Editorial Commentary on The Use of Advanced Cardiac MRI in Heart Failure and Cardiac Hypertrophy

Should CMR be the default imaging modality in clinical trials for heart failure?

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Heart failure (HF) is a complex syndrome with a broad heterogeneity of underlying aetiologies. Anatomically, it may result from pathologic conditions in the myocardium, pericardium, endocardium or the heart valves (1). However, HF can just as well be a maladaptive response to extra-cardiac conditions. This diagnostic ambiguity creates difficulties in matching clinical presentations and underlying aetiology once HF is clinically overt. Furthermore, pre-clinical stages of the disease often remain undiagnosed leading to dissatisfactory rates of primary prevention. The lack in understanding and revealing a potential common molecular basis of the syndrome is currently reflected by clinician's approaches to phenotype it (2).

At present, the definition of HF according to both the European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) is based on non-physiological cut-off values of left ventricular ejection fraction (LVEF) and divides the disease in two (AHA/ACC) or three (ESC) different categories (1,3). HF with a reduced ejection fraction (HFrEF) is hereby defined as left ventricular ejection fraction ≤40% (LVEF) whereas HF with a preserved ejection fraction (HFpEF) incorporates patients with a LVEF ≥50%. The latest addendum to this group is HF with a mid-range ejection fraction (HFmrEF, LVEF 41–49%) which, thus far, exclusively appears in European guidelines, mainly to stimulate research in this frequently neglected patient group.

Guideline recommended EF cut-offs for HF are arbitrary constructs adapted from early stages of HF outcome trials and mirror patient selection for these studies rather than disease processes or underlying pathophysiology (4). Therefore, optimal reproducibility and reliability of imaging techniques used in these trials is vital. In HFrEF, there is significant progress and multiple aetiologies are now identified by enhanced imaging tests at earlier stages translating into informed care decisions and thus, improved care of patients (5-9). However, despite a declining incidence and availability of novel treatment options in HFrEF over the last 2 decades, hospital admissions due to HF are rising, 5-year mortality rates remain around 50% and survival rates in elderly populations are stagnant (10-12). Diagnosing HFpEF is significantly more time-consuming and no single test is yet available to ascertain a diagnosis (13). Adding to the confusion is the difficulty in discerning underlying pathophysiological mechanisms in patients with a high burden of multi-morbidity and concomitant conditions. Unsurprisingly, it is estimated that the currently diagnosed patients are only the "*tip of the iceberg*" as the syndrome often goes unrecognised (14). Furthermore, prognostic treatment is absent and current disease management is based on risk factor optimisation and symptom control.

Subsequently, there is a clear unmet need for novel medical therapies in patients with HFpEF and HFrEF.

Randomised controlled trials (RCT) provide the least biased method to assess efficacy and safety of emerging therapies in many diseases, including HF, and are therefore considered the gold standard (15,16). Nevertheless, evidence generated by different clinical trials on the same topic may be conflicting and translating results into clinical practice challenging (17). Disparities in trial designs have

previously been identified as a frequent cause for the aforementioned and it has been shown that generating meta-analyses of published RCTs does not necessarily increase generalisability of results (17,18). In addition, individual trials have used distinctive imaging modalities for screening and/or outcome measures and evidence comparing the various techniques is scarce (19-23). With this in mind, the question arises whether a certain imaging test should be favoured when designing clinical trials and if so, which imaging technique offers the best overall value?

Firstly, the ideal imaging test for trials in HF patients has to have gatekeeping function for screening purposes but also reveal underlying phenocopies of a disease and thus offer best possible patient selection. In HFpEF, with its varying definitions and high phenotypic heterogeneity, insufficient exclusion of imaging phenocopies like hypertrophic cardiomyopathy, constrictive pericarditis or microvascular dysfunction might interfere with overall outcomes and could be a possible explanation for negative trial results in this population (24).

Secondly, if the imaging technique improves phenotyping and patient characterisation, it may lead to enhanced definition of subgroups within the trial cohort. As a growing number of trials report detailed subgroup analyses in various contexts, this feature could generate ideas for future dedicated outcome trials. A positive example for this approach is the success story of the anti glycaemic sodium glucose co-transporter 2 (SGLT-2) inhibitors for HF treatment, which began with a positive signal in a subgroup of the patients enrolled in the EMPAREG-OUTCOME trial and has now shown efficacy in a dedicated HF outcome trial (25,26).

Thirdly, despite available prognostic treatment options for HFrEF, it has to be noted that most phase III trials in both HFrEF and HFpEF patients were overall negative hence, not meeting their primary outcomes (27,28). This makes a trial a luxurious but equally necessary experiment with many uncertainties involved and may be one of the reasons why drug development and trial conduct in cardiovascular diseases are stagnant (29). Consequently, the imaging technique should be able to reduce costs by improving stratification of promising investigational agents in phase II trials and allow for reduced sample sizes. Furthermore, by providing a plethora of surrogate endpoints it may increase mechanistic understanding of the investigational agent at the same time (30).

Lastly, as HF incidence and prevalence increases with age, patients frequently present with one or more comorbidities. One of the most important comorbidities is renal dysfunction and many experts refer to both HFrEF and HFpEF as cardio-renal diseases as the incidence of renal dysfunction in chronic HF is increasing (31). Consequently, it is clear that a deeper understanding of mechanisms that link cardiac and renal dysfunction is required. Therefore, the imaging technique should allow multi-organ assessment during a single session.

Cardiovascular magnetic resonance (CMR) is a unique non-invasive imaging technique to assess HF patients without using ionising radiation or radionuclides and with excellent image quality independently of anatomical variations (5). Its high temporal and spatial resolution offer assessment of anatomical structures and functional cardiovascular parameters alike (32,33). It allows for comprehensive assessment of cardiac remodelling including tissue characterisation, quantification of extracellular volume content and identification of myocardial fibrosis, infarction, inflammation and oedema (7). In addition, novel sequences (4D-Flow) permit quantification of ventricular blood flow and kinetic energy in a single, short acquisition (34). As signal generation by CMR works via stimulating nuclei, when generating images these are hydrogen nuclei in water bonds within any given structure, it is not limited to image creation but with different spectroscopic techniques can also assess myocardial energy metabolism and fat composition (35-37). Furthermore, it has an excellent diagnostic accuracy, reproducibility and is less operator dependent when compared to echocardiography (5,38). Finally, it allows assessment of multiple organs in one session which are closely related to the clinical syndrome of HF and may provide improved mechanistic understanding of inter-organ links in pathophysiology.

Nevertheless, using CMR in the context of clinical trials implies certain limitations. The need for the participant to lie flat and hold their breath for a certain amount of time may reduce applicability of CMR in trials enrolling acutely decompensated HF patients. As HF is more prevalent in elderly, frail patients there is reduced tolerance to the confined space in the MR-scanner and patients may be less enthusiastic about participating in trials using this imaging technique, specifically when used at multiple timepoints. Furthermore, it has to be taken into consideration that patients with implanted cardiac devices and/or metal implants usually present with a reduced diagnostic accuracy as the implants produce artefacts. Conversely, assessment by echocardiography is more convenient and nowadays available in any hospital. It can be used in any patient group

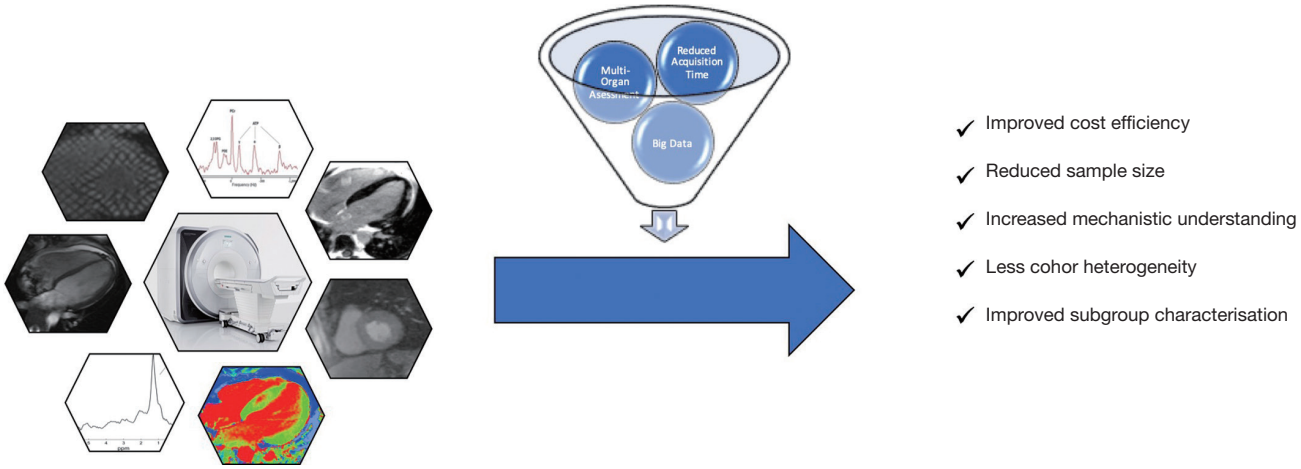

Figure 1 Schematic overview of how the various imaging and spectroscopic techniques CMR has to offer combined with new acquisition and post-processing approaches improve design and results of phase II and phase III clinical trials in HF patients.

and therefore is the customary imaging technique used in clinical trials involving HF patients (39).

However, use of CMR in HF trials is rapidly increasing and although large scale data from randomised trials comparing the imaging modalities is scarce, registry data suggests that use of CMR in HF patients may be more cost-effective due to its superior diagnostic accuracy (40,41). The recent randomised controlled OUTSMART-HF trial investigating routine versus selective use of CMR in chronic HF patients confirmed these results (42,43). Use of CMR increased the diagnostic accuracy in determining HF aetiology by 16%, when compared to transthoracic echocardiography. Nonetheless, routine CMR use did not yield more specific heart failure aetiologies which is concerning as patients with a distinct aetiology were at higher risk for cardiovascular events. More than 25% of the study population in each group had HF conditions lacking characteristic imaging findings highlighting the need to improve our categorisation of HF. Follow-up trials of the IMAGE-HF project are designed to identify novel imaging biomarkers in HF patients and will hopefully lead to better stratification (43).

With the expansion of shorter, free-breathing acquisitions, new sequences to assess haemodynamic parameters, refined contrast free tissue characterization and enhanced multi-organ assessment acceptance, accuracy and cost-effectiveness of CMR in trials will further improve (44). Increasing precision of automated post-processing techniques will advance its efficiency and promote new big data algorithms to identify novel imaging targets.

All of the above makes CMR, when compared to the most frequently used echocardiography, the ideal imaging technique to be utilised in phase II and phase III HF trials (*Figure 1*).

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