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ORIGINAL PAPER

Non-invasive imaging as the cornerstone of cardiovascular precision medicine

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Aims To provide an overview of the role of cardiovascular (CV) imaging in facilitating and advancing the field of precision medicine in CV disease.

Methods and results Non-invasive CV imaging is essential to accurately and efficiently phenotype patients with heart disease, including coronary artery disease (CAD) and heart failure (HF). Various modalities, such as echocardiography, nuclear cardiology, cardiac computed tomography (CT), cardiovascular magnetic resonance (CMR), and invasive coronary angiography, and in some cases a combination, can be required to provide sufficient information for diagnosis and management. Taking CAD as an example, imaging is essential for the detection and functional assessment of coronary stenoses, as well as for the quantification of cardiac function and ischaemic myocardial damage. Furthermore, imaging may detect and quantify coronary atherosclerosis, potentially identify plaques at increased risk of rupture, and guide coronary interventions. In patients with HF, imaging helps identify specific aetiologies, quantify damage, and assess its impact on cardiac function. Imaging plays a central role in individualizing diagnosis and management and to determine the optimal treatment for each patient to increase the likelihood of response and improve patient outcomes.

Conclusions Advances in all imaging techniques continue to improve accuracy, sensitivity, and standardization of functional and prognostic assessments, and identify established and novel therapeutic targets. Combining imaging with artificial intelligence, machine learning and computer algorithms, as well as with genomic, transcriptomic, proteomic, and metabolomic approaches, will become state of the art in the future to understand pathologies of CAD and HF, and in the development of new, targeted therapies.

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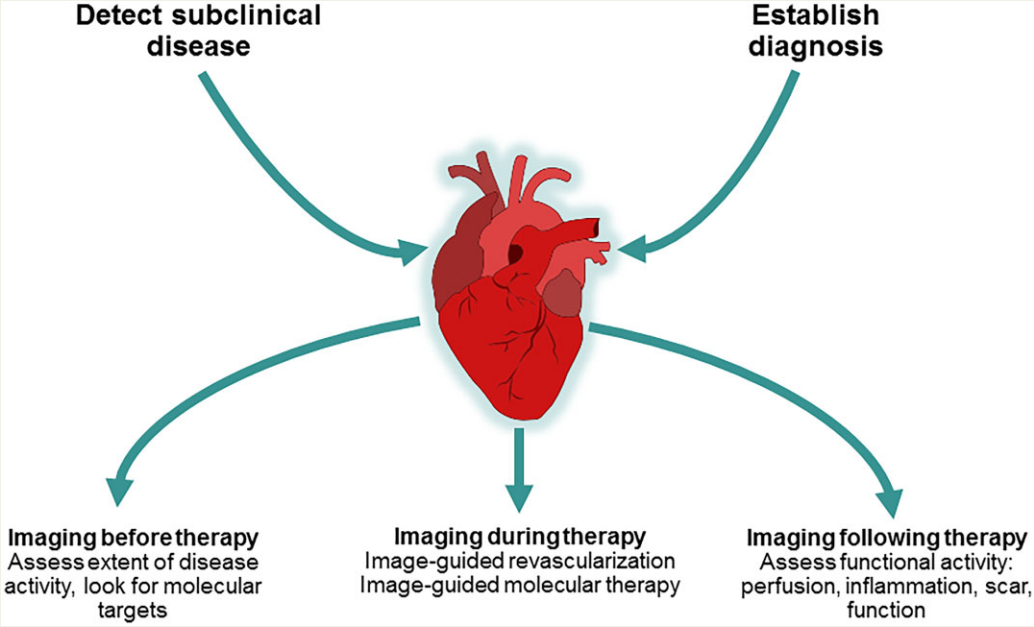
Graphical Abstract



Imaging is the foundation of precision medicine: before, during, and after therapy.

Keywords cardiovascular imaging • heart disease • cardiovascular magnetic resonance • coronary computed tomography angiography • echocardiography • molecular imaging

Introduction

Precision medicine refers to using multiple tools to distinguish an individual patient from others with a similar clinical presentation to target treatments to that patient's specific needs (*Figure 1*).[1–3] This requires precise phenotyping using individualized risk stratification, genetics, multi-modality imaging, and other biomarkers; as well as precision interventional imaging-guided treatments to improve the likelihood of response to a given treatment.[3]

Modern imaging generates very large data sets, and patients often undergo assessments with multiple imaging modalities, such as echocardiography, nuclear cardiology, cardiac computed tomography (CT), cardiovascular magnetic resonance (CMR), or invasive coronary angiography. Digital management systems using artificial intelligence and machine learning can help analyse the vast amounts of data and facilitate multi-modality cardiovascular (CV) imaging in the precision diagnosis and management of CV diseases (CVD).[4]

This document is the product of presentations and active discussions held at the Cardiovascular Round Table workshop organized in November 2020 by the European Society of Cardiology (ESC). The aim of this document is to provide an overview of the critical role of CV imaging in facilitating and advancing the management of CV disease by providing essential information that helps tailor diagnosis and treatment to the individual patient; key to the practice of 'precision medicine'.

The principle of precision medicine in cardiology involves the interplay between genotype and phenotype. A molecular and genomic understanding of CVD is essential, and efforts such as CARDIoGRAM (Coronary ARtery DIsease Genome-wide Replication And Meta-analysis) that assess aggregate data from vast cohorts, are enhancing the understanding of genetic variants associated with coronary artery disease (CAD) risk.[5] These advancements, including polygenic risk scores that have predictive power, can lead to a better understanding of underlying pathologies, with consequent development of new diagnostic and therapeutic strategies for distinct disease subgroups.

To date, only a few precise genetically actionable pathologies, such as Brugada syndrome, have been identified for CVD. Thus, precise, individualized phenotypic disease characterization using multi-modality CV imaging is of paramount importance to inform precise diagnosis and therapy of CV disease.[3] This article will demonstrate this in more detail using examples from CAD and heart failure (HF).

Imaging as a cornerstone of precision medicine in CAD

Given technological advancements in hardware, software, contrast agents, and targeted tracers, multi-modality CV imaging is becoming increasingly sophisticated, thus increasing its value in precision medicine. Imaging can be used to facilitate diagnosis at earlier disease

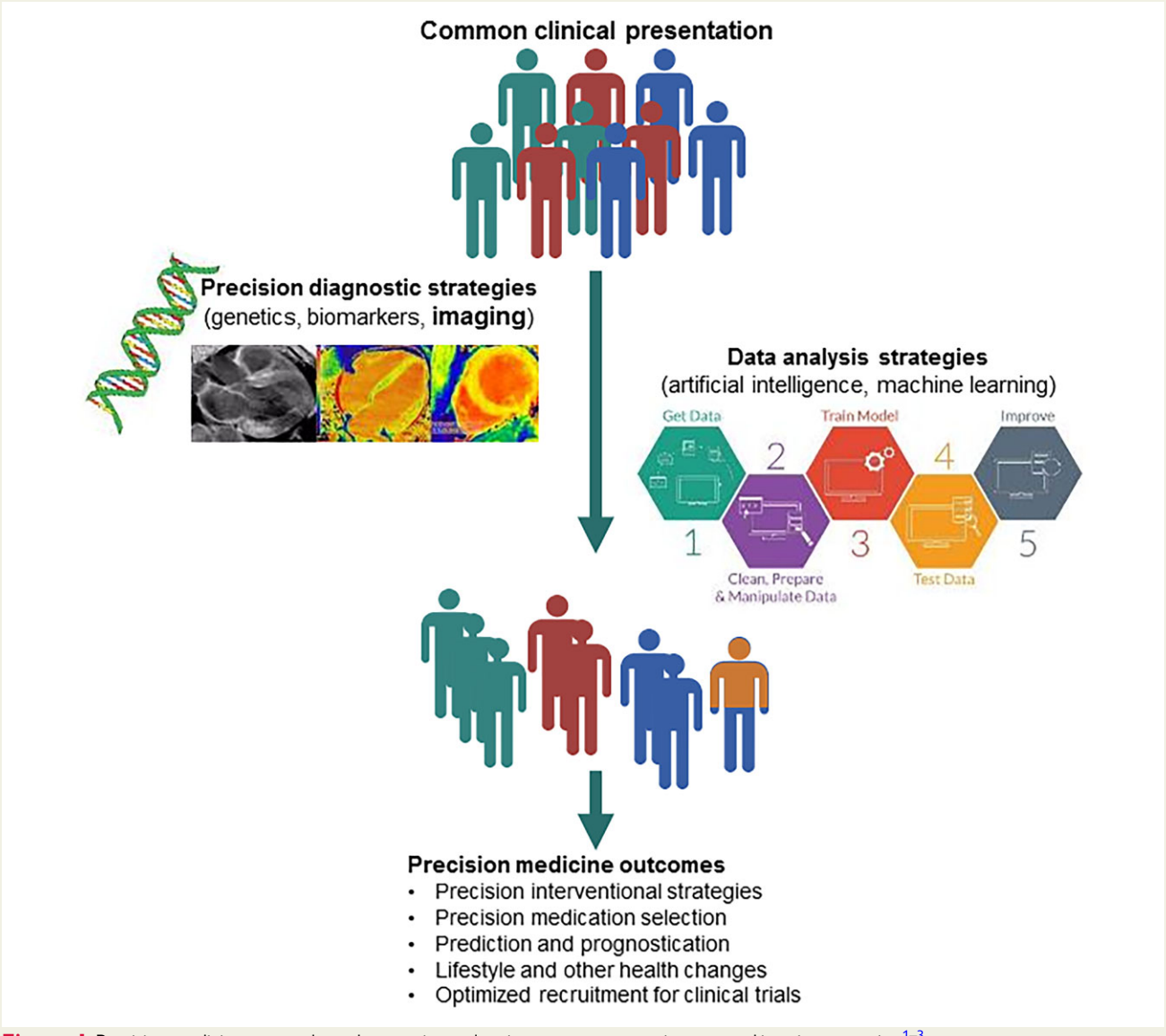


Figure 1 Precision medicine approach to phenotyping and patient management using targeted imaging strategies.[1–3]

stages with higher accuracy than clinical assessment, characterize the disease in a more detailed way, and help to predict the individual disease course. Using imaging to more accurately phenotype patients can help determine whom and what to treat when, and how to do so with the most promising approach and best possible accuracy.

As a vision, this approach might allow identification of patients at particular risk for acute coronary syndromes (ACS) through imaging characterization of high-risk plaques (HRP) and to determine the optimal way to treat (e.g. drug vs. invasive treatments, precision stent selection and placement, and in the future, targeted delivery of drugs, genes, or cells). Cardiac CT has evolved over the past decade and is increasingly used to identify disease features, like coronary plaque morphology, which are used to phenotype patients and accordingly to risk stratify (*Figure* 2). The large PROMISE trial (Prospective Multicenter Imaging Study for Evaluation of Chest Pain, $n = 10\ 003$) demonstrated that coronary CT angiography (CCTA) was superior to functional testing in identifying patients with non-obstructive CAD who are at risk for CV events.[6] Compared to normal CCTA test results there was a significantly greater risk of events associated with mildly [hazard ratios (HR) 2.94; 95% confidence interval (CI) 1.64–5.26] moderately (7.67; 95% CI 3.83–15.37), or severely (10.13; 95% CI 5.15–19.92) abnormal CCTA (all $P < 0.001$).[6] Introduction of preventative therapy based on CCTA findings was associated with a 34% relative risk reduction in all-cause mortality and myocardial infarction (MI) at 12 months (HR 0.66; 95% CI 0.44–1.00; $P = 0.049$).[7] In the SCOT-HEART (Scottish Computed Tomography of the HEART) randomized, open-label trial the addition of CCTA to standard care led to a significantly lower 5-year risk of CV death or non-fatal MI than standard care alone in patients with stable chest pain.[8] It should be noted that overall event rates were low (2.3% in patients randomized to CT vs. 3.9% in the standard of care group), and the small absolute, but substantial relative reduction of risk is typically interpreted

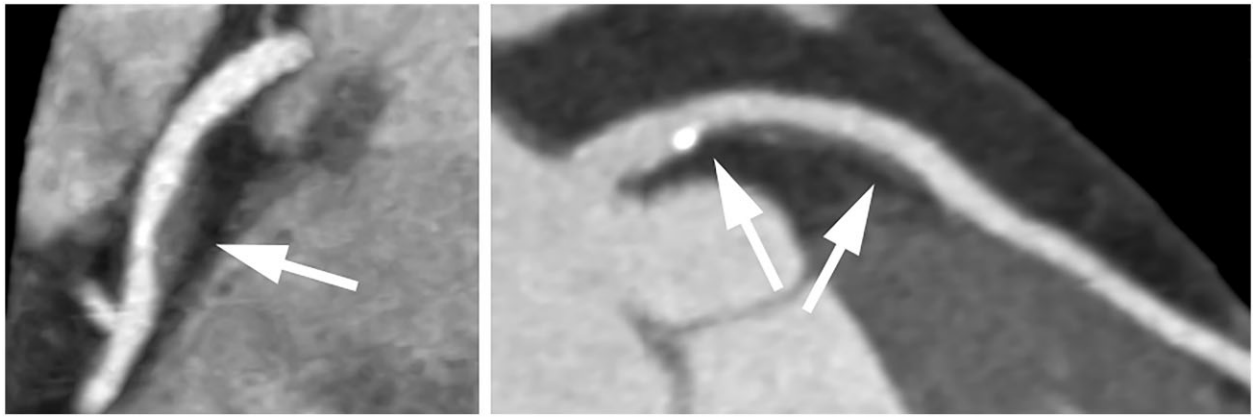


Figure 2 Non-obstructive coronary atherosclerosis in contrast-enhanced coronary CT angiography. *Left*: non-calcified plaque with pronounced positive remodelling in the proximal right coronary artery (arrow). *Right*: partially calcified non-obstructive plaque in the proximal left anterior descending coronary artery (arrows).

as a consequence of improved diagnosis, and subsequent changes in patient management, guided by the detection of both obstructive and non-obstructive CAD by CCTA. As an example, preventative medical therapy was initiated in 293 and discontinued in 77 of 2069 patients in the CT group while it was initiated in 84 and discontinued in 8 of 2070 patients in the standard of care group after initial testing. After 5 years of follow-up, statins were used in 59% of the CT group and 50% of the standard of care group. Hence, the SCOT-HEART trial is usually interpreted to demonstrate how imaging-guided therapy can lead to more tailored patient care and it provides insight for the design and conduct of future studies.

Based on a large body of evidence, current ESC guidelines for diagnosis and management of chronic coronary syndromes recommend coronary CCTA and imaging-based stress testing as non-invasive diagnostic tools, with a preferred use of CCTA in patients with low to medium likelihood of CAD.[9]

Role of imaging in phenotyping patients with high-risk coronary plaques

Invasive and non-invasive coronary imaging have been shown to provide accurate surrogate markers to identify plaques at increased risk of rupture and determine whether they are amenable to pre-emptive interventional treatment.

CCTA offers a non-invasive means to identify HRPs. In prospective studies, positive coronary remodelling, non-calcified plaques, spotty calcification, and plaque burden, as well as plaque progression on serial CCTA, were highly predictive of subsequent ACS.[10–12] In an early study, the rate of ACS in patients with HRPs was 16.3% compared to 1.4% among those without HRPs.[10] In the PROMISE trial, the rate of adverse events in individuals with HRPs was 6.4% compared to 2.4% in those without HRPs.[13] Using semi-quantitative CCTA, the SCOT-HEART trial found that plaque burden, especially low-attenuation plaque (LAP) burden was the strongest predictor of events.[12] A LAP burden >4% was associated with a significant 4.7 times higher risk of subsequent MI in patients with stable chest pain. The importance of plaque volume was demonstrated in the EVAPORATE study (Effect of Vascepa on Improving Coronary Atherosclerosis in People With High Triglycerides Taking Statin Therapy), which showed that therapy could significantly reduce LAP volume compared with placebo, and was likely the mechanism involved in the reduction of CV events see with icosapent ethyl in the REDUCE-IT trial.[14,15]

Use of the perivascular fat attenuation index (FAI) from CT data can further enhance cardiac risk prediction over CCTA alone by providing a quantitative measure of coronary inflammation.[16] In the Cardiovascular RISk Prediction using Computed Tomography (CRISP-CT) study, high values were an indicator of increased cardiac mortality and suggested the need for preventive therapy.[16]

Positron emission tomography (PET) and CMR imaging using established and emerging tracers and technologies can be used to assess disease activity further, including ischaemia detection and quantification, coronary calcification, and myocardial inflammation.[17,18] The PET tracer ^{18}F-sodium fluoride (^{18}F-NaF) is a marker of microcalcification and calcification activity across multiple CVDs.[19] 18F-NaF PET assessment of disease activity in the coronary arteries is an independent predictor of fatal or non-fatal MI in patients with established CAD.[19] Inflammatory cells [e.g. Ly6C^{high} monocytes, inflammatory macrophages (M4)] are not only present in active atherosclerotic lesions, but they also infiltrate the damaged myocardium after acute ischaemic events or in response to chronic tissue damage. Inflammatory M4 express receptors that can be targeted for molecular imaging, including CXC-motif chemokine receptor 4 (CXCR4), somatostatin receptor type 2 (SSTR2), glucose transporter (GLUT), L-type amino acid transporter (LAT), and mitochondrial translocator protein (TSPO).[17,18] Measures of inflammation in the vessel wall and in the acutely or chronically injured myocardium provide prognostic information, and the inflammatory molecules can be used as targets for novel therapeutics.

Role of imaging to direct and tailor treatment

Imaging plays a critical role in identifying those coronary atherosclerotic lesions that will respond to drug therapy vs. those that pose an

imminent risk and require invasive interventions.[20] In addition to luminal stenosis, lesion physiology is an essential factor in determining the need for and benefits of revascularization. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial demonstrated that revascularization based on anatomical stenosis alone did not reduce the risk of death and MI compared to optimal medical therapy (OMT).[21] Measuring fractional flow reserve (FFR) may provide a more accurate picture of disease activity. As shown in the FAME trials,[22,23] revascularization can safely be deferred in patients with FFR >0.8, compared to angiography-guided therapy (FAME[22]) or OMT (FAME2[23]).

However, in the FAME2 trial, about 50% of patients with FFR positive lesions treated with OMT remained event-free, with no difference in the rate of angina compared to those treated interventionally.[23,24] Similar to FFR negative lesions, there is a high negative predictive value associated with HRP negative lesions. Therefore, the next step may be to define a subgroup of patients with FFR positive, but HRP negative lesions in who could be safely treated with OMT rather than revascularization. It has been speculated that high wall shear stress may be useful to further identify these patients.[24]

Among other technological advancements, application of artificial intelligence for data analysis may further enhance role of imaging in precision medicine, facilitating more insightful and accurate diagnostic assessment and more exact guidance of interventions. FFR has traditionally been measured invasively with pressure wire placement during coronary angiography. Now, application of computational fluid dynamics to CCTA can provide an accurate, non-invasive measure of FFR.[25] Similarly, computer software can be used to simulate FFR from routine angiography alone with high concordance to invasively pressure wire-derived FFR.[26] Such software may in the future complement the traditional invasive coronary angiogram, and new software tools, such as 'dynamic road mapping', can offer real-time, dynamic overlays of coronary contours from non-invasive imaging on live fluoroscopy. This may help guide percutaneous coronary interventions (PCI) and may potentially even allow positioning of intracoronary devices without the need for further contrast injection.[27]

Imaging as a cornerstone of precision medicine in HF

Multi-modality CV imaging is also a cornerstone of precision medicine in HF management. Accurate phenotyping is needed to identify the specific causes of HF, to assess the disease stage, and to determine individual prognosis. Identification of a specific aetiology by means of imaging is the basis for disease-specific management strategies, especially the identification of those patients that may respond to a particular treatment.

Role of imaging to phenotype HF

HF has traditionally been characterized according to left ventricular ejection fraction (LVEF), as HF with reduced EF (HFrEF), HF with preserved EF (HFpEF), and more recently HF with mildly reduced EF (HFmrEF).[28] However, HF is a syndrome with a multitude of potentially underlying diseases, which may result in different therapeutic strategies (*Table 1*).[29,30]

Phenotyping patients with suspected HF typically includes echocardiography and CMR, with additional information provided by CCTA and nuclear imaging (*Figure 3*).[31] LVEF is the most common surrogate parameter to measure cardiac contractility and to assess myocardial performance and patient prognosis. However, there are some limitations associated with echocardiographic measures of LVEF, in terms of reproducibility,[32] and availability (e.g. cost/availability of real-time 3D echocardiography, *Figure 4*). Global longitudinal strain (GLS) provides a measure of global left ventricular function that correlates with EF.[33] It is sensitive and reproducible, and adds value to measures of EF, for example, to differentiate patients with cardiac amyloidosis from patients with other causes of left ventricular hypertrophy.[34,35] Strain measurements are used to identify regional abnormalities in contractility that occur in ischaemia, scar, and other pathology[36] and can be used to objectify mechanical dyssynchrony in conduction delays (*Figure 5*).[37]

A common pathological pathway in different forms of HF is myocardial fibrosis,[38] the extent of which is associated with all-cause mortality and event-free survival.[39,40] Myocardial fibrosis causes diastolic dysfunction of the ventricle which then requires higher filling pressures. Filling pressures can be estimated by echocardiography.[41] The novel shear wave elastography technique, based on high frame rate echocardiography, can measure myocardial stiffness directly.[42] In addition, CMR, especially with late gadolinium enhancement (LGE) (*Figure 6*) and parametric mapping techniques, offers a standardized, non-invasive method to detect and quantify myocardial scar and fibrosis.[43]

LGE can delineate and analyse the pattern of scar tissue, which is useful for the differentiation of ischaemic and non-ischaemic cardiomyopathies and helps in the differential diagnosis of cardiomyopathies (DCM, HCM, sarcoidosis, amyloidosis), and myocarditis.[44] The prognostic utility of LGE includes an assessment of the likelihood of functional recovery (improved contractility),[45] and prediction of event-free survival (e.g. mortality, myocardial infarct, HF, transplantation).[39,40] The presence of LGE CMR identified fibrosis is an important diagnostic tool when assessing the need for an implantable cardioverter-defibrillator (ICD) device, beyond LVEF alone.[46,47] LGE fibrosis can identify patients at high risk of sudden cardiac death, but also detect the patients with non-ischaemic cardiomyopathy who despite having a low LVEF (≤35%) are unlikely to benefit from an ICD. ESC guidelines recognize the benefits of LGE CMR, and recommend it be considered in patients who may require an ICD, particularly younger patients, to refine the diagnosis of conduction abnormalities.[48]

T1 mapping and extracellular volume fraction (ECV) by CMR allow diagnosis and quantification of the severity of diffuse fibrosis associated with a range of inflammatory and infiltrative conditions (*Figure 7*).[44] T1 mapping can aid in the differential diagnosis of cardiomyopathies (*Figure 8*), assess disease activity, evaluate prognosis, monitor disease progress, and guide treatment in a rapid, contrast-free fashion.[44,49–53] T2* mapping by CMR is the reference test to quantify myocardial iron content which is used to guide therapy in iron-overload diseases.

Table 1 Phenotyping is essential to determine the aetiology of heart failure[29,30]

Diseased myocardium	
Ischaemic heart disease	Myocardial scar
	Myocardial stunning/hibernation
	Epicardial coronary artery disease
	Abnormal coronary microcirculation
	Endothelial dysfunction
Toxic damage	Recreational substance abuse
	Heavy metals
	Medications (e.g. cytostatic drugs, immunomodulators, antidepressants, antiarrhythmics, NSAIDs, anaesthetics)
	Radiation
Immune-mediated and	Related to infection
inflammatory damage	Not related to infection (e.g. myocarditis, autoimmune diseases)
Infiltration	Related to malignancy
	Not related to malignancy (e.g. amyloidosis, sarcoidosis, haemochromatosis, glycogen, or lysosomal storage diseases)
Metabolic derangements	Hormonal (e.g. thyroid disease, diabetes, metabolic syndrome, pathologies related to pregnancy)
	Nutritional (e.g. deficiencies of various compounds, complex malnutrition, obesity)
Genetic disorders	Structural cardiomyopathies, channelopathies, syndromal forms (e.g. muscular dystrophies, laminopathies)
Abnormal loading conditions	
Arterial hypertension	
Valve and myocardium	Acquired (e.g. mitral, aortic, tricuspid, pulmonary valve diseases)
structural diseases	Congenital (e.g. atrial and ventricular septum)
Pericardial and endomyocardial	Pericardial (e.g. constrictive pericarditis, pericardial effusion)
pathologies	Endomyocardial (e.g. endomyocardial fibrosis or fibroelastosis)
High output states	(e.g. severe anaemia, sepsis, pregnancy)
Volume overload	(e.g. renal failure, iatrogenic fluid overload)
Arrhythmias	
Tachyarrhythmias	(e.g. atrial, ventricular arrhythmias)
Bradyarrhythmias	(e.g. sinus node dysfunctions, conduction disorders)

NSAID, non-steroidal anti-inflammatory drugs.

Role of molecular imaging to direct and tailor treatment for HF

Multi-modality CV imaging takes a leading role in moving the field of precision medicine for HF forward (*Graphical Abstract*). For example, PET radiotracer techniques can be used to identify, monitor and target molecular structures involved in HF progression, such as excessive tissue inflammation or fibroblast activation. Imaging is performed to determine if a patient expresses the respective target, and if the patient was an appropriate candidate for the treatment, molecular imaging would be used to directly guide application and timing of the molecular-targeted agent.[54,55] Post-therapy imaging is then used to monitor the therapeutic effect on the adversely activated mechanism. For example, molecular imaging has been used to identify early up-regulation of CXCR4, which is associated with left ventricular remodelling.[54,56] Early studies suggest, that PET-guided CXCR4-directed inhibitors can accelerate the resolution of inflammation and improve outcome.[54,56]

Finally, imaging has a central role in stratifying HF patients for drug treatments and to enrich patient populations in clinical trials. Trials in patients with HFpEF have shown that risk increases with an increasing number of abnormal measures on echo (e.g. LV structure, diastolic function, and PA pressure).[57–59] Impaired left ventricular systolic function (longitudinal strain) has also been shown to be a powerful predictor of CV death and HF hospitalization in HFpEF.[60] More precisely, phenotyping patients will allow selection of those most likely to respond to a specific treatment, not just in randomized trials, but in clinical practice.

Summary

Sophisticated non-invasive multi-modality CV imaging is key for accurately and efficiently phenotyping patients with heart disease, prominently including CAD and HF. In patients with CAD, imaging can identify HRP, assess the haemodynamic relevance of coronary lesions and quantify MI-induced myocardial damage. In patients with HF, imaging allows identification of specific HF aetiologies, quantification of damage (risk of sudden cardiac death) and impact on cardiac function. Imaging plays a central role in a patient's

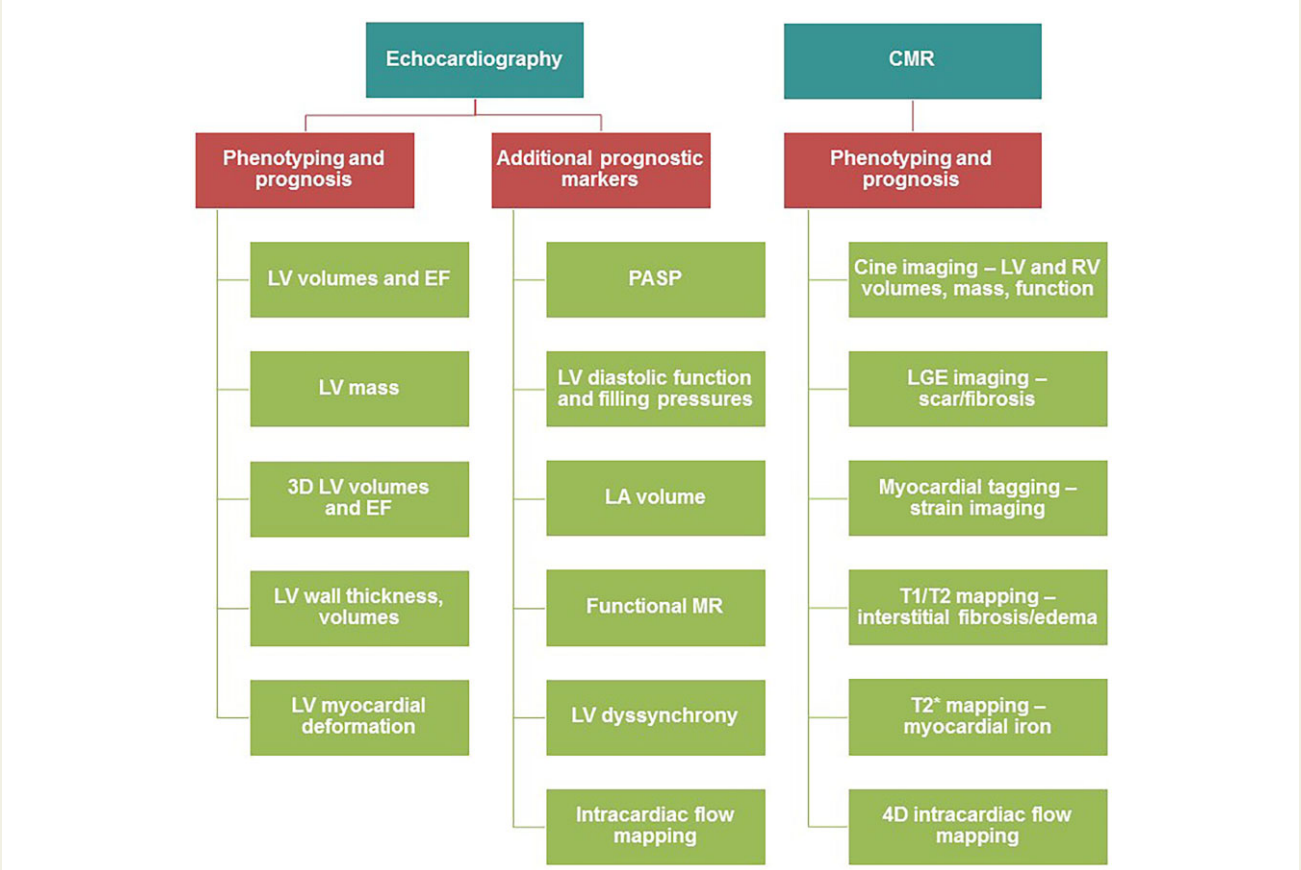


Figure 3 Role of echocardiography and CMR in the evaluation of heart failure.[31] CMR, cardiac magnetic resonance; EF, ejection fraction; LA, left atrial; LGE, late gadolinium enhancement; LV, left ventricular; MR, mitral regurgitation; PASP, pulmonary artery systolic pressure.

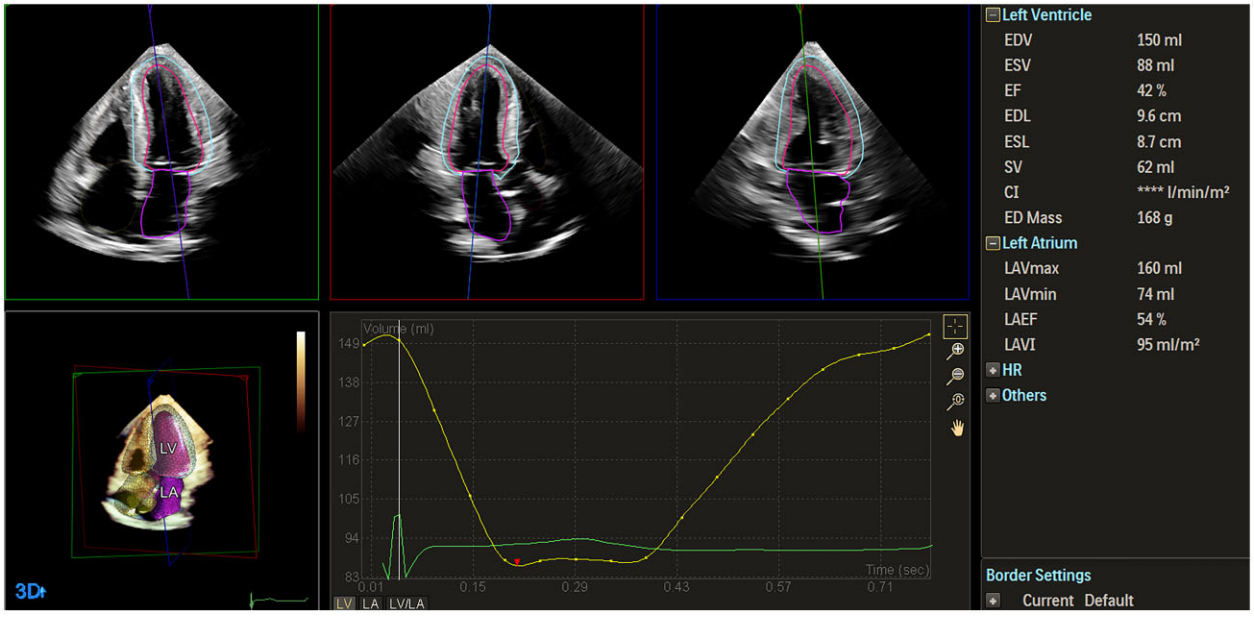


Figure 4 Left ventricular ejection fraction and left atrium volumes measured by 3D transthoracic echocardiography.

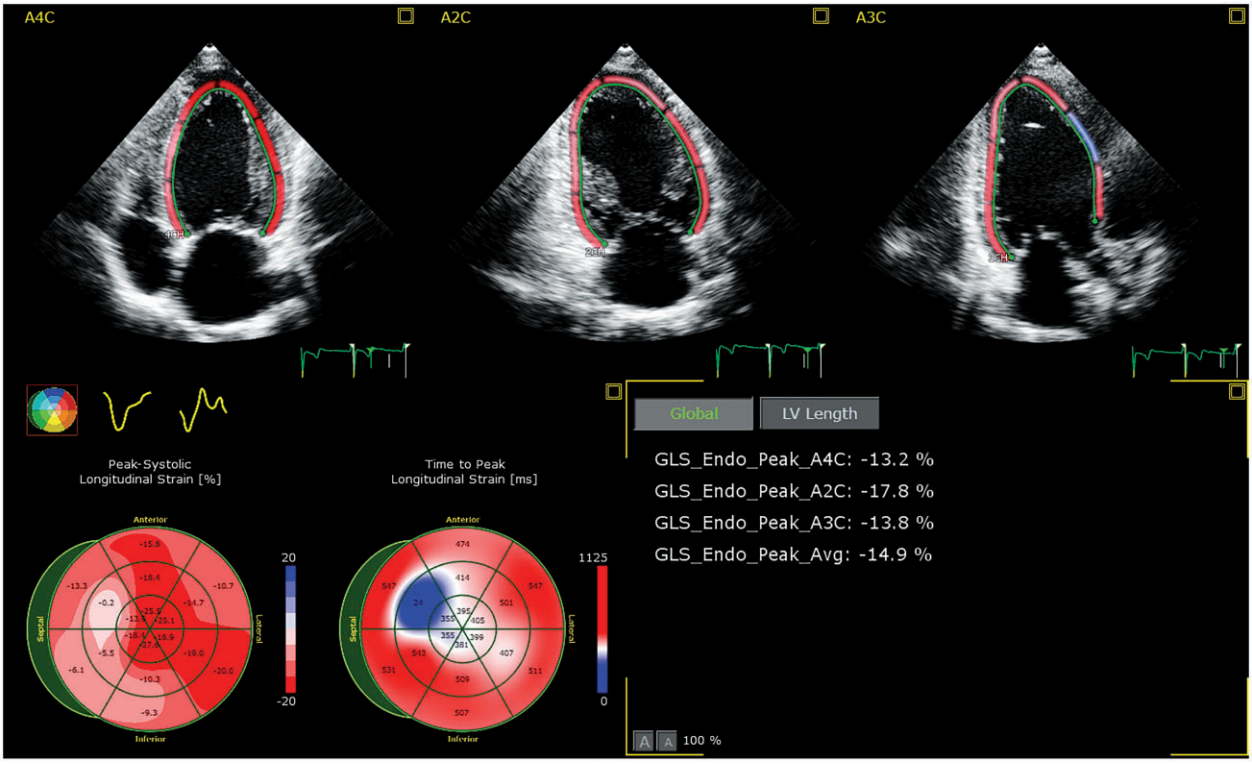


Figure 5 Automated left ventricular strain analysis by transthoracic echocardiography.

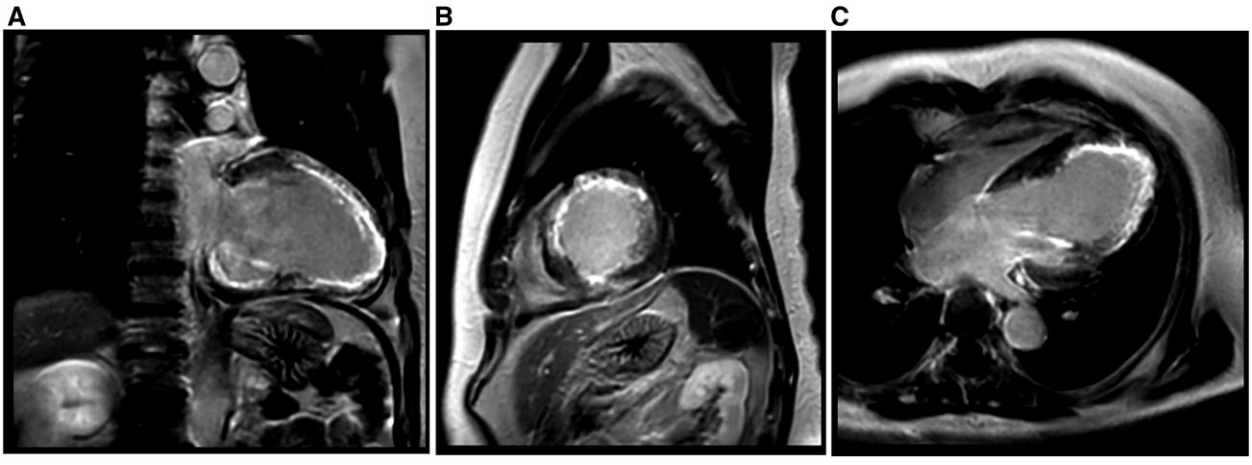


Figure 6 Left ventricular late enhancement by cardiac magnetic resonance image, courtesy of St. Marianna University School of Medicine, Japan. (*A*) Left ventricular long-axis view (*B*) Left ventricular short-axis view (*C*) Four-chamber view.

individualized management and therapy. The enhanced ability to determine the optimal treatment for each patient at the right time increases the likelihood of response to treatment, and improves patient outcomes.

Advances in all imaging techniques continue to hone accuracy, sensitivity, and standardization of functional and prognostic assessments, and identify new and novel therapeutic targets. Further progress in artificial intelligence, machine learning, and computer algorithms, combined with translational genomic, transcriptomic, proteomic, and metabolomic approaches, will become increasingly valuable in better understanding pathologies and in the development of new, targeted therapies.

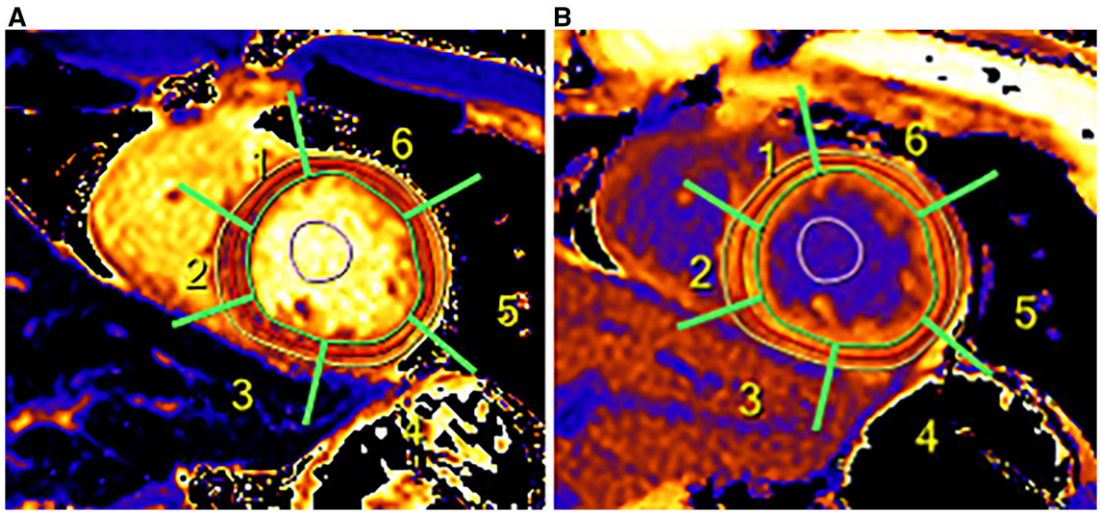


Figure 7 T1 mapping and extra cellular volume with segmentation in a case of myocarditis. (*A*) T1 Native SA, 1.1 × 1.1 × 10 mm, 12 s and (*B*) T1 Enhance SA, 1.1 × 1.1 × 10 mm, 12 s.

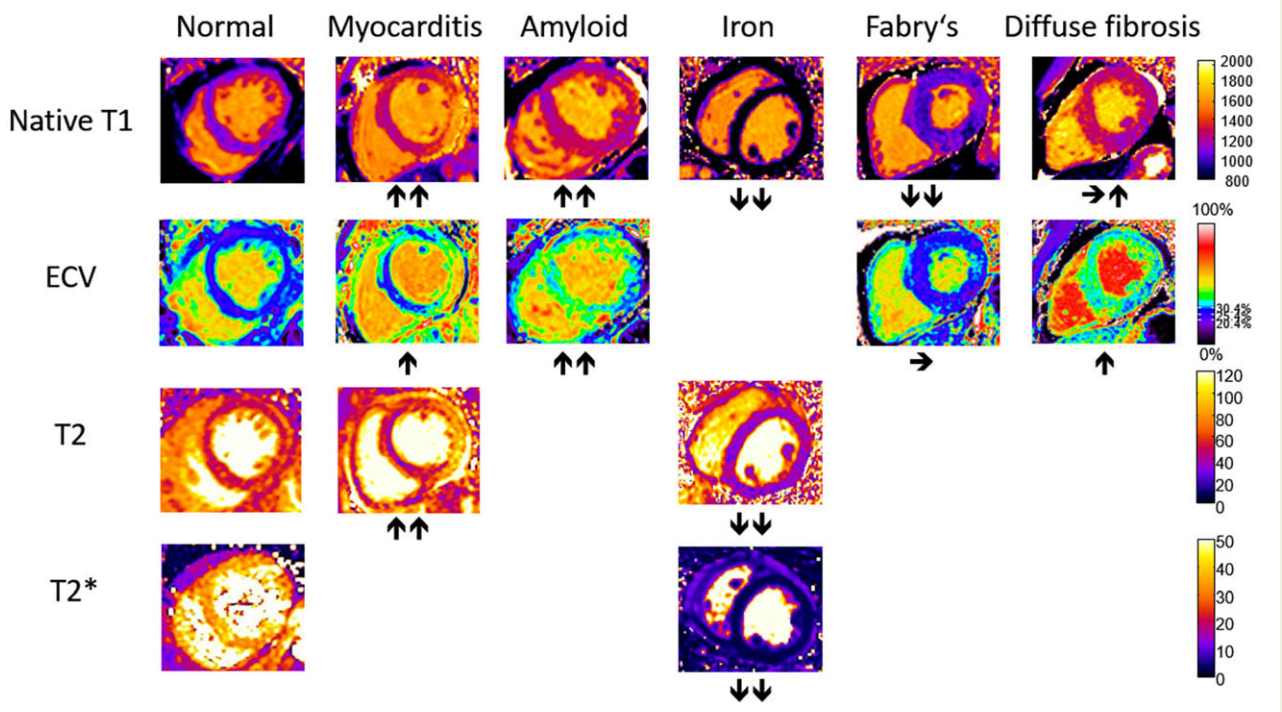


Figure 8 Examples of typical T1, T2, T2*, and ECV maps in healthy subjects and in patients with myocardial disease. Reprinted from Messroghli *et al.*[53] Arrows denote relative change in respective parametric maps.

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Data availability

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