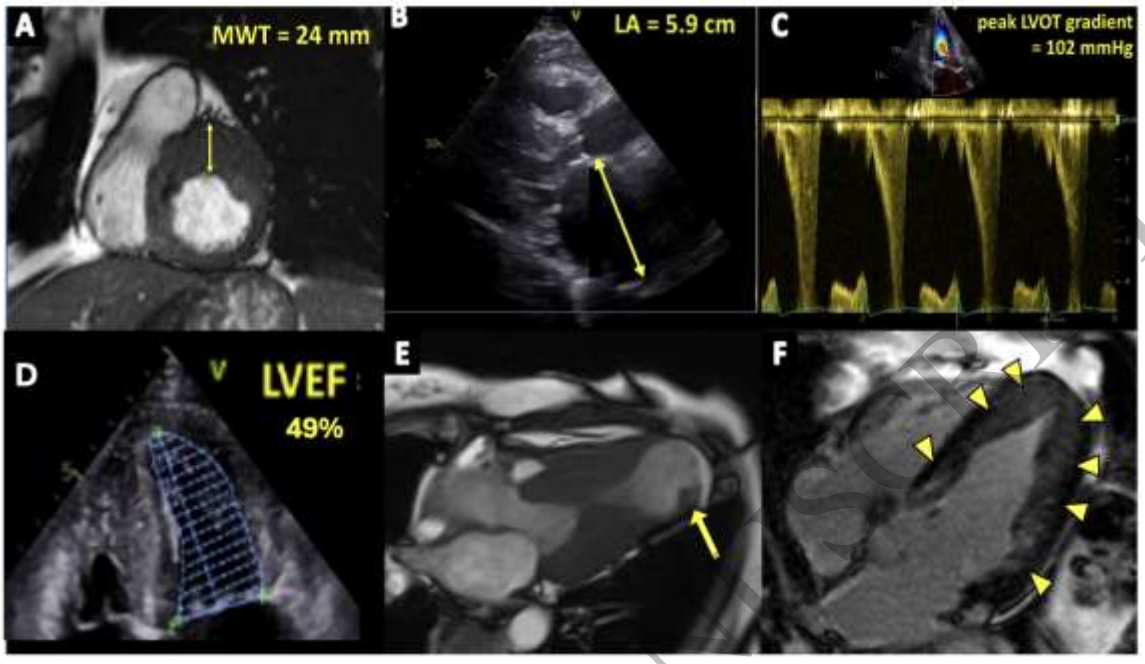

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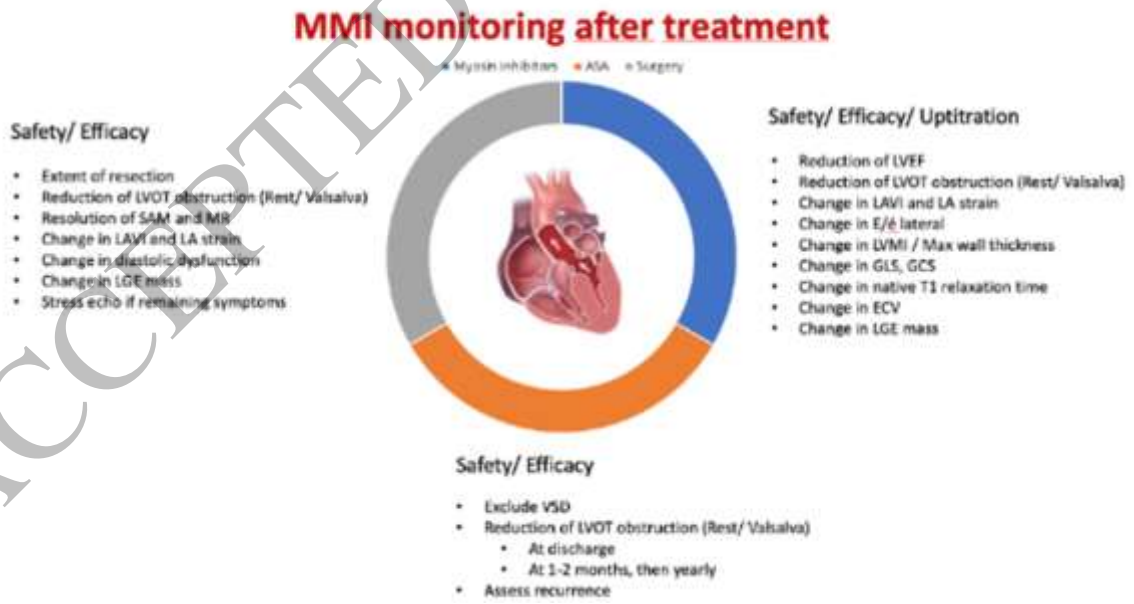

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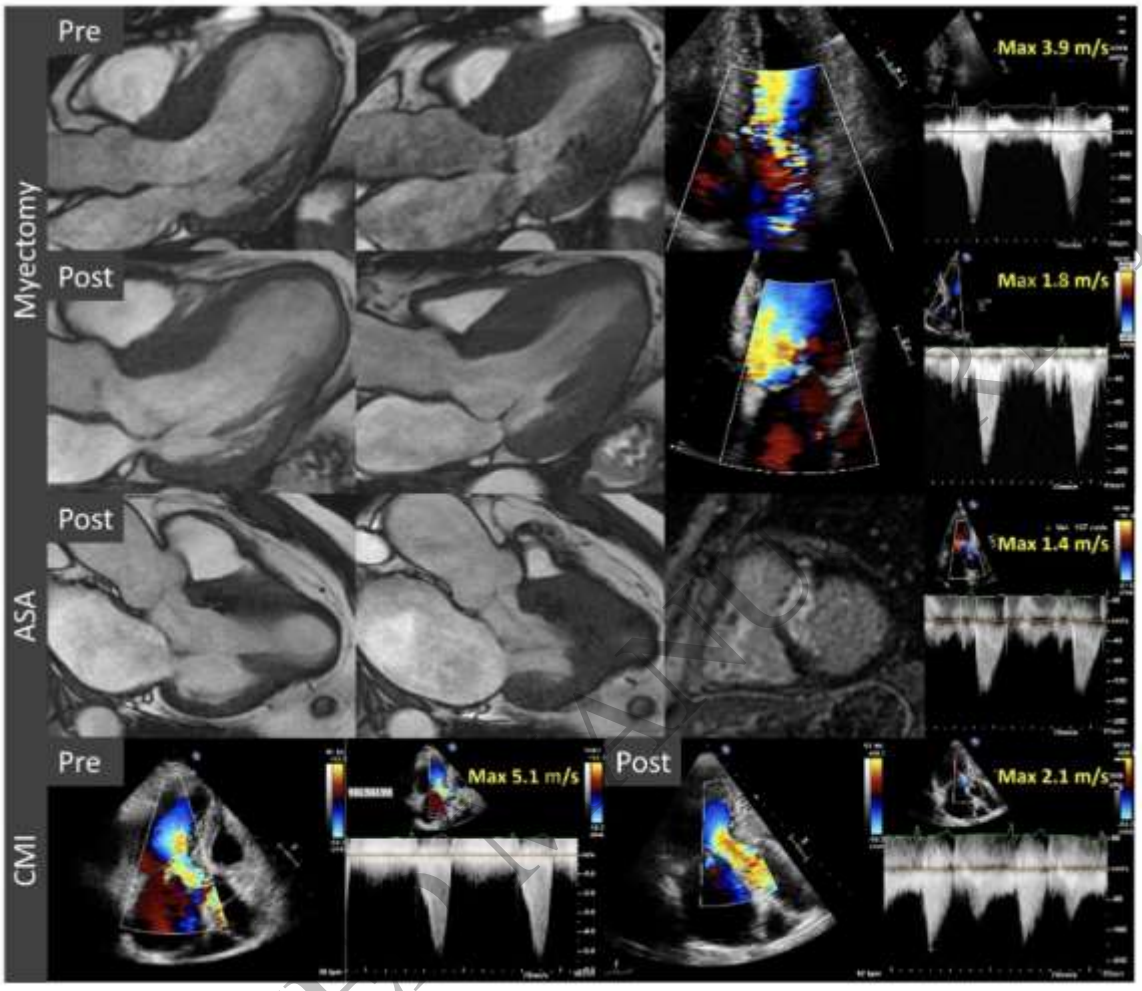

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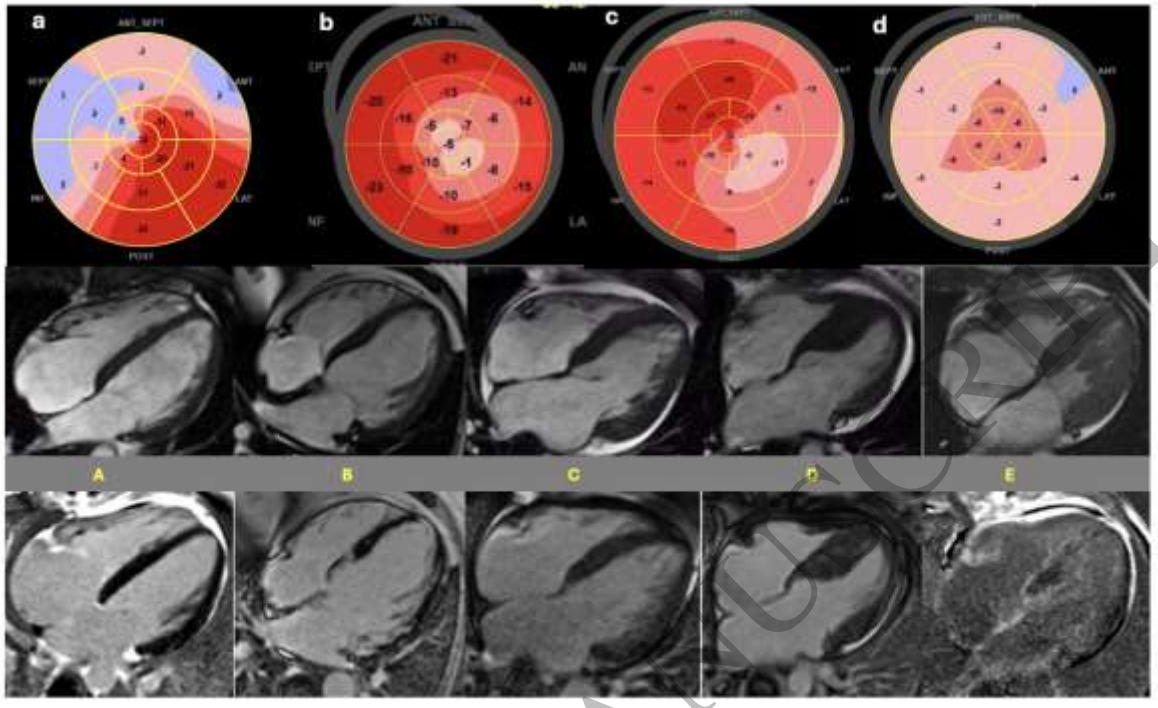

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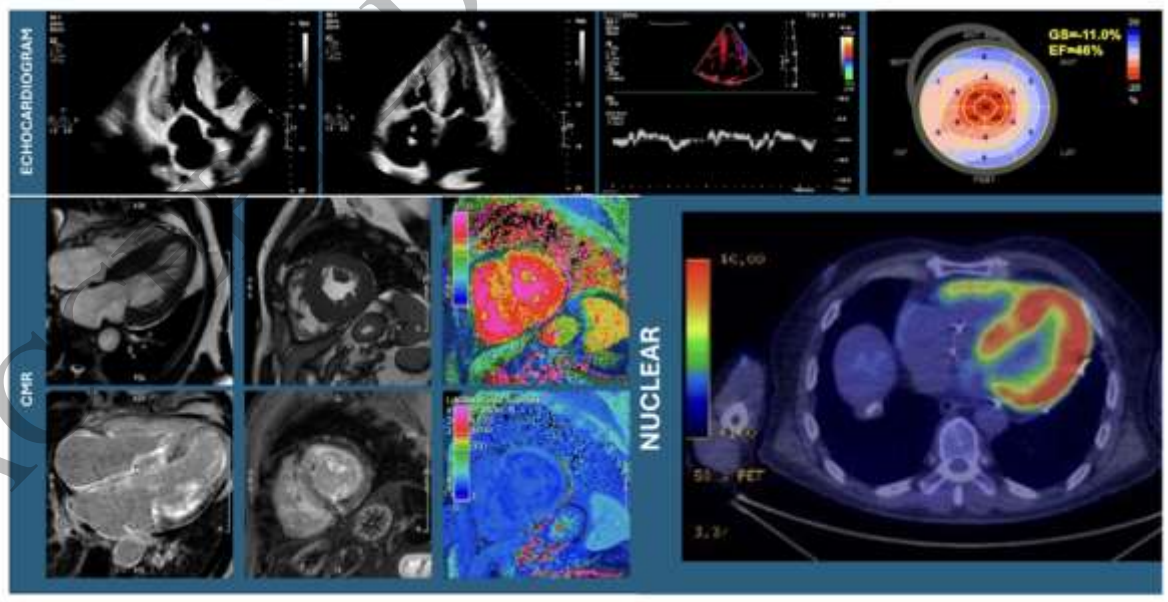

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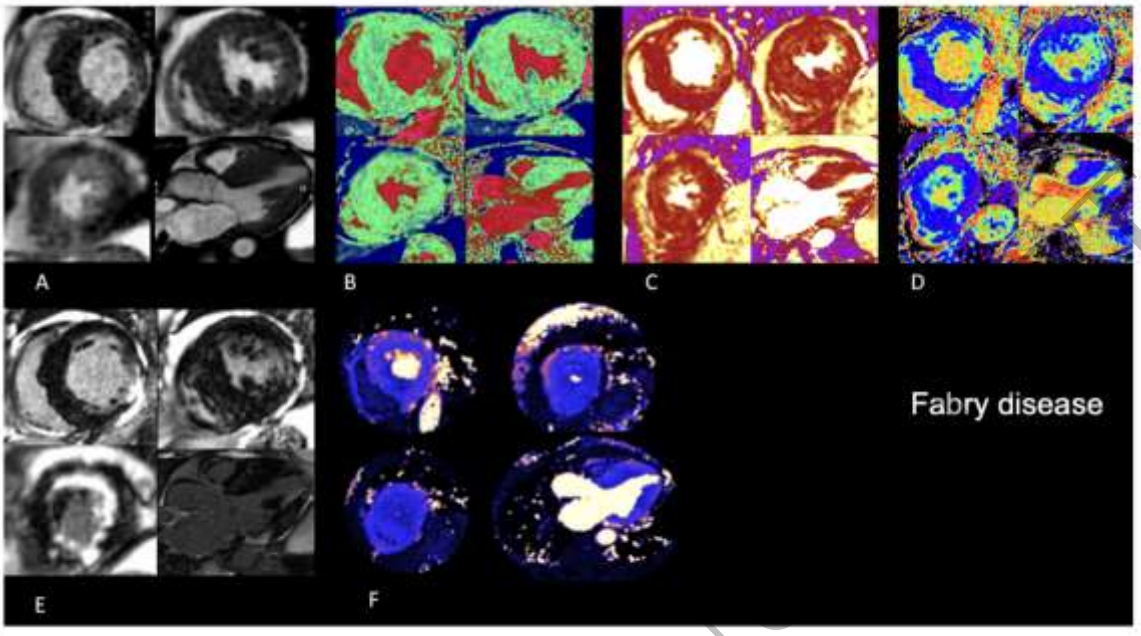

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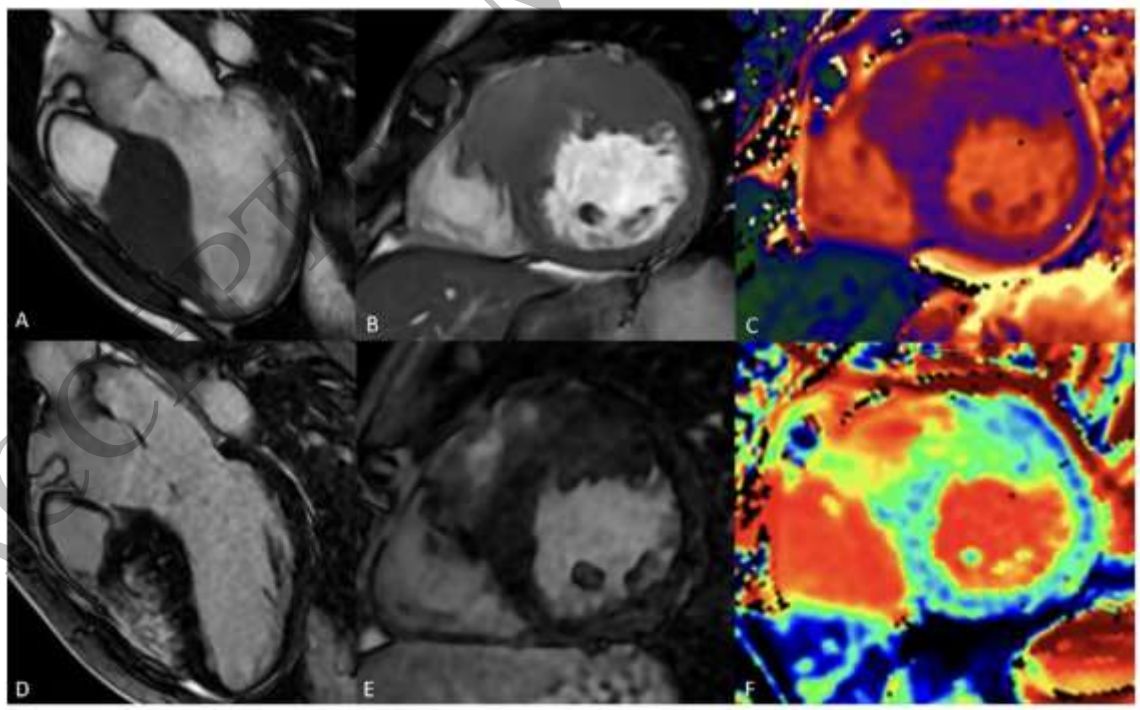

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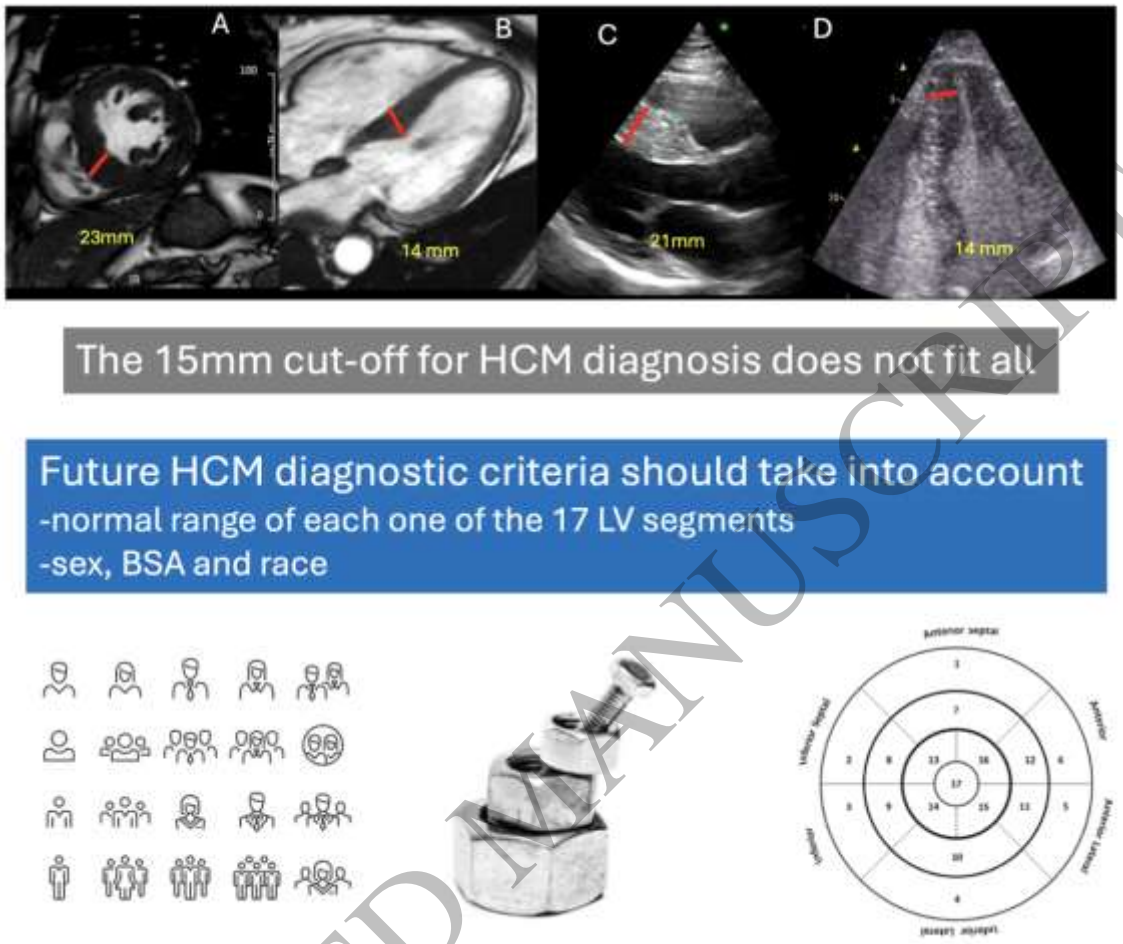

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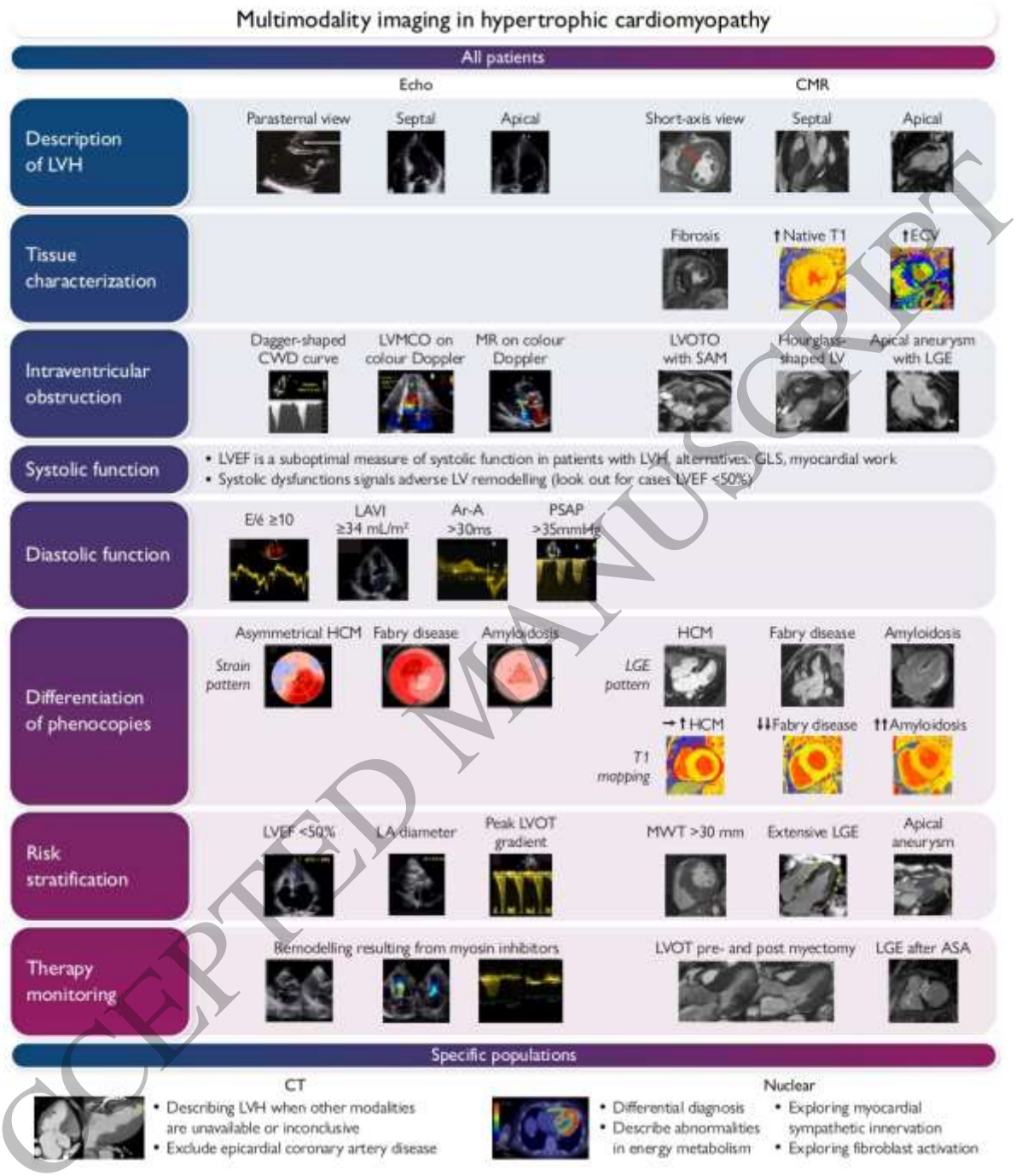

Graphical Abstract
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