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REVIEW ARTICLE

The Utility of Circulating and Imaging Biomarkers Alone and in Combination in Heart Failure

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Abstract: Clinical trials in the treatment of heart failure have relied on the use of a composite of hard clinical endpoints to evaluate the efficacy of the treatment arm. This has led to prolonged trials requiring large patient cohorts and extensive funding to reach statistical significance.

In this paper, we have explored the potential of currently available circulating and imaging biomarkers associated with heart failure as a surrogate for hard clinical end points in clinical trials. This would be expected to result in shorter trials, smaller patient cohorts and limited funding required. We have subsequently theorized on combining circulating and imaging biomarkers as a surrogate for clinical end points such as hospitalization from heart failure and cardiac mortality.

Keywords: Circulating and imaging biomarkers, heart failure, cardiac mortality, myocardial injury, CMR, ECG.

1. INTRODUCTION

Heart failure (HF) is a global pandemic affecting at least 26 million people worldwide [1] and is associated with high morbidity and mortality [2]. It is a clinical syndrome characterised by signs and symptoms of dyspnoea, fatigue, oedema and pulmonary rales. The syndrome may represent either systolic dysfunction causing HF with reduced ejection fraction (HFrEF) or diastolic dysfunction resulting in HF with preserved ejection fraction (HFpEF). No single diagnostic test exists, which is why diagnosis is made with a combination of history, examination, laboratory testing and imaging [3]. Biomarkers are now frequently relied upon to aid diagnosis, monitor treatment and identify those at the highest risk of deterioration [4]. A number of circulating and imaging biomarkers for HF exist but alone have limited prognostic power [5]. A combination of biomarkers typically yields the best results, and although limited, there is some evidence to suggest this may also be true in HF [6].

This review will discuss available circulating and imaging (*i.e.,* echocardiographic and Cardiovascular Magnetic Resonance imaging (CMR)) biomarkers used in the assessment and prognostication of HF patients. The review will also discuss the available evidence for combining these biomarkers with a focus on their utility in describing cardiac inflammation and fibrosis. Lastly, mortality and HF admissions are used as endpoints in pharmacological and device trials in HF. They require large study cohorts over an extended trial duration. The review will allude to the unique potential of combining these biomarkers as a surrogate for outcome assessments.

2. BIOMARKERS

A biomarker can be defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to therapeutic interventions [7]. Biomarkers are utilised frequently to improve patient care; this is most prominently seen in the field of medical oncology. Biomarkers such as oestrogen receptor status in breast cancer directly dictate the use of tamoxifen treatment to improve outcomes. This direct relationship between biological processes and targeted treatment is not well-established in cardiology [8]. This individualised precise medical management is attractive, and there have been large volumes of research into biomarkers in HF. Some such as B-type Natriuretic Peptide (BNP) or Ejection Fraction (EF) are routine in clinical practice, while others are regularly employed in research settings. For an HF biomarker to be clinically useful, it should fulfill a number of suggested criteria: 1 -) testing should be low cost, 2 -) assays used to detect that the biomarker must be robust with quick turnaround, 3 -) the biomarker should reflect an important pathophysiological pathway involved in the HF disease process, 4 -) the biomarker should provide in-

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formation beyond what is available from routine examination and laboratory evaluation, and 5 -) it should add to clinical judgement for understanding diagnosis, prognosis and management of HF [9, 10].

3. METHODS

We completed a review of the literature for articles discussing biomarkers in HF. We searched the PubMed database in March 2020 for studies published between January 2010 and February 2020. We used a number of search terms, including free-text terms such as heart failure biomarkers, circulating biomarkers in heart failure, imaging biomarkers in heart failure and combining biomarkers in heart failure. Article references were also searched further for additional relevant studies.

4. CIRCULATING BIOMARKERS

4.1. Myocardial Stretch

The first natriuretic peptide introduced as a marker of myocardial stretch was Atrial Natriuretic Peptide (ANP) [11]. ANP was a marker of elevated cardiac filling pressures [11], but its use was limited by instability [12]. As a result, ANP was replaced by the largely ventricular-derived BNP and its amino-terminal propeptide equivalent N-terminal pro-BNP (NT-proBNP). Their use is now widespread in the management of HF [9]. Ventricular wall stress is the most significant trigger for the induction of the BNP gene, which releases the prepeptide proBNP. This is cleaved both within the cardiomyocyte and in peripheral sites to the biologically active BNP and inactive NT-proBNP [9]. BNP binds to natriuretic peptide receptors, stimulating natriuresis, vasodilation, lusitropy and reducing cardiac remodelling [9]. BNP and NT-proBNP play a role in diagnosis with values less than 35 pg/ml and 100 pg/ml, respectively, effective in excluding HF, while values of less than 100pg/ml and 300pg/ml, respectively, are appropriate cut-offs in acute presentations [2, 13]. Both BNP and NT-proBNP are established markers predicting prognosis in HF, and their raised levels are independently associated with mortality and other adverse outcomes [14-16]. The 2017 American College of Cardiology (ACC) guidelines for the management of heart failure endorse the use of BNP and NT-proBNP, with class I recommendations for its use in diagnosis and prognosis [17]. The use of both markers alone to guide therapy in HF is less clear and controversial due to conflicting results. Few studies have shown significant survival benefits with natriuretic peptide-guided therapy, while others have only shown positive trends or even neutral results [18-24].

Despite ANP's lack of stability, its precursor protein mid-regional-proANP (MR-proANP) is stable and can be measured [9]. Data suggests that MR-proANP is a robust marker in HF [25]. It is non-inferior to BNP and NT-proBNP in the diagnosis of HF and can even reclassify patients with BNP results that are difficult to interpret [26]. In addition, MR-proANP has prognostic power and can predict mortality in patients with chronic HF [27].

4.2. Myocardial Injury

Troponin was first identified as an integral protein within the cardiac muscle in 1963 [28]. It is superior to traditional markers of injury such as myoglobin and creatine kinase-MB due to its clinical sensitivity and tissue specificity. It has formed the basis of acute myocardial infarction diagnosis for many years [29]. High sensitivity assays now exist measuring troponin T (TnT) and troponin I (TnI), two distinct troponin subunits. Both TnT and TnI are found in individual isoforms encoded in three genes, slow skeletal, fast skeletal and cardiac muscle [30]. These high sensitivity assays detect the cardiac-specific isoforms. TnT and TnI assays are often used interchangeably, and their use clinically is often determined by local biochemistry laboratory supply. Comparisons between the assays in certain populations have shown only a modest correlation ($r=0.54$) between TnT and TnI, suggesting that some care is required in interpreting these assays [31].

Cardiac troponin is almost completely found bound to the sarcomere, but 5% can be found in the cytoplasm [32]. During episodes of ischaemia, this cytoplasmic troponin is released first and causes the initial rapid rise in serum troponin levels [32]. However, rises in detectable troponin occur most commonly in the absence of ischaemia [33]. This is now termed myocardial injury and occurs through a number of mechanisms, including HF [33]. Myocardial injury in HF arises as a result of a number of factors, including subendocardial stress and myocyte degeneration [10]. A number of studies have confirmed that elevation of high sensitivity troponin T (despite undetectable levels on conventional troponin assays) in patients with acute HF predicts mortality [34, 35]. High sensitivity troponin T remains prognostic in patients with chronic stable HF, with elevated levels predicting adverse cardiovascular outcomes, hospitalisation for cardiovascular causes and mortality [36, 37]. The use of troponin as a prognostic marker in HF has a class I recommendation from the ACC guidelines [17].

4.3. Cardiac Inflammation

The myocardium is sensitive to inflammatory cytokines, which can promote inflammation and cardiac injury [38, 39]. The resulting damage can impair heart function and cause HF. The most prominent and frequently used marker for the overall systemic burden of inflammation is the acute phase reactant C-Reactive Protein (CRP), which is produced by hepatocytes and stimulated by the inflammatory cytokine interleukin IL-6 [40]. Interest in inflammation and HF outcomes began as early as 1956 when it was found that chronic HF patients with elevated levels of CRP had more severe cardiac dysfunction [41]. More recently, high sensitivity CRP (hsCRP) has become available to detect low-grade inflammation in conditions such as HF [42]. Elevated hsCRP in chronic HF is now an established marker of poor prognosis, predicting more severe disease and increased morbidity and mortality [43-45]. For patients presenting with acute HF, the role of hsCRP as a marker of prognosis is less clear and is not recommended [38].

Tumour necrosis factor-alpha (TNFα) is a proinflammatory cytokine that forms part of the innate immune system's inflammatory response [46]. It was in 1990 that it was first identified that circulating levels of TNF-α were elevated in patients with chronic HF [47]. Further research into the association between TNFα and chronic HF demonstrates that raised levels can predict the development of HF in healthy individuals [48], predict symptom severity [49] and predict mortality [50, 51]. These findings are explained by TNFα downregulating myocardial sarcoplasmic reticulum Ca^{2+} ATPase and promoting cardiac remodelling resulting in impaired cardiac function [38].

4.4. Cardiac Fibrosis

Fibrotic diseases, including HF, are a proven cause of morbidity and mortality, accounting for over 800,000 deaths around the world each year [52]. Cardiac fibrosis is triggered following an insult, most frequently ischaemia. It is a protective mechanism but, over time, leads to irreversible ventricular remodelling and cardiac dysfunction [52]. The fibrosis-related dysfunction is a result of increased ventricular stiffness and compromised electrical conduction [53]. Given the impact of fibrosis on the heart, there is great interest in novel markers of cardiac fibrosis [54].

The suppression of the tumorigenicity-2 (ST2) network plays a critical role in mediating fibrosis and myocardial and vascular remodelling. Usually, IL-33 binds to the ST2 receptor causing the downstream reduction in programmed cell death and activation of profibrotic pathways. Soluble ST2 (sST2) acts as a decoy receptor for IL-33, preventing binding to the ST2 receptor promoting myocardial cell death and fibrosis [9]. Levels of sST2 may be elevated in the absence of heart failure in 10-18% of men and 2-8% of women, but measurement still has value in both acute and chronic HF [55]. Serial measurements of sST2 in the acute setting predicts mortality [56], and in chronic HF, it is superior to BNP and NT-proBNP in predicting worsening HF, rehospitalisation, heart transplantation and death [57]. In contrast to the natriuretic peptides, sST2 concentrations are also unchanged by obesity, age, atrial fibrillation or renal function [9].

Galectin-3 is produced by activated macrophages and stimulates macrophage migration and fibroblast proliferation-inducing cardiac fibrosis [58]. The concentration of galectin-3 is maximal during peak fibrosis and is almost absent after recovery, making it a dynamic marker of fibrosis [59]. It has been shown to be a superior predictor to NT-proBNP in patients with acute HF in predicting episodes of recurrent HF and death [60]. Despite being a useful marker in acute HF, its role in diagnosis is limited, and it is inferior to the natriuretic peptides in this regard [61]. In chronic HF, galectin-3 is effective in predicting mortality [62], and the use of serial levels has been shown to predict the first morbid event, hospitalisation for HF and mortality [63]. In addition, elevated levels of galectin-3 in healthy individuals predict the development of new-onset HF and also mortality [64]. Galectin-3 is an effective marker in HFpEF, elevated levels correspond to more severe diastolic dysfunction [65, 66], and it is the most accurate marker of hospitalisation and mortality in these patients [67].

Despite the available evidence for cardiac fibrosis biomarkers, their utilisation in clinical settings remains limited. At this time, a class IIb recommendation by the ACC exists for their use in HF, and it has been suggested that more benefit may be derived through the combination with other biomarkers (circulating or imaging) [17].

4.5. Future Directions

The search continues for novel circulating biomarkers in heart failure despite the wide range currently available. Recent work has identified the potential of MicroRNAs (miRNAs) and metabolomics as biomarkers.

MiRNAs are endogenous, conserved, single-stranded, small (~22 nucleotides) non-coding ribonucleic acid (RNA) with critical roles in cardiovascular biology. They have shown promise in challenging clinical settings where currently established biomarkers perform poorly, such as atrial fibrillation or obesity, discriminating between HFrEF and HFpEF, and determining heart failure aetiology [68-70]. Further investigation is still required in validating miRNA panels and clarifying their role in prognosis, diagnosis and management.

The heart is a highly metabolically active organ that is capable of generating adenosine triphosphate (ATP), the energy-carrying molecule in cells, from a diverse range of sources, including carbohydrates, lipids, lactate, amino acids and ketones. Despite the heart's adaptability, it remains susceptible to disruptions in cardiac metabolism, frequently seen in most cardiovascular diseases. Metabolomics investigates metabolites affecting genetic, epigenetic, transcription and protein factor variation that remain responsive to environmental exposures, dietary intake and the gut microbiome [71]. Measurement of these circulating metabolites exposes changes in both cardiac and systemic metabolism [72]. Studies have already identified metabolites such as long-chain acylcarnitines levels that are related to heart failure severity and are sensitive to treatment [73, 74]. Metabolomics has also revealed that patients with HFrEF and HFpEF, currently thought to be unique clinical entities, share common metabolic derangements with raised levels of long-chain acylcarnitines [75]. Despite currently being in its infancy, metabolomics has the potential to identify clinically relevant biomarkers that add to our understanding of heart failure pathophysiology and may lead to the development of targeted metabolic therapies.

5. IMAGING BIOMARKERS

5.1. Echocardiogram

Echocardiogram is a safe and available resource for cardiac imaging. The use of transthoracic echocardiogram is the mainstay of HF assessment and cardiac function [2].

The EF is the basis of ventricular systolic function and can be defined as the percentage of blood ejected in systole

in relation to the volume of blood in the ventricle at the end of diastole. It can be calculated by a number of methods, most frequently by using a biplane technique [76]. The Left Ventricular EF [LVEF] is a strong predictor of clinical outcomes in patients with HF. Reduction in LVEF strongly predicts the severity of symptoms and all-cause mortality [77]. Furthermore, a declining trajectory of LVEF also predicts mortality [78]. In addition to its prognostic power, LVEF is vital in guiding medical and device therapy [2].

Increases in Left Ventricular Mass (LVM) are caused by cardiac remodelling, and it is associated with high blood pressure, increased body mass index, smoking status and diabetes mellitus. LVM can be estimated by using either two-dimensional (2D) or three-dimensional (3D) echocardiography. The LVM is based on the myocardial density (1.05g/ml) multiplied by the myocardial volume (left ventricular (LV) volume subtracted from the volume enclosed by the epicardium). Echocardiogram-derived LVM has been shown to be a reliable predictor of adverse cardiovascular events [79].

The term strain in echocardiography describes local shortening, lengthening and thickening of the myocardium to evaluate regional LV function. Strain is frequently calculated using speckle-tracking echocardiography. This technique employs the speckles in myocardial tissue caused by acoustic markers on ultrasound. The speckles throughout the myocardium are stable over a short time period, and their 2D displacement can be calculated. With these results, strain can be calculated for the LV in circumferential, longitudinal and radial directions. In 2D echocardiography, strain can be only be calculated in two axes, whilst strain in all three axes can be recorded with 3D echocardiography. Typically to measure global LV function, strain is recorded as Global Longitudinal Strain (GLS), the average strain of all speckles in the longitudinal direction [80]. In acute HF, GLS predicts HF readmission [81], adverse cardiac events [82], and it has been shown to be superior to LVEF in predicting mortality [83]. In chronic HF, GLS effectively predicts HF exacerbation, ventricular assist device placement, cardiac transplantation and all-cause mortality [84, 85]. Furthermore, in asymptomatic individuals, GLS can predict the development of new-onset HF [86]. This has led to increasing utility within the cardio-oncology specialty for monitoring LV function in patients at risk of chemotherapy-related cardiac toxicity [87]. This allows timely initiation of HF therapy to avoid cessation of potential lifesaving cancer therapy, an area with further studies underway [88].

Myocardial Work (MW) is a novel non-invasive echocardiographic approach that assesses regional myocardial work by LV Pressure-Strain Loop (PSL) analysis *via* echocardiographic software, thus incorporating both strain and afterload with non-invasively estimated pressure from brachial cuff blood pressure. This technique has been validated with invasive LV Pressure-Volume Loops (PVL) and regional myocardial metabolism with glucose turnover measured by positron emission tomography, providing a robust method for LV performance assessment taking loading conditions into account [89]. The association between non-invasive derived global MW by PSL and favourable response to Cardiac Resynchronisation Therapy (CRT) was demonstrated in patients with HF of both ischaemic and non-ischaemic aetiology, predicting subsequent reverse remodelling [90, 91]. MW efficiency is distinctly reduced in HFrEF patients [92]. A Global Work Index (GWI) of <500 mmHg% was shown to be a predictor of poor prognosis with established prognostic parameters of HF [94]. Non-invasive myocardial work is still at an early developmental stage. The published results to date are promising whilst requiring further validation to reach routine clinical practice.

Diastolic dysfunction of the LV or HFpEF may be challenging to detect with echocardiography. During diastole, the left atrium is exposed to increasing LV pressures. Subsequently, left atrial pressures rise to maintain appropriate filling. This sustained increase in pressure leads to dilatation and stretching of the atrial myocardium. Therefore, left atrial volume is an established marker of the severity of diastolic dysfunction [94]. Despite this clear association, up to one-third of patients with diastolic dysfunction have normal left atrial volume [94, 95]. This triggered an investigation into assessing left atrial function by evaluating parameters such as left atrial strain. Work in this area has identified that left atrial strain is a marker of diastolic dysfunction, worsening atrial fibrillation, stroke and may be a predictor of adverse cardiovascular events [96, 97].

The Right Ventricle (RV) can be defined as low pressure, high volume pump in contrast to the LV, which is a high pressure, high volume pump [98]. Consequently, due to exposure to lower pressures, the overall mass of the RV is approximately one-sixth of the LV. The RV and LV are interconnected by networks of muscle fibres and are functionally interdependent. As a result, impairment of RV function is detrimental to overall cardiac function [99]. Assessment of the RV, although not the gold standard, is possible with the use of echocardiography through a number of methods [5]. RV fractional area change is a percentage change in cavity area from end-diastole to end-systole and is a predictor of stroke, HF, cardiovascular death and all-cause mortality [100]. Tricuspid Annular Plane Systolic Excursion (TAPSE) is a relatively simple measure of RV function. It is calculated with the use of M-mode in the apical four-chamber view measuring the displacement of the tricuspid ring in the longitudinal plane of the RV. TAPSE has been shown in healthy individuals to predict the development of cardiovascular disease [101]. Given the success of strain measurements in the LV, RV strain has also been investigated. The results show that RV strain in chronic HF patients is a powerful predictor of admission for HF, cardiac transplantation, emergency ventricular assist device implantation and death, and may even be superior to other measurements of RV and LV function [102].

5.2. CMR

CMR is the gold standard cardiac imaging modality for the measurement of volumes, mass, and EF. It also plays a

pivotal role in determining HF aetiology, visualising myocardial fibrosis and assessing viability. Weaknesses include availability, cost, limited use of gadolinium-based contrast in renal impairment due to the risk of nephrogenic systemic fibrosis and patient compliance factors such as orthopnoea and claustrophobia [2]. Detailed images produced by CMR rely on hydrogen nuclei which are abundant in water and fat. The use of a strong magnetic field followed by a radiofrequency wave causes the randomly spinning nuclei with their own magnetic vector to initially align and subsequently resonate. The magnetic field and radiofrequency wave are then terminated, causing the nuclei to emit a signal which is used to create the images seen in MRI. Multiple radiofrequency pulses can be used in sequence to emphasise different mediums. Each medium has a different rate of relaxation and can be measured in two ways, the first is T1 relaxation which is the time for the nuclei to return to the resting magnetic vector and T2 relaxation is the time taken for the nuclei to return to their resting spin [103]. The use of gadolinium-based contrast is commonplace. The contrast reduces the T1 relaxation time of tissues, and the factors contributing to the greatest changes are local perfusion, the extracellular volume of distribution and water exchange rates (between vascular, interstitial and cellular spaces) [104, 105].

As discussed earlier, myocardial fibrosis has a significant impact on heart function. CMR is an effective tool in measuring fibrosis with the use of Late Gadolinium Enhancement (LGE) to measure focal localised fibrosis and T1 mapping to measure diffuse interstitial fibrosis. The use of LGE to measure cardiac fibrosis was first described in animal models in 1984 [106]. Since this time, it has been increasingly used to accurately measure cardiac fibrosis in a wide range of conditions, including HF, myocardial infarction, hypertrophic cardiomyopathy, aortic valve disease, sarcoidosis, amyloidosis, hypertensive cardiomyopathy and diabetic cardiomyopathy [107]. LGE has also been shown to predict adverse outcomes in many of these conditions [108-112] and more recently has been proposed to guide implantable cardioverter defibrillator therapy [113]. Native T1 mapping to measure fibrosis and inflammation is more novel and could be used in the absence of gadolinium without limitation by renal impairment. There are a number of different techniques to acquire a T1 map, the more common ones being a Modified Look-Locker inversion recovery (MOLLI) and the Shortened Modified Look-Locker inversion recovery (SchMOLLI), which have been shown to accurately measure fibrosis both in the intracellular and extracellular space, in myocardial infarction [114, 115], amyloidosis [116], systemic sclerosis [117], diabetic cardiomyopathy [118], hypertrophic cardiomyopathy [119] and chronic HF [120, 121]. The map is an image of each pixel which is colour-coded according to the absolute T1 time. There is also evidence now demonstrating that fibrosis detected by T1 mapping predicts adverse outcomes [122]. Increased TI times may also indicate inflammation and, therefore, will need to be interpreted in conjunction with T2 mapping described in a later section.

The other method of evaluating extracellular volume (ECV) is by creating pre and post-contrast T1 maps (ECV mapping). The extracellular volume is a marker of volume expansion, which can be due to diffuse myocardial fibrosis or myocardial inflammation. There was a prospective observational multi-centre longitudinal study in 637 consecutive patients with dilated non-ischemic cardiomyopathy undergoing CMR with T1 mapping and LGE at 1.5-T and 3.0-T [123]. The primary endpoint was all-cause mortality, and a composite of HF mortality and hospitalization was a secondary endpoint. During a median follow-up period of 22 months (interquartile range: 19 to 25 months), a total of 28 deaths (22 cardiac) and 68 composite HF events were observed. T1 mapping indices (native T1 and extracellular volume fraction), as well as the presence and extent of LGE, were predictive of all-cause mortality and HF endpoint ($p < 0.001$ for all). In multivariable analyses, native T1 was the sole independent predictor of all-cause mortality and HF composite endpoints (hazard ratio: 1.1; 95% confidence interval: 1.06 to 1.15; hazard ratio: 1.1; 95% confidence interval: 1.05 to 1.1; $p < 0.001$ for both), followed by the models including the extent of LGE and RV EF, respectively. Non-invasive measures of diffuse myocardial disease by T1 mapping are significantly predictive of all-cause mortality and HF events in non-ischaemic dilated cardiomyopathy. The average LVEF in the initial cohort was about 47%, suggesting that the sensitivity of detecting changes is very high using these methods in a cohort with early disease.

The combination of other poor prognostic markers such as LVEF <35% or LGE with native T1 did not improve the predictive value of native T1 values alone, indicating the independent pathophysiological role of a diffuse myocardial disease as indicated by an elevated native T1 value [124]. Vita *et al.* further refined the assessment of diffuse myocardial disease by mapping 6 anatomical locations using all 4 CMR tissue-characterizing methods (native T1, extracellular volume mapping, partition coefficient (λGD) and late gadolinium enhancement) associating this with outcome [125]. The authors performed T1 mapping of the myocardium and the blood pool, before and serially after contrast injection, using a Look-Locker cine gradient-echo technique to obtain T1 and the corresponding reciprocal R1(1/T1) values. λGd values were derived from the slopes of the least-squares regression lines for myocardial *versus* blood R1, then adjusted to serum haematocrit to yield ECV.

After a median of 3.8 years, 36 (15%) experienced major adverse cardiac events (MACE), including 22 HF hospitalizations and 14 deaths. Non-ischemic LGE was detected in 34%, whereas ECV was elevated (in more than 1 location) in 58%. Comparing the 4 methods, mean ECV and λGd both demonstrated a strong association with MACE (both $p < 0.001$). In contrast to native T1 and LGE, ECV values from all 6 locations were associated with MACE and death, with the anteroseptum being the most significant ($p < 0.0001$). The number of abnormal ECV locations correlated linearly with annual MACE rates ($p = 0.0003$). Mean ECV was the only predictor to enter a prognostic model that contained age, sex, New York Heart Association functional class, and LVEF. For every 10% increase, mean ECV portended to 2.8-fold adjusted increase risk to MACE ($p < 0.001$). These

newer non-invasive imaging techniques, namely serial T1 mapping imaging characterizing ECV fraction, have been validated against diffuse interstitial fibrosis by histology in non-ischaemic dilated cardiomyopathy [126, 127].

Detection of myocardial inflammation-causing cardiac dysfunction is significant as it is treatable with a number of management options available [128, 129]. The gold standard in diagnosis is the endomyocardial biopsy, but it is prone to sampling errors, is invasive and has risks [130]. The use of CMR with T2 mapping presents an opportunity for non-invasive detection of myocardial inflammation. Research comparing the use of T2 mapping to endomyocardial biopsy suggests that it may be a reasonable alternative [131], and increased T2 has also been shown to be a predictor of MACE [132].

As with any diagnostic test, standardization of data acquisition and post-processing, as well as predefined reference ranges, are a prerequisite for the application of quantifiable imaging biomarkers in clinical routine. Achieving this and standardizing the various vendor platforms remain the main impediments to this being used in routine clinical practice, but in the setting of clinical trials, these obstacles may be overcome, especially with the use of a core lab to acquire and process the images.

6. COMBINING CIRCULATING AND IMAGING BIOMARKERS

An extensive range of biomarkers is now available in HF [5, 133]. Both circulating and imaging biomarkers have much to offer, but most research has investigated their utility in isolation. Risk models do exist but largely only incorporate circulating biomarkers [134]. The limited work available combining circulating and imaging biomarkers has been confined to mostly natriuretic peptides and echocardiogram [5].

Natriuretic peptides have been considered the gold standard biomarker in HF and are routinely used in its management [135]. However, as discussed earlier, the benefits of using natriuretic peptides alone to guide HF therapy are unclear. The work by Simioniuc *et al.* highlights the potential benefits of combining circulating and imaging biomarkers. The authors compared clinically guided HF therapy and BNP combined with echocardiogram-derived measures of increased LV pressure (E wave deceleration time as a surrogate of pulmonary capillary wedge pressure and for patients in atrial fibrillation deceleration time of mitral flow velocity) guided HF therapy. Patients were not randomised, and propensity score matching of confounding baseline variables was utilized to minimise bias. The results demonstrated that combining these biomarkers reduced rates of acute kidney injury (9.8% *vs.* 21.4%, p<0.0001) and death (hazard ratio: 0.45; 95% confidence interval: 0.30-0.67, p<0.0001) [6] (Fig. **1**). Furthermore, Bajraktari *et al.* compared 794 outpatients with heart failure treated in three groups: group I with BNP combined with echocardiogram (E/e' and E wave deceleration time as surrogates of increased LV pressure together with lung ultrasound to assess B lines) guided therapy, group II with clinically guided therapy and group III with those managed with no specific specialist follow up. They found a 60 months survival of 88% in group I, 75% in group II and 54% in group III (p<0.0001) [136]. These results highlight a clinical role for the combination of BNP and echocardiogram in improving HF outcomes.

BNP: B-type natriuretic peptide; HR: Hazard ratio; CI: Confidence interval. Figure used with permission from Simioniuc *et al.* [6].

As discussed previously, circulating biomarkers of fibrosis exist, such as galectin-3, which have been proposed to not be just a by-product but an active culprit in the development of myocardial fibrosis [137]. CMR and possible myocardial works with echocardiography is an effective tool for visualising both focal and diffuse myocardial fibrosis. The combination of CMR and markers of fibrosis presents an opportunity to directly visualise the underlying pathological process. There is some evidence to suggest that galectin-3 and Matrix Metalloproteinase-2 (MMP-2), a marker of extracellular matrix remodelling, may best correlate with the level of fibrosis seen on CMR with the use of T1 mapping and LGE [138]. Further work is needed to develop models combining CMR and circulating fibrosis markers to predict outcomes.

Multiple circulating biomarkers of myocardial inflammation also exist. There has been work performed to investigate combining T1 mapping and LGE findings of fibrosis together with circulating inflammatory biomarkers. Mateus *et al.* investigated a population of 1345 patients from the Multi-Ethnic Study of Atherosclerosis (MESA), a multicentre prospective cohort study. These patients had CMR with T1 mapping using the MOLLI recovery sequence. Patients were excluded if they self-reported medical conditions that could elevate non-specific inflammatory markers. 772 participants remained in the final study population. The results showed that in men, elevated IL-6 was associated with a 0.4% higher ECV (p=0.05), and elevated CRP was associated with a 4.9ms higher native T1 (p=0.03). However, no such correlation between inflammatory markers and CMR detected fibrosis was present in women [139]. Markers of inflammation and CMR were also explored by Wu *et al.* to identify HF patients at the highest risk of malignant cardiac rhythms. In total, 235 patients with chronic ischaemic and non-ischaemic cardiomyopathy with an LVEF <35% undergoing insertion of an Implantable Cardioverter-Defibrillator (ICD) had hsCRP and CMR to assess grey zone (scar related heterogenous myocardium *via* LGE) performed and the median follow-up was 3.6 years. The primary end point was appropriate ICD shock for ventricular tachycardia/fibrillation or cardiac death. The adjusted hazard ratio for the primary end point for hsCRP was up to 2.8 (95% confidence interval: 1.1-7.1, p=0.03), and for the grey zone, it was 4.6 (95% confidence interval: 1.4-15.4, p<0.01). Significantly, the combination of hsCRP and grey zone was associated with a hazard ratio of up to 24.0 (95% confidence interval: 3.1-184, p=0.002), suggesting the combination of hsCRP and CMR may assist in identifying low-risk patients, with the least po-

tential benefit, meeting current guidelines for ICD insertion [140]. Ongoing work in this area may continue to identify further prognostic indicators.

CMR with T2 mapping provides an alternative to endomyocardial biopsy to evaluate myocardial inflammation [131]. However, to our knowledge, no studies exist that combine circulating biomarkers of inflammation and T2 mapping, providing an opportunity for future studies.

7. UTILITY OF BIOMARKER(S) AS A SURROGATE FOR AN OUTCOME MEASURE

The selection of the primary 'endpoint' or 'outcome measure' has a major impact on the reliability and interpretability of clinical trials designed to study the effect of an intervention. As HF studies, especially interventional studies, with hard outcome measures such as mortality, are difficult to conduct, the use of biomarkers as a surrogate measure becomes attractive for a number of reasons [7]. Biomarkers are far cheaper, easier and faster to measure than the actual outcome measure and also require smaller sample sizes which can subsequently reduce costs and the time for trial completion. However, to prevent confounding factors from nullifying the value of surrogate outcome measures, a thorough knowledge of the pathophysiology of the disease and the intervention being performed is required [141]. While HF biomarkers strongly correlate with clinical efficacy measures in natural history observations, they are not causal in the pathway of the disease process and may provide misleading information about clinical efficacy.

HF is a complex heterogenous condition, and in some respects, such as HFpEF, it is still poorly understood [142]. In addition, our understanding of biomarkers is still not comprehensive, the timing of measuring biomarkers to confirm benefit is uncertain, and we have limited knowledge in regard to how significant a change in biomarker levels is needed before there is any benefit [143]. Vaduganathan *et al.* evaluated the use of ANP, BNP and NT-proBNP biomarkers known to be associated with mortality as a surrogate endpoint for HF therapy. The authors found that the changes in natriuretic peptides levels were associated with HF hospitalisation but not mortality [144]. These findings highlight that we still lack a complete understanding of the relationships between HF and its biomarkers. It would be reasonable to conclude that despite an array of promising biomarkers available to us, we are not yet in a position to completely replace mortality as a primary endpoint, but considering biomarkers as a composite of surrogate outcomes may have potential [145].

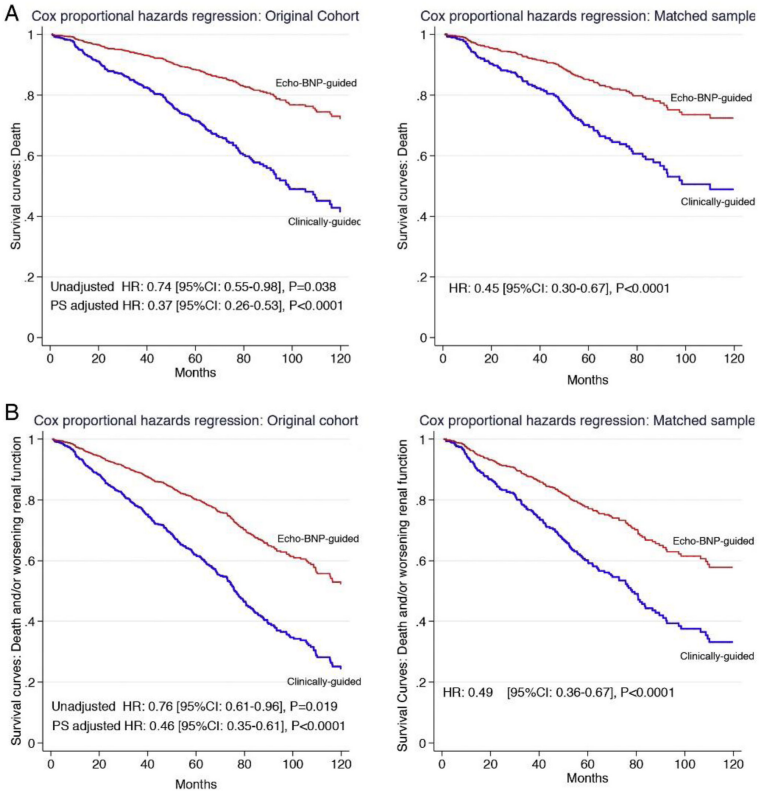

Fig. (1). (**A**) Kaplan-Meier curves for all-cause death in patients of the echo-BNP guided and clinically guided groups before (left) and after (right) propensity score matching. (**B**) Kaplan-Meier curves for the combined end point of and worsening renal function in echo-BNP guided and clinically guided groups before (left) and after (right) propensity score matching. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Fibrosis, a marker of cell death, represents the last stage of the pathophysiological process of myocardial injury from a range of disease processes [146]. We posit that targeting cardiac fibrosis as the surrogate endpoint for HF therapy with the use of a combination of circulating and imaging biomarkers is a future research area. Based on available evidence from previous studies, the combination of Galectin-3 and either myocardial works with echocardiography or T1 mapping with CMR holds the most promise as they represent the closest surrogate for fibrotic replacement of the myocardium [59, 107, 147]. Future studies should evaluate a combination of fibrosis biomarkers as a composite end point that would also include HF hospitalization as the latter has been shown to result in poorer quality of life, prognosis, as well as represents a huge economic burden on the health system [148].

CONCLUSION

A vast range of circulating and imaging biomarkers are used for HF diagnosis, monitoring treatment and also identifying patients who are at the highest risk of deterioration. Preliminary studies indicate that a strategy based on the combination of circulating and imaging biomarkers is superior to when either one is used alone for such purposes. Larger studies are, however, needed before such approaches can be adopted into clinical practices.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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