Integration of imaging and circulating biomarkers in heart failure

Moura, Brenda; Aimo, Alberto; Al-Mohammad, Abdallah; Flammer, Andreas; Barberis, Vassilis; Bayes-Genis, Antoni; Brunner-La Rocca, Hans-Peter; Fontes-Carvalho, Ricardo; Grapsa, Julia; Huelsmann, Martin

Published in:
European Journal of Heart Failure

DOI:
10.1002/ejhf.2339

Publication date:
2021

ESC European Society of Cardiology

European Journal of Heart Failure (2021) **23**, 1577–1596
doi:10.1002/ejhf.2339

POSITION PAPER

Integration of imaging and circulating biomarkers in heart failure: a consensus document by the Biomarkers and Imaging Study Groups of the Heart Failure Association of the European Society of Cardiology

Brenda Moura[1,2]*†, Alberto Aimo[3]†, Abdallah Al-Mohammad[4], Andreas Flammer[5], Vassilis Barberis[6], Antoni Bayes-Genis[7,8], Hans-Peter Brunner-La Rocca[9], Ricardo Fontes-Carvalho[10,11], Julia Grapsa[12], Martin Hülsmann[13], Nasrien Ibrahim[14], Christian Knackstedt[9], James L. Januzzi[14], Tomas Lapinskas[15], Axel Sarrias[7], Simon Matskeplishvili[16], Wouter C. Meijers[17], Daniel Messroghli[18], Christian Mueller[19], Noemi Pavo[13], Justas Simonavičius[9,20], Arco J. Teske[21], Roland van Kimmenade[22], Petar Seferovic[23,24], Andrew J.S. Coats[25], Michele Emdin[3], and A. Mark Richards[26,27]

[1]Faculty of Medicine, University of Porto, Porto, Portugal; [2]Cardiology Department, Porto Armed Forces Hospital, Porto, Portugal; [3]Scuola Superiore Sant'Anna, and Fondazione G. Monasterio, Pisa, Italy; [4]Medical School, University of Sheffield and Sheffield Teaching Hospitals, Sheffield, UK; [5]Cardiology, University Hospital Zurich, Zurich, Switzerland; [6]American Medical Center, American Heart Institute, Nicosia, Cyprus; [7]Heart Institute, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; [8]CIBERCV, Instituto de Salud Carlos III, Madrid, Spain; [9]Department of Cardiology, Cardiovascular Research Institute Maastricht, Maastricht University Medical Centre, Maastricht, The Netherlands; [10]Cardiovascular Research and Development Unit (UnIC), Faculty of Medicine University of Porto, Porto, Portugal; [11]Cardiology Department, Centro Hospitalar de Vila Nova Gaia/Espinho, Espinho, Portugal; [12]Department of Cardiology, Guys and St Thomas NHS Hospitals Trust, London, UK; [13]Department of Internal Medicine, Division of Cardiology, Medical University of Vienna, Vienna, Austria; [14]Cardiology Division, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA; [15]Department of Cardiology, Lithuanian University of Health Sciences, Kaunas, Lithuania; [16]Lomonosov Moscow State University Medical Centre, Moscow, Russia; [17]University Medical Centre Groningen, Groningen, The Netherlands; [18]Department of Internal Medicine-Cardiology, Deutsches Herzzentrum Berlin and Charité-Universitätsmedizin Berlin, Berlin, Germany; [19]Department of Cardiology, University Hospital Basel, Basel, Switzerland; [20]Vilnius University Hospital Santaros klinikos, Vilnius, Lithuania; [21]Department of Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands; [22]Department of Cardiology, Radboud University Medical Center, Nijmegen, The Netherlands; [23]Faculty of Medicine, University of Belgrade, Belgrade, Serbia; [24]Serbian Academy of Sciences and Arts, Belgrade, Serbia; [25]University of Warwick, Coventry, UK; [26]Christchurch Heart Institute, University of Otago, Dunedin, New Zealand; and [27]Cardiovascular Research Institute, National University of Singapore, Singapore

Received 26 March 2021; revised 28 July 2021; accepted 29 August 2021; online publish-ahead-of-print 14 September 2021

Circulating biomarkers and imaging techniques provide independent and complementary information to guide management of heart failure (HF). This consensus document by the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) presents current evidence-based indications relevant to integration of imaging techniques and biomarkers in HF. The document first focuses on application of circulating biomarkers together with imaging findings, in the broad domains of screening, diagnosis, risk stratification, guidance of treatment and monitoring, and then discusses specific challenging settings. In each section we crystallize clinically relevant recommendations and identify directions for future research. The target readership of this document includes cardiologists, internal medicine specialists and other clinicians dealing with HF patients.

Keywords Biomarkers • Imaging • Diagnosis • Management • Heart failure • Consensus document

*Corresponding author. Armed Forces Hospital, Av. Boavista, 4050-115, Porto, Portugal. Email: brendamoura.c@gmail.com
†These authors contributed equally.

Introduction

Heart failure (HF) remains an important cause of morbidity and mortality worldwide, mandating ongoing efforts to optimize its management.[1] The screening, diagnosis, risk stratification and treatment of HF are all informed by imaging findings and levels of circulating biomarkers, especially transthoracic echocardiogram (TTE) and natriuretic peptides (NPs). The combination of imaging and laboratory findings of biomarkers has been proposed, most notably in the case of the diagnosis of HF with preserved ejection fraction (HFpEF).[2] Imaging and biomarkers have been most often considered separately, without searching for accurate and cost-effective ways to integrate the information derived from both into global algorithms that can be used in clinical practice.

The term 'biomarker' (from 'biological marker') was coined in 1989 to identify a 'measurable and quantifiable biological parameter used to assess the health and physiology of patients in terms of disease risk and diagnosis'.[3] While imaging findings could be named as biomarkers, this term is most commonly used to define circulating molecules that convey information on disease processes. At present, no position paper deals specifically with the integration of biomarkers and imaging in HF: this consensus document by the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) presents current evidence base for the integrated use of imaging techniques and biomarkers in HF. The document first covers broad applications of imaging and biomarkers (i.e. population screening, diagnosis, outcome prediction, guidance of therapy and follow-up), and then discusses specific challenging settings. In each section, clinically relevant recommendations are produced, and possible directions for future research are identified. The target readership of this document includes cardiologists, internal medicine specialists and all the physicians dealing with HF patients.

Screening

In studies incorporating systematic screening of the general population, several imaging findings were associated with HF development, most notably left ventricular (LV) systolic dysfunction and dilatation,[4,5] but also diastolic dysfunction[5,6] and LV hypertrophy.[7,8] In addition, a few studies have highlighted the prognostic value of abnormal LV deformation on speckle-tracking TTE or cardiac magnetic resonance (CMR) strain analysis in asymptomatic subjects.[9,10] Elevated B-type NP (BNP) or N-terminal pro-BNP (NT-proBNP) may be present in asymptomatic individuals with structural heart disease, who have a high risk of progressing to clinical HF.[11–16] High-sensitivity (hs) troponin I and T have very low coefficients of intra-individual variability (around 9% for hs-troponin I measured with the Architect method),[17] which is lower than NPs (e.g. 36% for NT-proBNP).[18] Therefore, even small increases in hs-troponin on repeated measurements may signal worsening cardiac damage and predict higher risk of future HF.[19,20]

The 2016 ESC position paper on cancer treatments recommended a systematic assessment using a combination of echocardiography and biomarkers in all patients before, during and after cardiotoxic cancer therapies.[21] Conversely, ESC guidelines on hypertension recommend an echocardiographic evaluation in specific cases, namely in the presence of 'ECG abnormalities or signs or symptoms of LV dysfunction' [class I, level of evidence (LOE) B], and optionally 'when the detection of LV hypertrophy may influence treatment decisions' (class IIb, LOE B).[22] The 2019 ESC guidelines on diabetes just state that 'routine assessment of circulating biomarkers is not recommended for cardiovascular risk stratification' (class III, LOE B), without any specific recommendations on echocardiography.[23] Furthermore, an ESC position paper states that 'NP measurement by general practitioners and diabetologists in high-risk populations such as those with hypertension or diabetes mellitus helps the targeted initiation of preventive measures, including medicine up-titration of renin–angiotensin system antagonists and, therefore, prevent or slow the development of HF'.[24]

A possible perspective for future research is to identify the optimal (i.e. most cost-effective) strategies to identify subclinical HF among subjects with predisposing conditions, most notably hypertension and diabetes. An integrated approach to screening might prove valuable. The finding of elevated biomarkers [BNP >50 ng/L,[25] NT-proBNP >125 ng/L,[20] or hs-troponin > upper reference limit (URL)] or increasing levels across repeated measurements (including small elevations in hs-troponin) warrants further evaluation that frequently includes performing TTE. A point-of-care TTE screening might be considered as an alternative to a two-step screening (biomarkers and then TTE) when plasma biomarker results are less accessible. Evidence of structural heart disease (such as LV dilatation and systolic dysfunction) may prompt commencing cardiac protective therapies to delay the onset of symptomatic HF (*Figure 1*). More subtle abnormalities, such as impaired global longitudinal strain (GLS),[22] may suggest intensified surveillance or the initiation of cardiac protective medications. The need for advanced imaging techniques, including CMR, should be decided on a case-by-case basis following a TTE examination.

Key point

Systematic screening for HF in the general population is likely not to be cost-effective. Screening might be considered in patients with conditions predisposing to HF, such as hypertension and diabetes, to identify subclinical HF that warrants initiation of cardiac protective therapies. A possible alternative to the current approach to HF screening in hypertensive and diabetic individuals is a two-step screening with the measurement of NPs or hs-troponin and then TTE, when circulating biomarkers are either elevated or rising. This combined approach should be evaluated in dedicated studies.

Diagnosis

The use of NPs to diagnose acute HF is well-established and recommended by major guidelines.[2,26,27] The diagnosis of non-acute HF, particularly in patients with preserved ejection fraction (HFpEF) or mildly reduced ejection fraction (HFmrEF), is more challenging.

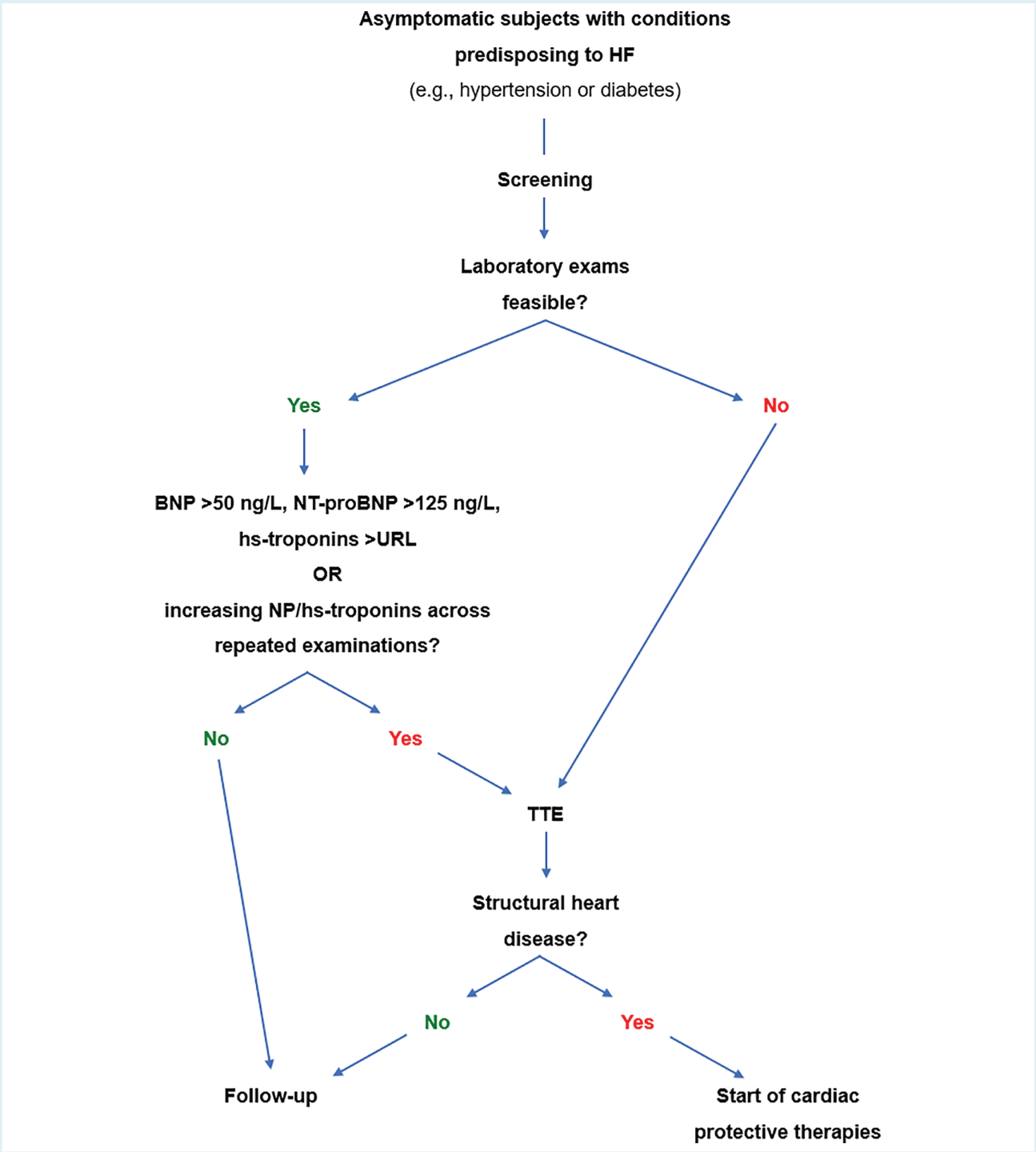

Figure 1 Proposed algorithm to screen for individuals at risk for heart failure (HF). See text for details. BNP, B-type natriuretic peptide; NP, natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TTE, transthoracic echocardiogram; URL, upper reference limit.

Heart failure with preserved ejection fraction

The diagnosis of HFpEF is a perfect example of integration between imaging and biomarkers. The 2016 ESC guidelines defined HFpEF as the combination of symptoms and/or signs of HF, LV ejection fraction (LVEF) ≥50%, elevated NP levels (BNP >35 ng/L and/or NT-proBNP >125 ng/L) together with evidence of structural heart disease [LV hypertrophy and/or left atrial (LA) enlargement] or diastolic dysfunction[2] (online supplementary *Table S1*). Indeed, the

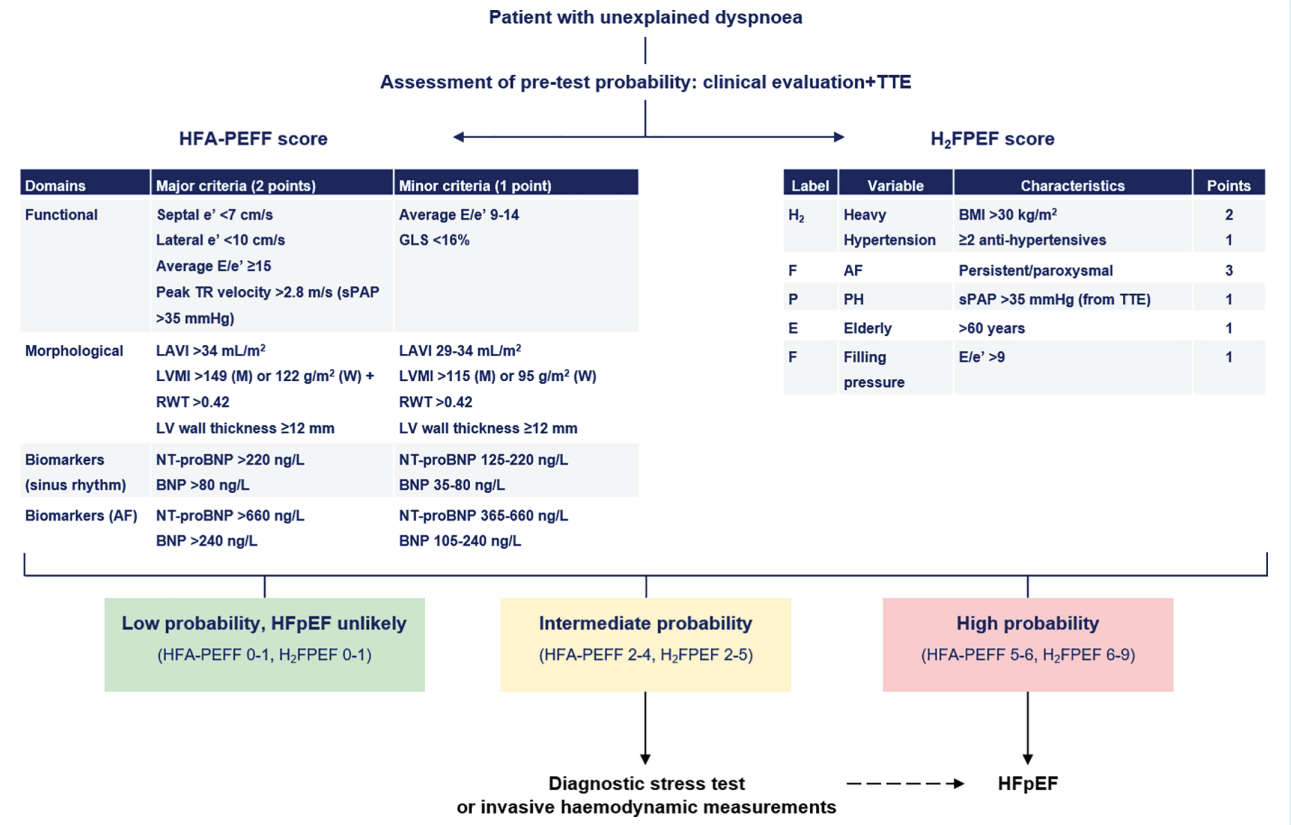

Figure 2 The HFA-PEFF and H_2FPEF scores. AF, atrial fibrillation; BMI, body mass index; BNP, B-type natriuretic peptide; GLS, global longitudinal strain; HFpEF, heart failure with preserved ejection fraction; LAVI, left atrial volume index; LV, left ventricular; LVMI, left ventricular mass index; M, men; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PH, pulmonary hypertension; RWT, relative wall thickness; sPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation; TTE, transthoracic echocardiogram; W, women.

2021 ESC guidelines defined HFpEF as the condition characterized by HF symptoms and/or signs, LVEF ≥50% and 'objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressure, including raised NPs'[28].

Overt congestion is often readily detectable from physical examination and chest X-ray, and can be corroborated by high NP levels. The diagnosis of HFpEF is more challenging in outpatients with early-stage HF who may complain of dyspnoea on effort, but do not display overt congestion.[29,30] Patients with HFpEF have lower plasma NPs than those with HF and reduced ejection fraction (HFrEF) for the same degree of congestion,[31] but differential cut-off levels of plasma NPs for HFpEF and HFrEF have not been found. Importantly, NP levels may be influenced by many cardiac and non-cardiac factors[31–33] (online supplementary *Table S2*), and should be interpreted accordingly.[24] Other biomarkers have not been systematically evaluated for their role in HFpEF diagnosis.

Right heart catheterization with measurement of pulmonary capillary wedge pressure at rest or during exercise is the gold standard for the diagnosis of HFpEF in patients with exertional dyspnoea of unclear aetiology. Costs, risks of complications, and requirements for specialized training and equipment limit its broad application. A diagnostic approach relying uniquely on exercise echocardiography is also limited.[30] The search for non-invasive alternatives to diagnose HFpEF has led to the introduction of the stepwise diagnostic algorithm HFA-PEFF,[34] the H_2FPEF score (using dichotomized variables)[35] and a HFpEF nomogram (using continuous variables)[36] (*Figure 2*).

The HFA-PEFF algorithm includes first an evaluation of risk factors and exercise intolerance. The likelihood of HFpEF is then estimated based on three domains (functional, morphological and biomarkers). A high HFA-PEFF score (5–6) allows diagnosis of HFpEF with 93% specificity, and a low HFA-PEFF score (0–1) rules out HFpEF with 99% sensitivity. Patients with an intermediate score (2–4) require further evaluation with exercise echocardiography or invasive measurement of cardiac filling pressures.[34,35,37]

The H_2FPEF score includes obesity, hypertension, atrial fibrillation (AF), pulmonary hypertension, age > 60 years and increased filling pressures. The likelihood of HFpEF is classified as low (scores 0–1), intermediate (2–5) or high (6–9), and score values are interpreted as in the case of the HFA-PEFF score.[35] Notably, the HFA-PEFF score includes NPs while the H_2FPEF score and the HFpEF nomogram do not. Head-to-head comparisons of

the two diagnostic scores are warranted to examine the added value of NP assessment beyond assessment of filling pressure by the E/e′ ratio. Another focus for future studies is integration of LA strain into the diagnostic algorithm of HFpEF. LA reservoir strain showed higher area under the curve for discrimination of HFpEF compared to E/e′ ratio, e′ velocity, LV GLS, concentric remodelling, LV hypertrophy, elevated tricuspid regurgitation (TR) velocity or indexed LA minimal volume. Therefore, LA reservoir strain may provide enhanced diagnostic accuracy beyond conventional echocardiographic measures to discriminate HFpEF from non-cardiogenic dyspnoea.[38] The added value of LA reservoir strain over NPs or other biomarkers of congestion remains to be established.

Heart failure with mildly reduced ejection fraction

The 2016 ESC HF guidelines gave separate consideration to diagnosis of HF with mid-range ejection fraction, which required symptoms and/or signs of HF, LVEF 40–49%, elevated NP levels (BNP >35 ng/L and/or NT-proBNP >125 ng/L) and at least one additional criterion: relevant structural heart disease (LV hypertrophy and/or LA enlargement) or diastolic dysfunction.[2] The recent Universal Definition of HF modified the name of HF with mid-range ejection fraction to become HF with mildly reduced ejection fraction, and introduced novel diagnostic criteria for HFmrEF, which include: (i) symptoms and/or signs caused by a structural and/or functional cardiac abnormality, (ii) elevated NP levels and/or objective evidence of pulmonary or systemic congestion, and (iii) LVEF values 41–49%.[39] Therefore, raised NPs are not mandatory where there are signs of congestion. The 2021 HF guidelines reflect this new approach and allow diagnosis of HFmrEF when symptoms and/or signs of HF are coupled with a LVEF of 41–49%.[28] Similarly, HFrEF is diagnosed when there are symptoms and signs of HF plus a LVEF ≤40%.[28]

Key point

The HFA-PEFF and H_2FPEF scores can standardize the diagnosis of HFpEF. The HFA-PEFF score includes the evaluation of NPs, but its relative diagnostic performance compared with the simpler H_2FPEF score is unclear. Diagnostic criteria for HFpEF require an integration of imaging and circulating biomarkers, while HFmrEF can be diagnosed even without evaluating NPs.

Risk prediction

Many imaging findings, including LV systolic and diastolic dysfunction,[40,41] the presence and extent of late gadolinium enhancement by CMR,[42] pulmonary hypertension and impaired right ventricular (RV) function,[43] have been associated with worse outcomes in patients with chronic HF. Circulating levels of NPs, hs-troponin and soluble suppression of tumorigenesis-2 (sST2) reflect different disease pathways and consistently improve risk prediction beyond the most extensively investigated imaging parameter, namely echocardiographic LVEF.[44,45]

Natriuretic peptides

More than 1000 studies have evaluated single and/or repeated measurements of NPs for prediction of outcomes in patients with acute or chronic HF, consistently showing high prognostic accuracy, additive to imaging findings.[24,46,47] A 2019 ESC position paper stressed the importance of NP measurement for outcome prediction in HF outpatients, but it did not provide any recommendation on risk prediction in patients with acute HF.[24]

Future development of the integrated use of NPs and imaging in chronic HF should include identification of different NP cut-offs across the spectrum of LVEF, and stratification of patients according to key confounding variables including age, sex, renal function, body mass index (BMI) and/or the presence of AF.

In acute HF, higher levels of NT-proBNP at discharge, or an inadequate decline of their levels during hospitalization, confer higher risk of readmission and/or death within 180 days. Notably, the prognostic model did not include any imaging parameter.[48] The prognostic value of admission and discharge NPs and their changes from admission to discharge should be further investigated across categories of LVEF.

High-sensitivity troponins

Increased circulating levels of hs-troponin I and T can be found in HF even in the absence of myocardial ischaemia or coronary artery disease,[49] reflecting the intensity of the ongoing cardiomyocyte damage.[50] Elevated troponin is associated with worse clinical outcomes and/or mortality irrespective of LVEF.[44,51–57] Significant and persistent falls in troponin with treatment confer a better prognosis compared to no fall or a transient decrease.[52,54–58] The 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guideline recommends troponin measurement for risk stratification in acute or chronic HF (class I, LOE A)[27] while the 2016 ESC guideline does not.[2] Hs-troponin T improved risk prediction over LVEF in a cohort of 9289 patients, mostly (85%) with HFrEF. The best cut-off for the prediction of all-cause mortality, cardiovascular mortality and hospitalization for cardiovascular causes was 18 ng/L. The latter maintained prognostic significance independent of the effects of age, sex, the presence of ischaemic aetiology, LVEF, estimated glomerular filtration rate (eGFR), and NT-proBNP.[44]

The 2016 ESC HF guidelines recommend hs-troponin measurement on admission in patients with suspected acute HF within a laboratory analysis panel including full blood count, electrolytes, renal function, blood glucose, thyroid and liver function tests (class I, LOE C), with the main goal of excluding an acute coronary syndrome.[2] Conversely, the ACC/AHA guidelines recommend measuring hs-troponin T/I on admission for the purpose of risk stratification (class I, LOE A).[26] The possible integration between hs-troponin measurement and imaging is not considered in either guideline.

Soluble suppression of tumorigenesis-2

Soluble ST2 is the circulating form of the interleukin-33 membrane receptor released in response to vascular congestion,

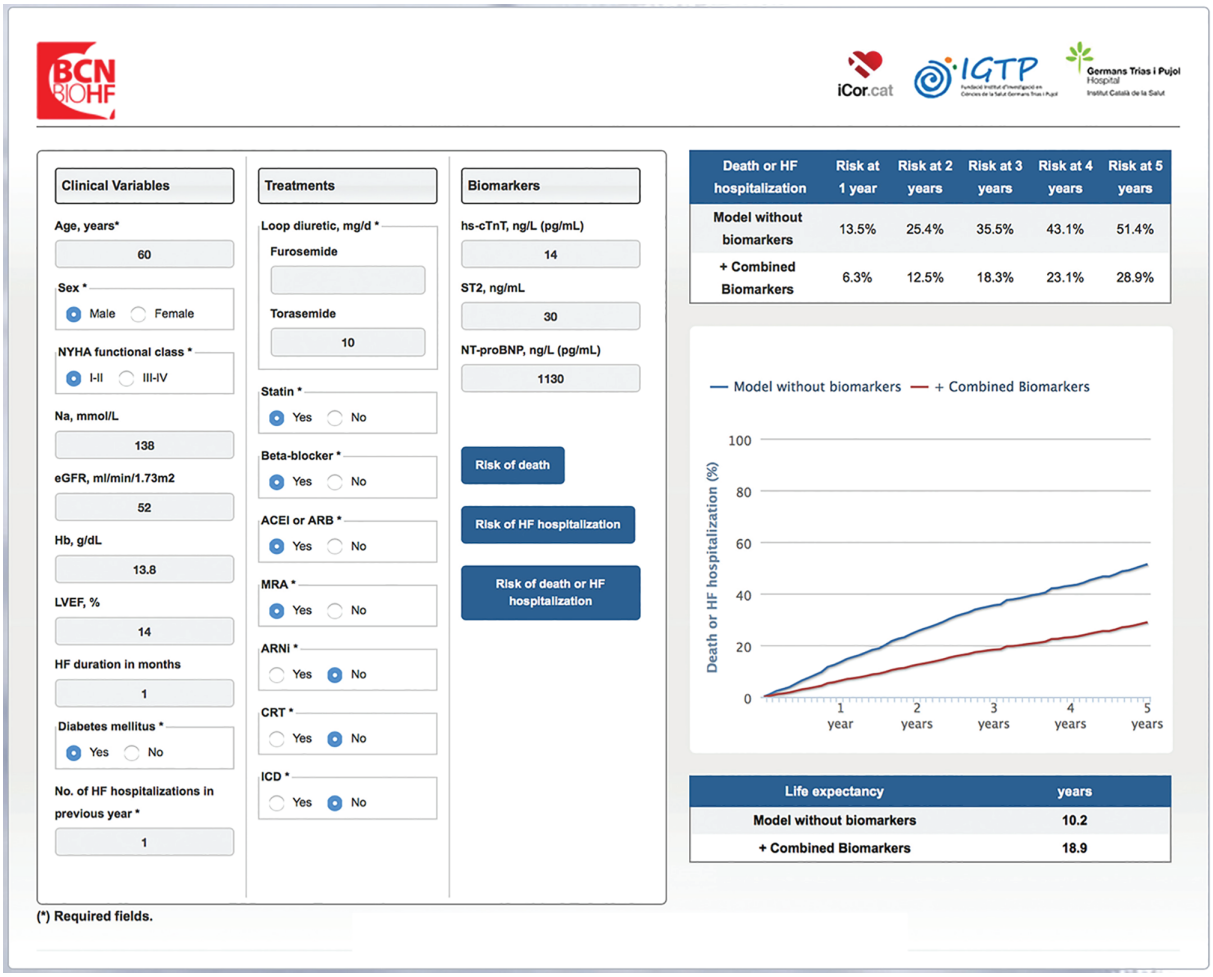

Figure 3 The Barcelona Bio-HF Calculator Version 2.0. This score provides risk estimates for 1-, 2-, 3-, 4- and 5-year mortality, heart failure (HF)-related hospitalization, and the composite endpoint for an individual patient. On the graph, the blue line represents the estimation without biomarkers (clinical model) and the red line represents the estimation with the addition of biomarkers. Reproduced from Lupón *et al.*[62]

inflammatory and pro-fibrotic stimuli.[57,58] sST2 levels are unaffected by age, sex, renal function or HFrEF/HFpEF status.[59,60] However, it can be altered by many inflammatory comorbidities,[59] which underlies its lack of utility as a diagnostic biomarker. An automated turbidimetric immunoassay for ST2 has recently been developed and validated, which may prompt increased adoption of sST2 in clinical practice.[61]

Despite these limitations, sST2 is a strong predictor of outcome in HF, the most commonly used cut-off being 35 ng/mL, predicting mortality and hospitalization in acute or chronic HF regardless of NT-proBNP, hs-troponin T, and LVEF.[45,59] The Barcelona Bio-HF Calculator Version 2.0 incorporates LVEF and other clinical variables, HF therapies (including sacubitril/valsartan) and biomarkers (sST2, NT-proBNP and hs-troponin T as continuous levels) (*Figure 3*). This score predicts all-cause mortality, HF-related hospitalization and the composite of both endpoints for up to 5 years. Biomarkers values are not mandatory for calculating this score, though their addition improves model performance. The score has been externally validated for up to 2 years.[62,63] Finally, the ST2-R2 score estimates the likelihood of reverse remodelling in HFrEF, and includes sST2 <48 ng/mL, together with baseline LVEF <24% and other variables.[64] Of note, ST2, as opposed to NPs, is weakly influenced by obesity, advanced age and chronic kidney disease (CKD).

Key point

Natriuretic peptides are established predictors of outcome in acute and chronic HF. Measurement of an hs-troponin, on at least one occasion, should be considered in outpatients with HFrEF. Patients with hs-troponin T ≥18 ng/L have a greater risk of all-cause and cardiovascular mortality and hospitalization for cardiovascular causes regardless of LVEF, NT-proBNP, age, sex, renal function and ischaemic aetiology. sST2 levels further refine risk prediction of outpatients with HFrEF with 35 ng/mL as a useful cut-off. The clinical impact and therapeutic consequences of assessing risk, however, need to be investigated in clinical trials.

Guide to treatment and follow-up

Imaging and biomarkers complement clinical history and physical examination and help guide therapy within an episode of HF decompensation and during follow-up.

Assessment of congestion

Patients with HF often develop congestion that may require urgent hospitalization, especially if lung congestion is present. Development of congestion leading to HF decompensation is a powerful predictor of poor patient outcome.[65,66] Therefore, we need to detect and monitor congestion before progression to decompensation. Congestion can be difficult to assess, especially when extrapulmonary signs of congestion are mild.[67] Increased intracardiac filling pressures often silently precede the appearance of congestive symptoms by days or weeks and mild congestion is not readily detected through bedside physical examination.[67] A history of progressive increase in body weight, dyspnoea, orthopnoea, systemic oedema, increased jugular venous pressure, and pathological third heart sound (after the age of 25 years) are all important clinical clues to congestion. However, these are often detected only once decompensation has become established.[67]

B-lines are observed on lung ultrasonography and are non-specific signs of interstitial oedema. Two small trials showed the potential of B-lines as a treatment target in chronic HF (<3 B-lines in eight thoracic sites).[68,69] A higher threshold (≥3 B-lines in at least two windows bilaterally) was suggested in acute HF.[70,71] Other aetiologies for B-lines, such as pulmonary fibrosis, should be excluded. Circulating biomarkers (most notably elevated NPs) improve the specificity of B-lines on lung ultrasonography.

The role of echocardiography in assessing congestion was specifically analysed in a previous position paper from the ESC.[72] Briefly, echocardiography allows a point-of-care assessment of LV filling pattern and pulmonary artery pressure. An E/e′ ratio ≥15 denotes increased LV diastolic pressure consistent with HF decompensation,[73] and effective decongestion results in a rapid decrease in E/e′.[74] In a small trial, a therapeutic strategy relying on lung and inferior vena cava ultrasound and on E/e′ measurement resulted in greater decongestion during shorter hospitalization without increased adverse events, compared to standard care, although the therapeutic workup was not standardized based on echocardiographic findings.[75]

Haemoconcentration, as assessed by increasing haemoglobin, haematocrit, albumin and total protein during decongestion, is predictive of outcome,[75] but there are no reliable cut-offs to differentiate euvolaemic from congested patients. Early haemoconcentration offers little prognostic information, as rapid intravascular refilling from the interstitial compartment can counterbalance the initial response to decongestive therapies.[76,77] Creatinine, often used as a biomarker to adjust diuretic therapy, is not reliable as it may rise in both hyper- and hypovolaemia.[78] Importantly, a rising creatinine in the setting of successful decongestion may predict a better outcome,[79] nevertheless its rise should prompt a re-evaluation of fluid status. Effective decongestion is also accompanied by decreasing NPs, with some reports of a better survival of patients with a more pronounced decrease.[80] Furthermore, sST2 acts as a biomarker of congestion, and percent changes in sST2 are predictive of 90-day mortality regardless of NP levels.[81] At present, we lack sufficient evidence to define plasma thresholds to trigger further clinical assessment or adjustment of therapy.

An algorithm for congestion management integrating imaging and biomarkers is shown in *Figure 4*. It incorporates signs and symptoms and the dynamics of blood biomarkers, including NPs, creatinine and full blood count. Asymptomatic patients with low NPs and no unfavourable changes in NPs, creatinine and haemoglobin/haematocrit should be followed routinely. Symptomatic patients or those with blood biomarkers suggestive of congestion should undergo sonographic volume status assessment. The selection of imaging markers of congestion depends on available time, ultrasound device availability and the experience of the echocardiographer. At least two imaging markers for congestion should be positive to trigger escalation of therapy. Prospective randomized clinical trials are needed to ascertain if interventions based on this integrated approach improve outcomes.

Key point

Circulating biomarkers play an important role as indicators for sonographic fluid status assessment and will improve the specificity of sonographic findings. We need well-designed randomized clinical trials to test the concept of echo-guided decongestion with defined cut-offs for both echocardiographic measures and adjunctive circulating markers. Meanwhile, imaging markers and concurrent circulating biomarkers should be interpreted on a case-by-case basis.

Guide to heart failure therapy and follow-up

Imaging is required for allocation of certain HF treatments and to detect complications such as adverse LV remodelling[82] and functional mitral regurgitation.[83,84] Follow-up examinations are typically represented by serial echocardiograms; repeated CMR exams may be considered in selected cases. The latter allow accurate characterization of changes in chamber volumes and function and longitudinal assessment of tissue composition over time.

Among patients with chronic ambulatory HFrEF, reducing NT-proBNP to below 1000 ng/L within 12 months was associated with LV reverse remodelling and better outcomes.[85] Sustained reduction of NT-proBNP in HFrEF has been found to be associated with stable improvement in LV function and low likelihood of progressive remodelling.[86] A low NT-proBNP might obviate needless serial imaging in such patients.

Several meta-analyses of small-to-medium scale prospective trials have found a prognostic benefit from NP-guided therapy in HFrEF.[87–90] The Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) trial did not show a sustained difference in intensity of pharmacotherapy between study groups and no survival benefit from NT-proBNP-guided therapy. However, this trial achieved no difference in pharmacotherapy between study limbs.[91]

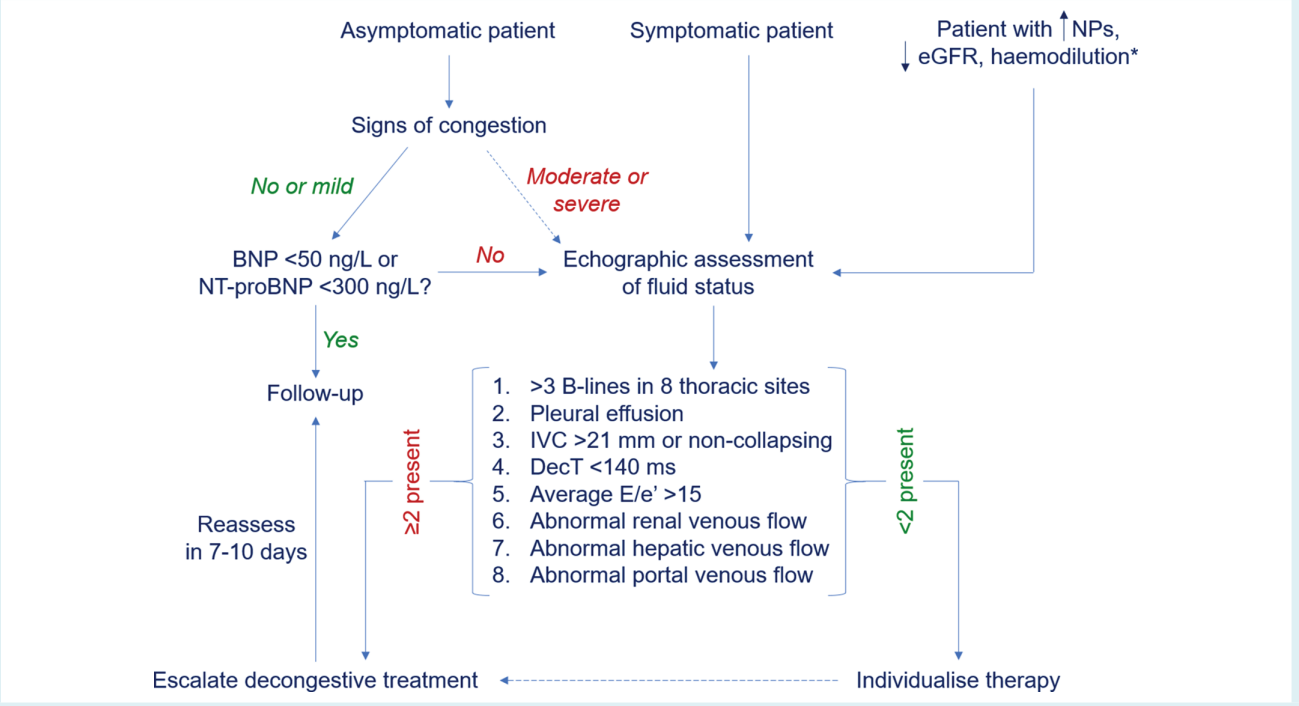

Figure 4 Proposed algorithm for integrated imaging and laboratory evaluation to guide congestion management. The dashed arrow means that asymptomatic patients are unlikely to have moderate or severe signs of congestion. BNP, B-type natriuretic peptide; DecT, E-wave deceleration time; eGFR, estimated glomerular filtration rate; IVC, inferior vena cava; NP, natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide. *Decreasing haemoglobin or haematocrit or albumin or total protein, unexplained by other reasons than progressing congestion.

Other biomarkers such as sST2, eGFR or the combination of multiple markers have been retrospectively investigated as tools to individualize therapy.[92–95] Prospective trials of marker-based guidance of treatment, including assessment of multi-marker approaches, are needed.

Key point

In chronic HFrEF, achieving concentrations of NT-proBNP <1000 ng/L is associated with LV reverse remodelling and a better prognosis. Sustained reduction in NT-proBNP below this level may allow a less intensive patient follow-up.

Heart failure with recovered/improved ejection fraction

The Universal Definition of HF has recently highlighted HF with improved ejection fraction (HFimpEF), defined as symptomatic HF with a baseline LVEF ≤40%, a ≥ 10-point increase from baseline LVEF, and a second LVEF measurement >40%.[40] This group replaces the previous entity of HF with recovered ejection fraction, which lacked a standard definition.

Left ventricular ejection fraction recovery has long been described in patients with HFrEF due to peripartum cardiomyopathy, alcohol abuse, myocarditis and ischaemic heart disease.[96–98] In recent-onset dilated cardiomyopathy, LVEF improved in 45% of patients at 12 months,[99] and in one third of cases within a 2-year follow-up when dilated cardiomyopathy was present for more than 1 year (thus excluding resolving acute myocarditis).[100] Significant improvement in LVEF has been observed in elderly patients with chronic HFrEF with intensification of therapy, regardless of the underlying cause.[96,97]

High rates of restoration of cardiac function have also been described in Takotsubo cardiomyopathy, toxic cardiomyopathy and peri-partum cardiomyopathy.[98,101] However, recovery cannot be defined solely by normalization of LVEF, as outcomes in this group remain worse than in controls (giving further support to the replacement of its old name by HFimpEF).[102] Other relevant parameters of reverse remodelling include changes in LV end-diastolic volume or GLS.[103,104] An increase in absolute GLS values >16% is predictive of sustained normalization of LVEF and good prognosis.[105]

Patients with HFimpEF may display continuing elevations of plasma NPs and troponin, denoting active haemodynamic overload and ongoing cardiomyocyte damage.[106] Although older age, discontinuation of therapy and longer HF duration are all associated with recurrence of HFrEF in HFimpEF, reliable prediction of future deterioration of cardiac function in individual patients remains challenging.[106] In a randomized study, HF therapy was withdrawn in a controlled setting in HF patients with improved LVEF, normal LV end-diastolic volume and NT-proBNP <250 ng/L (around 10% of an unselected HF cohort).[104] During and after down-titration of HF therapy, nearly half of the patients exhibited

recurrent LV abnormalities without significant symptomatic clinical events. The combination of persistently elevated NT-proBNP and reduced radial strain on CMR best predicted new deterioration of LV parameters.

Key point

Heart failure recovery is revealed by longitudinal changes in imaging findings, most commonly from repeated echocardiography, and is accompanied by a reduction in NPs. Our current state of knowledge suggests that HF medications should be continued in patients with HFimpEF to prevent a new decline of cardiac function in a large proportion of this group. Rising NT-proBNP portends new deterioration of LV function in HFimpEF.

Guide to defibrillator implantation

The indications for an implantable cardioverter defibrillator (ICD) for primary prevention currently comprise LVEF <35% and ischaemic (LOE A) or non-ischaemic (LOE B) HF.[2] However, the Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality (DANISH) trial recruited patients on modern pharmacotherapy, as per the 2012 ESC guidelines,[107] and failed to demonstrate a survival benefit of ICDs in non-ischaemic HF.[108] Thus, although risk stratification based on LVEF is practical, there is a clear need to further refine patient selection. Patients with a high burden of fibrosis (such as late gadolinium enhancement >5% of the left ventricle) are at increased risk of arrhythmic death and should be considered for ICD therapy even if their LVEF is not severely depressed.[109–111] Likewise, the absence of fibrosis is a powerful predictor of freedom from ventricular arrhythmias, possibly supporting deferred implantation. As for biomarkers related to fibrosis, several studies have linked higher sST2 levels to a higher risk of sudden cardiac death (SCD) in several settings, such as patients without an ICD but severe systolic dysfunction at baseline (mean LVEF 30%),[112] or patients with better systolic function (mean LVEF 37%), but still no ICD at baseline.[113] In the latter setting, a model including sST2 >45 ng/mL, LVEF <45%, HF duration >3 years, eGFR <55 mL/min/1.73 m^2, age ≥60 years and male sex (the ST2-SCD score) has been proposed and validated.[112,113] It is reasonable to state that raised sST2 strengthens the indication for ICD for primary prevention, although prospective tests of this strategy are required.

Key point

Raised sST2 is associated with an increased risk of SCD and supports the decision to implant an ICD for primary prevention.

Guide to cardiac resynchronization therapy

Cardiac resynchronization therapy (CRT) is currently indicated according to clinical, imaging and electrocardiographic findings. Imaging may assist decision-making on CRT implantation. On CMR, a large transmural myocardial scar predicted lack of benefit from CRT.[114] In a single small study, diffuse myocardial fibrosis assessed by T1 mapping did not correlate with response to CRT.[115]

With respect to circulating markers, an observational study found that lower pro-collagen type I C-terminal pro-peptide (PICP, a marker of myocardial fibrosis) displayed an association with response to CRT independent of other predictors such as left bundle branch block, QRS duration, non-ischaemic aetiology, or lead position.[116] However, this conflicts with a previous report that higher fibrogenesis (as assessed by the ratio of PICP to C-terminal telopeptide of type I collagen) correlated with greater response to CRT.[117] Similarly, in a sub-study of the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT), patients with the highest baseline levels of galectin-3 (a mediator of fibrogenesis) derived greater benefit from CRT with defibrillator capability.[118]

Key point

The current discrepant state of evidence does not allow any clear recommendation about the possibility to guide CRT implantation based on circulating biomarkers or imaging findings related to myocardial fibrosis. Larger data sets with longer periods of follow-up assessing a wider range of candidate markers are required.

Specific scenarios

Atrial fibrillation

Patients with AF have higher NPs at any given filling pressure.[119] Accordingly, AF reduces the performance of NT-proBNP in discriminating acute HF from other causes of new-onset dyspnoea, with an area under the curve of 0.7 vs. 0.9 in patients in sinus rhythm. The widely accepted rule-out threshold of 300 ng/L remains highly sensitive, but poorly specific (<20%).[120] Different diagnostic cut-offs have been proposed to improve specificity. The HFA-PEFF algorithm suggests an elevation of BNP >240 ng/L or NT-proBNP >660 ng/L as a major criterion for the diagnosis of HFpEF in patients with AF, compared to BNP >80 ng/L or NT-proBNP >220 ng/L in patients in sinus rhythm[35] (*Figure 1*). These cut-offs should be critically interpreted, and patients with AF suffering dyspnoea without overt congestion should be referred to exercise testing given the high probability of underlying HFpEF.[121]

The HFA-PEFF algorithm lists an LA volume index >40 mL/m^2 as a major diagnostic criterion,[35] a higher threshold than in sinus rhythm. An Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48 (ENGAGE AF-TIMI 48) echocardiographic sub-study demonstrated that two functional indices (LA emptying fraction and expansion index) are stronger predictors of cardiovascular death or HF hospitalization than LA volume index.[122] LA strain analysis might be considered in patients with HFpEF who have paroxysmal or persistent AF to predict the likelihood of progression to permanent AF.[123]

Table 1 Approximate cut-off levels of natriuretic peptides to diagnose heart failure in obese individuals

	Cut-off levels (ng/L)					
	NT-proBNP			BNP		
	<50 years	50–75 years	>75 years	<50 years	50–75 years	>75 years
Acute setting, patient with acute dyspnoea						
HF unlikely		<150			<50	
'Grey zone'	150–225	150–450	150–900		50–200	
HF likely	>225	>450	>900		>200	
Non-acute setting, patient with mild symptoms						
HF unlikely		<63			<18	
'Grey zone'		63–300			18–75	
HF likely		>300			>75	

Modified from Mueller *et al.*[24]
BNP, B-type natriuretic peptide; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Echocardiographic estimation of pulmonary artery pressure from TR velocity correlates well with invasive measurements irrespective of AF, and a peak TR velocity >2.8 m/s (corresponding to a systolic pulmonary artery pressure >35 mmHg) discriminates patients with HFpEF from those with hypertension but no HF.[124] Both E/e′ ≥15 and a peak TR velocity >3.4 m/s are used to diagnose HF during exercise echocardiography (diastolic stress test), but their use in AF is more challenging.[35]

Obesity

Obesity is a common risk factor for HF, particularly HFpEF.[125] While obese patients with HFpEF are often highly symptomatic,[126,127] correct identification of symptoms and signs of HF in obese individuals may be challenging. The transthoracic acoustic window is frequently poor in the obese and LA dilatation may be missed because of indexing issues. Furthermore, NP levels can be misleading in this population given the inverse relationship between NPs and obesity. This is maintained in the setting of HF, with lower levels of circulating NPs in obese individuals with acute and chronic HF compared to lean individuals with HF.[128–131] The inverse relationship of NPs with high BMI is present in both HFrEF and HFpEF, although median levels are higher in HFrEF. As discussed in detail in a recent review paper,[132] the need for BMI-specific cut-offs is debated, but has been endorsed by an ESC HFA position paper, which proposed the use of 50% lower NP cut-offs to diagnose acute or non-acute HF in obese individuals (*Table 1*).[24] The prognostic value of NPs in acute and chronic HF is preserved across BMI classes.[133–136]

Chronic kidney disease

Reduced eGFR has little influence on plasma NPs until it falls to <30 mL/min/1.73 m^2.[137,138] In CKD stages 4–5, particularly in patients on dialysis, NPs are markedly elevated and no established diagnostic thresholds exist. Integration between laboratory and imaging data then becomes particularly important. For example, the combination of elevated NP together with echocardiographic indicators of increased LV filling pressure (E/e′ ≥15) aid to diagnose HF in patients with new-onset dyspnoea.

Natriuretic peptide values retain a prognostic role even in patients with advanced CKD,[139] and several echocardiographic variables, including from speckle-tracking analysis, help predict patient outcome. For example, LV GLS holds greater prognostic value than LVEF in advanced CKD,[140,141] and RV GLS is a specific marker of subclinical RV dysfunction in CKD even when RV fractional area change remains normal.[142] Use of contrast-enhanced CMR is restricted to patients with eGFR ≥30 mL/min/1.73 m^2. New modalities, such as native T1 mapping, are being considered with interest.[143–145]

Overall, circulating and imaging biomarkers convey complementary diagnostic and prognostic information in patients with advanced CKD, but optimal integration remains to be defined and formally evaluated.

Right ventricular dysfunction and pulmonary hypertension

Imaging data, particularly those from TTE, define RV dysfunction and indicate pulmonary artery pressure. There are no specific plasma biomarkers for the diagnosis of RV dysfunction and pulmonary hypertension, but NPs are strongly prognostic in both.[146–148] Therefore, the integration of echocardiographic findings and NP levels refines risk stratification, as reported for the combination of tricuspid annular plane systolic excursion <15 mm and NT-proBNP ≥500 ng/L in patients with pulmonary hypertension due to congenital heart disease.[148] The roles of biomarkers other than NPs (troponin, sST2, galectin-3 and growth differentiation factor-15) and advanced imaging techniques are under investigation.[149,150]

Heart valve disease

Optimal timing of valve surgery or repair to preserve LV geometry and function and relieve HF symptoms is often challenging. The

combined assessment of biomarkers and imaging can help plan surgical or percutaneous interventions, especially when patients are asymptomatic or have unclear symptoms.

The strongest indication for valve surgery for aortic regurgitation is the presence of symptoms (either at rest or during exercise); however, even if the patient was asymptomatic, surgery is indicated in the presence of any one of the following: LVEF <50%, LV end-diastolic diameter >70 mm, LV end-systolic diameter (LVESD) >50 mm or an indexed LVESD >25 mm/m^2.[151] In severe asymptomatic aortic regurgitation with normal LV function, BNP >130 ng/L identifies a subgroup with higher risk.[152]

Natriuretic peptides predict outcomes in severe aortic stenosis (AS), including low-flow AS.[153,154] In asymptomatic severe AS, BNP <130 ng/L and NT-proBNP <592 ng/L predict a lower risk of symptom development and a lower need for surgery over the following year.[153] BNP <100 ng/L was associated with a low rate of AS-related events.[155]

In patients with asymptomatic severe mitral regurgitation (MR), LVEF <60% or LVESD >45 mm, or in their absence systolic pulmonary artery pressure >50 mmHg should prompt the referral to surgery.[151,156,157] Elevated or increasing NPs are predictive of symptom development and adverse outcome. In severe asymptomatic primary MR, BNP ≥105 ng/L predicts a higher risk of LV dysfunction, HF or death over 3 years.[158] The combination of BNP and GLS better defined risk than either variable alone in asymptomatic, significant primary MR with preserved LVEF.[159]

B-type natriuretic peptide is directly correlated with RV volume and inversely with LVEF after surgery for severe isolated TR. BNP <200 ng/L was associated with lower postoperative mortality at 1 year.[160]

Cardiac amyloidosis

In cardiac amyloidosis, misfolded proteins lead to accumulation of insoluble amyloid fibrils, composed of immunoglobulin light-chains (AL) or transthyretin (ATTR).[161,162] Both echocardiography and biomarkers are included in the first step of the diagnostic algorithm of CA. Echocardiographic features in CA include increased LV and/or RV wall thickness (often with a sparkling appearance) and diastolic dysfunction.[163] Speckle-tracking imaging is sensitive to early systolic dysfunction and typically displays preserved apical contractility.[164–166] GLS < −17%, lack of 'apical sparing' and hs-troponin T <35 ng/L help rule out cardiac involvement in systemic AL amyloidosis.[167] Risk stratification in AL- and ATTR-CA relies on biomarkers, as demonstrated by the proposed scores. Optimal integration of biomarkers and imaging remains to be defined and should be pursued in future studies.[168]

Myocarditis

Endomyocardial biopsy remains the gold standard for the diagnosis of myocarditis, but is usually reserved for cases with reduced LV function, recurrent troponin increases, or suspicion of specific aetiologies.[169] The non-invasive diagnosis of myocarditis requires CMR examination and relies on the Lake Louise criteria, which include oedema on T2-weighted imaging, hyperaemia on early gadolinium enhancement images and necrosis/oedema on late gadolinium enhancement images. Myocarditis can be diagnosed when at least two of these hallmarks of inflammation are present.[170] Troponin is usually raised in these patients, but normal concentrations do not exclude the diagnosis.[169]

Rejection after heart transplantation

Serial endomyocardial biopsies are routinely performed in the first year after heart transplantation to detect allograft rejection. Subsequently, annual non-invasive imaging is used to check for rejection.[171] Decreased LVEF is typically a late finding and does not correlate reliably with the grade of rejection found on endomyocardial biopsy.[172] The variability and low sensitivity and specificity of NPs limit their usefulness in this setting.[173]

In case of acute rejection, TTE typically reveals abnormal diastolic indices. Tissue Doppler diastolic velocities and isovolumic relaxation time are the most sensitive indicators.[174,175] RV free wall longitudinal strain <17% and LV GLS <15.5% are independent predictors of acute rejection with a negative predictive value of 100%, albeit with a low positive predictive value (<25%).[176,177] CMR can evaluate inflammation/rejection-related expansion of interstitial volume by calculation of extracellular volume. Myocardial T2 relaxation time is associated with myocardial oedema.[178] T2 mapping holds promise in acute rejection with sensitive threshold T2 values of ≥60 ms on 1.5 T CMR.[179–181] Cardiac biomarkers, including NT-proBNP and hs-troponin, have received limited attention as tools to detect or predict acute rejection.

Guideline recommendations and possible further roles of integration of imaging and circulating biomarkers

In *Table 2* we report the recommendations from ESC and ACC/AHA guidelines on the use of imaging and circulating biomarkers for screening, diagnosis, risk stratification and guiding treatment in HF, and we add the key points summarizing the contents of this paper.

With the growing number of therapeutic options for HF, an individually tailored approach is becoming increasingly important. This entails consideration of aetiology, type and severity of cardiac dysfunction, along with age, gender and comorbidities. The availability of circulating biomarkers associated with haemodynamic burden, neurohormonal activation, ongoing myocardial damage and activation of proinflammatory and profibrotic pathways can complement multi-modal imaging techniques for defining cardiac morphology and function, the progression of fibrosis and adverse or reverse remodelling. Integrating circulating markers with imaging will allow us to progressively identify patient-centred and condition-specific approaches to HF assessment and management.

Table 2 Current guidelines on biomarkers and imaging in heart failure and recommendations for their integrated use

Setting	2016 ESC HF Guideline	2017 ACC/AHA/HFSA Focused update of the 2013 ACCF/AHA HF guideline	Key points
Screening	TTE is recommended for the assessment of myocardial structure and function in subjects to be exposed to treatment which potentially can damage myocardium (e.g. chemotherapy) (class I, LOE C) Other techniques (including systolic tissue Doppler velocities and deformation indices, i.e. strain and strain rate), should be considered in a TTE protocol in subjects at risk of developing HF to identify myocardial dysfunction at the preclinical stage (class IIa, LOE C)	For patients at risk of developing HF, NP biomarker–based screening followed by team-based care, including a cardiovascular specialist optimizing GDMT, can be useful to prevent the development of LV dysfunction (systolic or diastolic) or new-onset HF	Systematic screening for HF in the general population is likely not to be cost-effective. Screening might be considered in patients with conditions predisposing to HF, such as hypertension and diabetes, to identify subclinical HF that warrants initiation of cardiac protective therapies. A possible alternative to the current approach to HF screening in hypertensive and diabetic individuals is a two-step screening with the measurement of NPs or hs-troponin and then TTE, when circulating biomarkers are either elevated or rising. This combined approach should be evaluated in dedicated studies
Diagnosis	Diagnostic criteria: elevated NP needed for HFmrEF/HFpEF diagnosis (BNP >35 ng/L and/or NT-proBNP >125 ng/L)	In ambulatory patients with dyspnoea, measurement of BNP or NT-proBNP is useful to support clinical decision-making regarding the diagnosis of HF, especially in the setting of clinical uncertainty (class I, LOE A) Measurement of BNP or NT-proBNP is useful to support clinical judgment for the diagnosis of acutely decompensated HF, especially in the setting of uncertainty for the diagnosis (class I, LOE A) Patients with suspected or new-onset HF, or those presenting with acute decompensated HF, should undergo a chest X-ray to assess heart size and pulmonary congestion and to detect alternative cardiac, pulmonary, and other diseases that may cause or contribute to the patient symptoms (class I, LOE C)	The HFA-PEFF and H_2FPEF scores can standardize the diagnosis of HFpEF. The HFA-PEFF score includes the evaluation of NPs, but its relative diagnostic performance compared with the simpler H_2FPEF score is unclear. Diagnostic criteria for HFpEF require an integration of imaging and circulating biomarkers, while HFmrEF can be diagnosed even without evaluating NPs
	TTE is recommended for the assessment of myocardial structure and function in subjects with suspected HF in order to establish a diagnosis of either HFrEF, HFmrEF or HFpEF (class I, LOE C)	A two-dimensional echocardiogram with Doppler should be performed during initial evaluation of patients presenting with HF to assess ventricular function, size, wall thickness, wall motion, and valve function (class I, LOE C)	
	CMR is recommended for the assessment of myocardial structure and function (including right heart) in subjects with poor acoustic window and patients with complex congenital heart diseases (taking account of cautions/contraindications to CMR) (class I, LOE C)	Radionuclide ventriculography or magnetic resonance imaging can be useful to assess LVEF and volume when echocardiography is inadequate (class IIa, LOE C)	

Table 2 (Continued)

Setting	2016 ESC HF Guideline	2017 ACC/AHA/HFSA Focused update of the 2013 ACCF/AHA HF guideline	Key points
	Non-invasive stress imaging (CMR, stress echocardiography, SPECT, PET) may be considered for the assessment of myocardial ischaemia and viability in patients with HF and CAD (considered suitable for coronary revascularization) before the decision on revascularization (class IIb, LOE B) CMR with LGE should be considered in patients with dilated cardiomyopathy to distinguish between ischaemic and non-ischaemic myocardial damage in case of equivocal clinical and other imaging data (taking account of cautions/contraindications to CMR) (class IIa, LOE C) Cardiac CT may be considered in patients with HF and low to intermediate pre-test probability of CAD or those with equivocal non-invasive stress tests in order to rule out coronary artery stenosis (class IIb, LOE C)	Non-invasive imaging to detect myocardial ischemia and viability is reasonable in patients presenting with de novo HF, who have known CAD and no angina, unless the patient is not eligible for revascularization of any kind (class IIa, LOE C) Magnetic resonance imaging is reasonable when assessing myocardial infiltrative processes or scar burden (class IIa, LOE B)	
Risk stratification	No specific recommendation	Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF (class I, LOE A) Measurement of other clinically available tests such as biomarkers of myocardial injury or fibrosis may be considered for additive risk stratification in patients with chronic HF (class IIb, LOE B) Measurement of BNP or NT-proBNP and/or cardiac troponin is useful for establishing prognosis or disease severity in acutely decompensated HF (class I, LOE A) Measurement of other clinically available tests such as biomarkers of myocardial injury or fibrosis may be considered for additive risk stratification in patients with acutely decompensated HF (class IIb, LOE A)	NPs are established predictors of outcome in acute and chronic HF. Measurement of an hs-troponin, on at least one occasion, should be considered in outpatients with HFrEF Patients with hs-troponin T $\geq$18 ng/L have a greater risk of all-cause and cardiovascular mortality and hospitalization for cardiovascular causes regardless of LVEF, NT-proBNP, age, sex, renal function and ischaemic aetiology. sST2 levels further refine risk prediction of outpatients with HFrEF with 35 ng/mL as a useful cut-off. The clinical impact and therapeutic consequences of assessing risk, however, need to be investigated in clinical trials

Table 2 (Continued)

Setting	2016 ESC HF Guideline	2017 ACC/AHA/HFSA Focused update of the 2013 ACCF/AHA HF guideline	Key points
Guide to treatment and follow-up	The following diagnostic tests are recommended/should be considered for initial assessment of a patient with newly diagnosed HF to evaluate the patient's suitability for particular therapies, to detect reversible/treatable causes of HF and comorbidities interfering with HF: • […] • NPs (class IIa, LOE C)	BNP- or NT-proBNP-guided HF therapy can be useful to achieve optimal dosing of GDMT in select clinically euvolaemic patients followed in a well-structured HF disease management programme (class IIa, LOE B)	Circulating biomarkers play an important role as indicators for sonographic fluid status assessment and will improve the specificity of sonographic findings. We need well-designed randomized trials to test the concept of echo-guided decongestion with defined cut-offs for both echocardiographic measures and adjunctive circulating markers. Meanwhile, imaging markers and concurrent circulating biomarkers should be interpreted on a case-by-case basis. In chronic HFrEF, achieving concentrations of NT-proBNP <1000 ng/L is associated with reverse LV remodelling and a better prognosis. Sustained reduction in NT-proBNP below this level may allow a less intensive patient follow-up. HF recovery is revealed by longitudinal changes in imaging findings, most commonly from repeated echocardiography, and is accompanied by a reduction in NPs. Our current state of knowledge suggests that HF medications should be continued in patients with HFimpEF to prevent a new decline of cardiac function in a large proportion of this group. Rising NT-proBNP portends new deterioration of LV function in HFimpEF. Raised sST2 is associated with an increased risk of SCD and supports the decision to implant an ICD for primary prevention. The current discrepant state of evidence does not allow any clear recommendation about the possibility to guide CRT implantation based on circulating biomarkers or imaging findings related to myocardial fibrosis. Larger data sets with longer periods of follow-up assessing a wider range of candidate markers are required.

ACCF/AHA, American College of Cardiology Foundation/American Heart Association; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CMR, cardiac magnetic resonance; CRT, cardiac resynchronization therapy; CT, computed tomography; GDMT, guideline-directed medical therapy; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFSA, Heart Failure Society of America; hs, high-sensitivity; ICD, implantable cardioverter defibrillator; LGE, late gadolinium enhancement; LOE, level of evidence; LV, left ventricular; LVEF, left ventricular ejection fraction; NP, natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PET, positron emission tomography; SCD, sudden cardiac death; SPECT, single-photon emission computed tomography; sST2, soluble suppression of tumorigenesis-2; TTE, transthoracic echocardiogram.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conflict of interest: none declared.

References

1. Savarese G, Lund LH. Global public health burden of heart failure. *Card Fail Rev* 2017;**3**:7–11.
2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891–975.
3. Vasan RS. Biomarkers of cardiovascular disease: molecular basis and practical considerations. *Circulation* 2006;**113**:2335–2362.
4. Yeboah J, Rodriguez CJ, Stacey B, Lima JA, Liu S, Carr JJ, Hundley WG, Herrington DM. Prognosis of individuals with asymptomatic left ventricular systolic dysfunction in the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation* 2012;**126**:2713–2719.
5. Lam CS, Lyass A, Kraigher-Krainer E, Massaro JM, Lee DS, Ho JE, Levy D, Redfield MM, Pieske BM, Benjamin EJ, Vasan RS. Cardiac dysfunction and noncardiac dysfunction as precursors of heart failure with reduced and preserved ejection fraction in the community. *Circulation* 2011;**124**:24–30.
6. Kane GC, Karon BL, Mahoney DW, Redfield MM, Roger VL, Burnett JC Jr, Jacobsen SJ, Rodeheffer RJ. Progression of left ventricular diastolic dysfunction and risk of heart failure. *JAMA* 2011;**306**:856–863.
7. Kawel-Boehm N, Kronmal R, Eng J, Folsom A, Burke G, Carr JJ, Shea S, Lima JAC, Bluemke DA. Left ventricular mass at MRI and long-term risk of cardiovascular events: the Multi-Ethnic Study of Atherosclerosis (MESA). *Radiology* 2019;**293**:107–114.
8. Almahmoud MF, O'Neal WT, Qureshi W, Soliman EZ. Electrocardiographic versus echocardiographic left ventricular hypertrophy in prediction of congestive heart failure in the elderly. *Clin Cardiol* 2015;**38**:365–370.
9. Cheng S, McCabe EL, Larson MG, Merz AA, Osypiuk E, Lehman BT, Stantchev P, Aragam J, Solomon SD, Benjamin EJ, Vasan RS. Distinct aspects of left ventricular mechanical function are differentially associated with cardiovascular outcomes and all-cause mortality in the community. *J Am Heart Assoc* 2015;**4**:e002071.
10. Choi EY, Rosen BD, Fernandes VR, Yan RT, Yoneyama K, Donekal S, Opdahl A, Almeida AL, Wu CO, Gomes AS, Bluemke DA, Lima JA. Prognostic value of myocardial circumferential strain for incident heart failure and cardiovascular events in asymptomatic individuals: the Multi-Ethnic Study of Atherosclerosis. *Eur Heart J* 2013;**34**:2354–2361.
11. Park SJ, Cho KI, Jung SJ, Choi SW, Choi JW, Lee DW, Lee HG, Kim TI. N-terminal pro-B-type natriuretic peptide in overweight and obese patients with and without diabetes: an analysis based on body mass index and left ventricular geometry. *Kor Circ J* 2009;**39**:538–544.
12. Pfister R, Sharp S, Luben R, Welsh P, Barroso I, Salomaa V, Meirhaeghe A, Khaw KT, Sattar N, Langenberg C, Wareham NJ. Mendelian randomization study of B-type natriuretic peptide and type 2 diabetes: evidence of causal association from population studies. *PLoS Med* 2011;**8**:e1001112.
13. Kroon MH, van den Hurk K, Alssema M, Kamp O, Stehouwer CD, Henry RM, Diamant M, Boomsma F, Nijpels G, Paulus WJ, Dekker JM. Prospective associations of B-type natriuretic peptide with markers of left ventricular function in individuals with and without type 2 diabetes: an 8-year follow-up of the Hoorn Study. *Diabetes Care* 2012;**35**:2510–2514.
14. Fathy SA, Abdel Hamid FF, Zabut BM, Jamee AF, Ali MA, Abu Mustafa AM. Diagnostic utility of BNP, corin and furin as biomarkers for cardiovascular complications in type 2 diabetes mellitus patients. *Biomarkers* 2015;**20**:460–469.
15. Ju C, Ye M, Li F. Plasma brain natriuretic peptide, endothelin-1, and matrix metalloproteinase 9 expression and significance in type 2 diabetes mellitus patients with ischemic heart disease. *Med Sci Monit* 2015;**21**:2094–2099.
16. Ballo P, Betti I, Barchielli A, Balzi D, Castelli G, De Luca L, Gheorghiade M, Zuppiroli A. Prognostic role of N-terminal pro-brain natriuretic peptide in asymptomatic hypertensive and diabetic patients in primary care: impact of age and gender: results from the PROBE-HF study. *Clin Res Cardiol* 2016;**105**:421–431.
17. van der Linden N, Hilderink JM, Cornelis T, Kimenai DM, Klinkenberg LJJ, van Doorn WP, Litjens EJR, van Suijlen JDE, van Loon LJC, Bekers O, Kooman JP, Meex SJR. Twenty-four-hour biological variation profiles of cardiac troponin I in individuals with or without chronic kidney disease. *Clin Chem* 2017;**63**:1655–1656.
18. Fradley MG, Larson MG, Cheng S, McCabe E, Coglianese E, Shah RV, Levy D, Vasan RS, Wang TJ. Reference limits for N-terminal-pro-B-type natriuretic peptide in healthy individuals (from the Framingham Heart Study). *Am J Cardiol* 2011;**108**:1341–1345.
19. Passino C, Aimo A, Masotti S, Musetti V, Prontera C, Emdin M, Clerico A. Cardiac troponins as biomarkers for cardiac disease. *Biomark Med* 2019;**13**:325–330.
20. Clerico A, Zaninotto M, Passino C, Aspromonte N, Piepoli MF, Migliardi M, Perrone M, Fortunato A, Padoan A, Testa A, Dellarole F, Trenti T, Bernardini S, Sciacovelli L, Colivicchi F, Gabrielli D, Plebani M. Evidence on clinical relevance of cardiovascular risk evaluation in the general population using cardio-specific biomarkers. *Clin Chem Lab Med* 2020;**59**:79–90.
21. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, Habib G, Lenihan DJ, Lip GYH, Lyon AR, Lopez Fernandez T, Mohty D, Piepoli MF, Tamargo J, Torbicki A, Suter TM; ESC Scientific Document Group. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur Heart J* 2016;**37**:2768–2801.
22. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018;**39**:3021–3104.
23. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, Huikuri HV, Johansson I, Jüni P, Lettino M, Marx N, Mellbin LG, Östgren CJ, Rocca B, Roffi M, Sattar N, Seferović PM, Sousa-Uva M, Valensi P, Wheeler DC. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2020;**41**:255–323.
24. Mueller C, McDonald K, de Boer RA, Maisel A, Cleland JGF, Kozhuharov N, Coats AJS, Metra M, Mebazaa A, Ruschitzka F, Lainscak M, Filippatos G, Seferovic PM, Meijers WC, Bayes-Genis A, Mueller T, Richards M, Januzzi JL Jr. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. *Eur J Heart Fail* 2019;**21**:715–731.
25. Ledwidge M, Gallagher J, Conlon C, Tallon E, O'Connell E, Dawkins I, Watson C, O'Hanlon R, Bermingham M, Patle A, Badabhagni MR, Murtagh G, Voon V, Tilson L, Barry M, McDonald L, Maurer B, McDonald K. Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. *JAMA* 2013;**310**:66–74.
26. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol* 2017;**70**:776–803.
27. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA Guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;**62**:e147–e239.
28. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Piepoli MF, Price S, Rosano GMC, Ruschitzka F, Skibelund AK; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;**42**:3599–3726.
29. Paulus WJ. H_2FPEF score: at last, a properly validated diagnostic algorithm for heart failure with preserved ejection fraction. *Circulation* 2018;**138**:871–873.
30. Obokata M, Kane GC, Reddy YN, Olson TP, Melenovsky V, Borlaug BA. Role of diastolic stress testing in the evaluation for heart failure with preserved ejection fraction: a simultaneous invasive-echocardiographic study. *Circulation* 2017;**135**:825–838.

31. Van Aelst LNL, Arrigo M, Placido R, Akiyama E, Girerd N, Zannad F, Manivet P, Rossignol P, Badoz M, Sadoune M, Launay JM, Gayat E, Lam CSP, Cohen-Solal A, Mebazaa A, Seronde MF. Acutely decompensated heart failure with preserved and reduced ejection fraction present with comparable haemodynamic congestion. *Eur J Heart Fail* 2018;**20**:738–747.
32. D'Souza SP, Baxter GF. B type natriuretic peptide: a good omen in myocardial ischaemia? *Heart* 2003;**89**:707–709.
33. Peeters JM, Sanders-van Wijk S, Bektas S, Knackstedt C, Rickenbacher P, Nietlispach F, Handschin R, Maeder MT, Muzzarelli SF, Pfisterer ME, Brunner-La Rocca HP. Biomarkers in outpatient heart failure management; are they correlated to and do they influence clinical judgment? *Neth Heart J* 2014;**22**:115–121.
34. Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, Edelmann F, Fu M, Guazzi M, Lam CSP, Lancellotti P, Melenovsky V, Morris DA, Nagel E, Pieske-Kraigher E, Ponikowski P, Solomon SD, Vasan RS, Rutten FH, Voors AA, Ruschitzka F, Paulus WJ, Seferovic P, Filippatos G. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur J Heart Fail* 2020;**22**:391–412.
35. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation* 2018;**138**:861–870.
36. Borlaug BA. Evaluation and management of heart failure with preserved ejection fraction. *Nat Rev Cardiol* 2020;**17**:559–573.
37. Barandiarán Aizpurua A, Sanders-van Wijk S, Brunner-La Rocca HP, Henkens M, Heymans S, Beussink-Nelson L, Shah SJ, van Empel VPM. Validation of the HFA-PEFF score for the diagnosis of heart failure with preserved ejection fraction. *Eur J Heart Fail* 2020;**22**:413–421.
38. Reddy YNV, Obokata M, Egbe A, Yang JH, Pislaru S, Lin G, Carter R, Borlaug BA. Left atrial strain and compliance in the diagnostic evaluation of heart failure with preserved ejection fraction. *Eur J Heart Fail* 2019;**21**:891–900.
39. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, Anker SD, Atherton J, Böhm M, Butler J, Drazner MH, Michael Felker G, Filippatos G, Fiuzat M, Fonarow GC, Gomez-Mesa JE, Heidenreich P, Imamura T, Jankowska EA, Januzzi J, Khazanie P, Kinugawa K, Lam CSP, Matsue Y, Metra M, Ohtani T, Francesco Piepoli M, Ponikowski P, Rosano GMC, Sakata Y, Seferović P, Starling RC, Teerlink JR, Vardeny O, Yamamoto K, Yancy C, Zhang J, Zieroth S. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. *Eur J Heart Fail* 2021;**23**:352–380.
40. Murphy SP, Ibrahim NE, Januzzi JL, Jr. Heart failure with reduced ejection fraction: a review. *JAMA* 2020;**324**:488–504.
41. Park JJ, Park JB, Park JH, Cho GY. Global longitudinal strain to predict mortality in patients with acute heart failure. *J Am Coll Cardiol* 2018;**71**:1947–1957.
42. Becker MAJ, Cornel JH, van de Ven PM, van Rossum AC, Allaart CP, Germans T. The prognostic value of late gadolinium-enhanced cardiac magnetic resonance imaging in nonischemic dilated cardiomyopathy: a review and meta-analysis. *JACC Cardiovasc Imaging* 2018;**11**:1274–1284.
43. Ghio S, Guazzi M, Scardovi AB, Klersy C, Clemenza F, Carluccio E, Temporelli PL, Rossi A, Faggiano P, Traversi E, Vriz O, Dini FL. Different correlates but similar prognostic implications for right ventricular dysfunction in heart failure patients with reduced or preserved ejection fraction. *Eur J Heart Fail* 2017;**19**:873–879.
44. Aimo A, Januzzi JL Jr, Vergaro G, Ripoli A, Latini R, Masson S, Magnoli M, Anand IS, Cohn JN, Tavazzi L, Tognoni G, Gravning J, Ueland T, Nymo SH, Brunner-La Rocca HP, Bayes-Genis A, Lupon J, de Boer RA, Yoshihisa A, Takeishi Y, Egstrup M, Gustafsson I, Gaggin HK, Eggers KM, Huber K, Tentzeris I, Tang WHW, Grodin J, Passino C, Emdin M. Prognostic value of high-sensitivity troponin t in chronic heart failure: an individual patient data meta-analysis. *Circulation* 2018;**137**:286–297.
45. Emdin M, Aimo A, Vergaro G, Bayes-Genis A, Lupon J, Latini R, Meessen J, Anand IS, Cohn JN, Gravning J, Gullestad L, Broch K, Ueland T, Nymo SH, Brunner-La Rocca HP, de Boer RA, Gaggin HK, Ripoli A, Passino C, Januzzi JL Jr. sST2 predicts outcome in chronic heart failure beyond NT-proBNP and high-sensitivity troponin T. *J Am Coll Cardiol* 2018;**72**:2309–2320.
46. Lam LL, Cameron PA, Schneider HG, Abramson MJ, Müller C, Krum H. Meta-analysis: effect of B-type natriuretic peptide testing on clinical outcomes in patients with acute dyspnea in the emergency setting. *Ann Intern Med* 2010;**153**:728–735.
47. Savarese G, Musella F, D'Amore C, Vassallo E, Losco T, Gambardella F, Cecere M, Petraglia L, Pagano G, Fimiani L, Rengo G, Leosco D, Trimarco B, Perrone-Filardi P. Changes of natriuretic peptides predict hospital admissions in patients with chronic heart failure: a meta-analysis. *JACC Heart Fail* 2014;**2**:148–158.
48. Salah K, Kok WE, Eurlings LW, Bettencourt P, Pimenta JM, Metra M, Bayes-Genis A, Verdiani V, Bettari L, Lazzarini V, Damman P, Tijssen JG, Pinto YM. A novel discharge risk model for patients hospitalised for acute decompensated heart failure incorporating N-terminal pro-B-type natriuretic peptide levels: a European coLlaboration on Acute decompeNsated Heart Failure: ELAN-HF Score. *Heart* 2014;**100**:115–125.
49. Januzzi JL Jr, Filippatos G, Nieminen M, Gheorghiade M. Troponin elevation in patients with heart failure: on behalf of the third Universal Definition of Myocardial Infarction Global Task Force: Heart Failure Section. *Eur Heart J* 2012;**33**:2265–2271.
50. Hammarsten O, Mair J, Möckel M, Lindahl B, Jaffe AS. Possible mechanisms behind cardiac troponin elevations. *Biomarkers* 2018;**23**:725–734.
51. Aimo A, Januzzi JL Jr, Mueller C, Mirò O, Pascual Figal DA, Jacob J, Herrero-Puente P, Llorens P, Wussler D, Kozhuharov N, Sabti Z, Breidthardt T, Vergaro G, Ripoli A, Prontera C, Saccaro L, Passino C, Emdin M. Admission high-sensitivity troponin T and NT-proBNP for outcome prediction in acute heart failure. *Int J Cardiol* 2019;**293**:137–142.
52. Latini R, Masson S, Anand IS, Missov E, Carlson M, Vago T, Angelici L, Barlera S, Parrinello G, Maggioni AP, Tognoni G, Cohn JN. Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. *Circulation* 2007;**116**:1242–1249.
53. Sato Y, Yamada T, Taniguchi R, Nagai K, Makiyama T, Okada H, Kataoka K, Ito H, Matsumori A, Sasayama S, Takatsu Y. Persistently increased serum concentrations of cardiac troponin t in patients with idiopathic dilated cardiomyopathy are predictive of adverse outcomes. *Circulation* 2001;**103**:369–374.
54. Fonarow GC, Peacock WF, Horwich TB, Phillips CO, Givertz MM, Lopatin M, Wynne J. Usefulness of B-type natriuretic peptide and cardiac troponin levels to predict in-hospital mortality from ADHERE. *Am J Cardiol* 2008;**101**:231–237.
55. Peacock WF 4th, De Marco T, Fonarow GC, Diercks D, Wynne J, Apple FS, Wu AH; ADHERE Investigators. Cardiac troponin and outcome in acute heart failure. *N Engl J Med* 2008;**358**:2117–2126.
56. Ather S, Hira RS, Shenoy M, Fatemi O, Deswal A, Aguilar D, Ramasubbu K, Bolos M, Chan W, Bozkurt B. Recurrent low-level troponin I elevation is a worse prognostic indicator than occasional injury pattern in patients hospitalized with heart failure. *Int J Cardiol* 2013;**166**:394–398.
57. de Boer RA, De Keulenaer G, Bauersachs J, Brutsaert D, Cleland JG, Diez J, Du XJ, Ford P, Heinzel FR, Lipson KE, McDonagh T, Lopez-Andres N, Lunde IG, Lyon AR, Pollesello P, Prasad SK, Tocchetti CG, Mayr M, Sluijter JPG, Thum T, Tschöpe C, Zannad F, Zimmermann WH, Ruschitzka F, Filippatos G, Lindsey ML, Maack C, Heymans S. Towards better definition, quantification and treatment of fibrosis in heart failure. A scientific roadmap by the Committee of Translational Research of the Heart Failure Association (HFA) of the European Society of Cardiology. *Eur J Heart Fail* 2019;**21**:272–285.
58. Chen W, Frangogiannis NG. The role of inflammatory and fibrogenic pathways in heart failure associated with aging. *Heart Fail Rev* 2010;**15**:415–422.
59. Aimo A, Januzzi JL Jr, Bayes-Genis A, Vergaro G, Sciarrone P, Passino C, Emdin M. Clinical and prognostic significance of sST2 in heart failure: JACC Review Topic of the Week. *J Am Coll Cardiol* 2019;**74**:2193–2203.
60. Mueller T, Dieplinger B. The Presage(®) ST2 Assay: analytical considerations and clinical applications for a high-sensitivity assay for measurement of soluble ST2. *Expert Rev Mol Diagn* 2013;**13**:13–30.
61. Aurora L, Peterson E, Gui H, Zeld N, McCord J, Pinto Y, Cook B, Sabbah HN, Keoki Williams L, Snider J, Lanfear DE. Suppression tumorigenicity 2 (ST2) turbidimetric immunoassay compared to enzyme-linked immunosorbent assay in predicting survival in heart failure patients with reduced ejection fraction. *Clin Chim Acta* 2020;**510**:767–771.
62. Lupón J, Simpson J, McMurray JJV, de Antonio M, Vila J, Subirana I, Barallat J, Moliner P, Domingo M, Zamora E, Bayes-Genis A. Barcelona Bio-HF Calculator Version 2.0: incorporation of angiotensin II receptor blocker neprilysin inhibitor (ARNI) and risk for heart failure hospitalization. *Eur J Heart Fail* 2018;**20**:938–940.
63. Bayés-Genís A, Lupón J. The Barcelona Bio-HF Calculator: a contemporary web-based heart failure risk score. *JACC Heart Fail* 2018;**6**:808–810.
64. Lupón J, Gaggin HK, de Antonio M, Domingo M, Galán A, Zamora E, Vila J, Peñafiel J, Urrutia A, Ferrer E, Vallejo N, Januzzi JL, Bayes-Genis A. Biomarker-assist score for reverse remodeling prediction in heart failure: the ST2-R2 score. *Int J Cardiol* 2015;**184**:337–343.
65. Ambrosy AP, Pang PS, Khan S, Konstam MA, Fonarow GC, Traver B, Maggioni AP, Cook T, Swedberg K, Burnett JC Jr, Grinfeld L, Udelson JE, Zannad F, Gheorghiade M. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart

failure with reduced ejection fraction: findings from the EVEREST trial. *Eur Heart J* 2013;**34**:835–843.
66. Coiro S, Rossignol P, Ambrosio G, Carluccio E, Alunni G, Murrone A, Tritto I, Zannad F, Girerd N. Prognostic value of residual pulmonary congestion at discharge assessed by lung ultrasound imaging in heart failure. *Eur J Heart Fail* 2015;**17**:1172–1181.
67. Girerd N, Seronde MF, Coiro S, Chouihed T, Bilbault P, Braun F, Kenizou D, Maillier B, Nazeyrollas P, Roul G, Fillieux L, Abraham WT, Januzzi J Jr, Sebbag L, Zannad F, Mebazaa A, Rossignol P. Integrative assessment of congestion in heart failure throughout the patient journey. *JACC Heart Fail* 2018;**6**:273–285.
68. Araiza-Garaygordobil D, Gopar-Nieto R, Martinez-Amezcua P, Cabello-López A, Alanis-Estrada G, Luna-Herbert A, González-Pacheco H, Paredes-Paucar CP, Sierra-Lara MD, Briseño-De la Cruz JL, Rodriguez-Zanella H, Martinez-Rios MA, Arias-Mendoza A. A randomized controlled trial of lung ultrasound-guided therapy in heart failure (CLUSTER-HF study). *Am Heart J* 2020;**227**:31–39.
69. Rivas-Lasarte M, Álvarez-García J, Fernández-Martínez J, Maestro A, López-López L, Solé-González E, Pirla MJ, Mesado N, Mirabet S, Fluvià P, Brossa V, Sionis A, Roig E, Cinca J. Lung ultrasound-guided treatment in ambulatory patients with heart failure: a randomized controlled clinical trial (LUS-HF study). *Eur J Heart Fail* 2019;**21**:1605–1613.
70. Liteplo AS, Marill KA, Villen T, Miller RM, Murray AF, Croft PE, Capp R, Noble VE. Emergency thoracic ultrasound in the differentiation of the etiology of shortness of breath (ETUDES): sonographic B-lines and N-terminal pro-brain-type natriuretic peptide in diagnosing congestive heart failure. *Acad Emerg Med* 2009;**16**:201–210.
71. Pivetta E, Goffi A, Lupia E, Tizzani M, Porrino G, Ferreri E, Volpicelli G, Balzaretti P, Banderali A, Iacobucci A, Locatelli S, Casoli G, Stone MB, Maule MM, Baldi I, Merletti F, Cibinel GA, Baron P, Battista S, Buonafede G, Busso V, Conterno A, Del Rizzo P, Ferrera P, Pecetto PF, Moiraghi C, Morello F, Steri F, Ciccone G, Calasso C, Caserta MA, Civita M, Condo C, D'Alessandro V, Del Colle S, Ferrero S, Griot G, Laurita E, Lazzero A, Lo Curto F, Michelazzo M, Nicosia V, Palmari N, Ricchiardi A, Rolfo A, Rostagno R, Bar F, Boero E, Frascisco M, Micossi I, Mussa A, Stefanone V, Agricola R, Cordero G, Corradi F, Runzo C, Soragna A, Sciullo D, Vercillo D, Allione A, Artana N, Corsini F, Dutto L, Lauria G, Morgillo T, Tartaglino B, Bergandi D, Cassetta I, Masera C, Garrone M, Ghiselli G, Ausiello L, Barutta L, Bernardi E, Bono A, Forno D, Lamorte A, Lison D, Lorenzati B, Maggio E, Masi I, Maggiorotto M, Novelli G, Panero F, Perotto M, Ravazzoli M, Saglio E, Soardo F, Tizzani A, Tizzani P, Tullio M, Ulla M, Romagnoli E. Lung ultrasound-implemented diagnosis of acute decompensated heart failure in the ED: a SIMEU multicenter study. *Chest* 2015;**148**:202–210.
72. Čelutkienė J, Lainscak M, Anderson L, Gayat E, Grapsa J, Harjola VP, Manka R, Nihoyannopoulos P, Filardi PP, Vrettou R, Anker SD, Filippatos G, Mebazaa A, Metra M, Piepoli M, Ruschitzka F, Zamorano JL, Rosano G, Seferovic P. Imaging in patients with suspected acute heart failure: timeline approach position statement on behalf of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2020;**22**:181–195.
73. Miglioranza MH, Gargani L, Sant'Anna RT, Rover MM, Martins VM, Mantovani A, Weber C, Moraes MA, Feldman CJ, Kalil RA, Sicari R, Picano E, Leiria TL. Lung ultrasound for the evaluation of pulmonary congestion in outpatients: a comparison with clinical assessment, natriuretic peptides, and echocardiography. *JACC Cardiovasc Imaging* 2013;**6**:1141–1151.
74. Öhman J, Harjola VP, Karjalainen P, Lassus J. Assessment of early treatment response by rapid cardiothoracic ultrasound in acute heart failure: cardiac filling pressures, pulmonary congestion and mortality. *Eur Heart J Acute Cardiovasc Care* 2018;**7**:311–320.
75. Öhman J, Harjola VP, Karjalainen P, Lassus J. Focused echocardiography and lung ultrasound protocol for guiding treatment in acute heart failure. *ESC Heart Fail* 2018;**5**:120–128.
76. Breidthardt T, Weidmann ZM, Twerenbold R, Gantenbein C, Stallone F, Rentsch K, Rubini Gimenez M, Kozhuharov N, Sabti Z, Breitenbucher D, Wildi K, Puelacher C, Honegger U, Wagener M, Schumacher C, Hillinger P, Osswald S, Mueller C. Impact of haemoconcentration during acute heart failure therapy on mortality and its relationship with worsening renal function. *Eur J Heart Fail* 2017;**19**:226–236.
77. Testani JM, Brisco MA, Chen J, McCauley BD, Parikh CR, Tang WH. Timing of hemoconcentration during treatment of acute decompensated heart failure and subsequent survival: importance of sustained decongestion. *J Am Coll Cardiol* 2013;**62**:516–524.
78. Damman K, Testani JM. The kidney in heart failure: an update. *Eur Heart J* 2015;**36**:1437–1444.
79. Martins JL, Santos L, Faustino A, Viana J, Santos J. Worsening or 'pseudo-worsening' renal function? The prognostic value of hemoconcentration in patients admitted with acute heart failure. *Rev Port Cardiol* 2018;**37**:595–602.
80. Cohen-Solal A, Logeart D, Huang B, Cai D, Nieminen MS, Mebazaa A. Lowered B-type natriuretic peptide in response to levosimendan or dobutamine treatment is associated with improved survival in patients with severe acutely decompensated heart failure. *J Am Coll Cardiol* 2009;**53**:2343–2348.
81. Boisot S, Beede J, Isakson S, Chiu A, Clopton P, Januzzi J, Maisel AS, Fitzgerald RL. Serial sampling of ST2 predicts 90-day mortality following destabilized heart failure. *J Card Fail* 2008;**14**:732–738.
82. Aimo A, Gaggin HK, Barison A, Emdin M, Januzzi JL Jr. Imaging, biomarker, and clinical predictors of cardiac remodeling in heart failure with reduced ejection fraction. *JACC Heart Fail* 2019;**7**:782–794.
83. Grayburn PA, Sannino A, Packer M. Proportionate and disproportionate functional mitral regurgitation: a new conceptual framework that reconciles the results of the MITRA-FR and COAPT trials. *JACC Cardiovasc Imaging* 2019;**12**:353–362.
84. Senni M, Adamo M, Metra M, Alfieri O, Vahanian A. Treatment of functional mitral regurgitation in chronic heart failure: can we get a 'proof of concept' from the MITRA-FR and COAPT trials? *Eur J Heart Fail* 2019;**21**:852–861.
85. Daubert MA, Adams K, Yow E, Barnhart HX, Douglas PS, Rimmer S, Norris C, Cooper L, Leifer E, Desvigne-Nickens P, Anstrom K, Fiuzat M, Ezekowitz J, Mark DB, O'Connor CM, Januzzi J, Felker GM. NT-proBNP goal achievement is associated with significant reverse remodeling and improved clinical outcomes in HFrEF. *JACC Heart Fail* 2019;**7**:158–168.
86. Januzzi JL, Jr., Rehman SU, Mohammed AA, Bhardwaj A, Barajas L, Barajas J, Kim HN, Baggish AL, Weiner RB, Chen-Tournoux A, Marshall JE, Moore SA, Carlson WD, Lewis GD, Shin J, Sullivan D, Parks K, Wang TJ, Gregory SA, Uthamalingam S, Semigran MJ. Use of amino-terminal pro-B-type natriuretic peptide to guide outpatient therapy of patients with chronic left ventricular systolic dysfunction. *J Am Coll Cardiol* 2011;**58**:1881–1889.
87. Brunner-La Rocca HP, Sanders-van Wijk S. Natriuretic peptides in chronic heart failure. *Card Fail Rev* 2019;**5**:44–49.
88. Brunner-La Rocca HP, Eurlings L, Richards AM, Januzzi JL, Pfisterer ME, Dahlstrom U, Pinto YM, Karlstrom P, Erntell H, Berger R, Persson H, O'Connor CM, Moertl D, Gaggin HK, Frampton CM, Nicholls MG, Troughton RW. Which heart failure patients profit from natriuretic peptide guided therapy? A meta-analysis from individual patient data of randomized trials. *Eur J Heart Fail* 2015;**17**:1252–1261.
89. Porapakkham P, Porapakkham P, Zimmet H, Billah B, Krum H. B-type natriuretic peptide-guided heart failure therapy: a meta-analysis. *Arch Intern Med* 2010;**170**:507–514.
90. De Vecchis R, Esposito C, Di Biase G, Ariano C, Giasi A, Cioppa C. B-type natriuretic peptide-guided versus symptom-guided therapy in outpatients with chronic heart failure: a systematic review with meta-analysis. *J Cardiovasc Med* 2014;**15**:122–134.
91. Felker GM, Anstrom KJ, Adams KF, Ezekowitz JA, Fiuzat M, Houston-Miller N, Januzzi JL Jr, Mark DB, Pina IL, Passmore G, Whellan DJ, Yang H, Cooper LS, Leifer ES, Desvigne-Nickens P, O'Connor CM. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA* 2017;**318**:713–720.
92. Ouwerkerk W, Zwinderman AH, Ng LL, Demissei B, Hillege HL, Zannad F, van Veldhuisen DJ, Samani NJ, Ponikowski P, Metra M, Ter Maaten JM, Lang CC, van der Harst P, Filippatos G, Dickstein K, Cleland JG, Anker SD, Voors AA. Biomarker-guided versus guideline-based treatment of patients with heart failure: results from BIOSTAT-CHF. *J Am Coll Cardiol* 2018;**71**:386–398.
93. Davarzani N, Sanders-van Wijk S, Maeder MT, Rickenbacher P, Smirnov E, Karel J, Suter T, de Boer RA, Block D, Rolny V, Zaugg C, Pfisterer ME, Peeters R, Brunner-La Rocca HP; TIME-CHF Investigators. Novel concept to guide systolic heart failure medication by repeated biomarker testing-results from TIME-CHF in context of predictive, preventive, and personalized medicine. *EPMA J* 2018;**9**:161–173.
94. Gaggin HK, Motiwala S, Bhardwaj A, Parks KA, Januzzi JL Jr. Soluble concentrations of the interleukin receptor family member ST2 and beta-blocker therapy in chronic heart failure. *Circ Heart Fail* 2013;**6**:1206–1213.
95. Brunner-La Rocca HP, Knackstedt C, Eurlings L, Rolny V, Krause F, Pfisterer ME, Tobler D, Rickenbacher P, Maeder MT; TIME-CHF investigators. Impact of worsening renal function related to medication in heart failure. *Eur J Heart Fail* 2015;**17**:159–168.
96. Lupón J, Díez-López C, de Antonio M, Domingo M, Zamora E, Moliner P, González B, Santesmases J, Troya MI, Bayés-Genís A. Recovered heart failure with reduced ejection fraction and outcomes: a prospective study. *Eur J Heart Fail* 2017;**19**:1615–1623.

97. Basuray A, French B, Ky B, Vorovich E, Olt C, Sweitzer NK, Cappola TP, Fang JC. Heart failure with recovered ejection fraction: clinical description, biomarkers, and outcomes. *Circulation* 2014;**129**:2380–2387.
98. Tanabe K, Sakamoto T. Heart failure with recovered ejection fraction. *J Echocardiogr* 2019;**17**:5–9.
99. Kubanek M, Sramko M, Maluskova J, Kautznerova D, Weichet J, Lupinek P, Vrbska J, Malek I, Kautzner J. Novel predictors of left ventricular reverse remodeling in individuals with recent-onset dilated cardiomyopathy. *J Am Coll Cardiol* 2013;**61**:54–63.
100. Amorim S, Campelo M, Martins E, Moura B, Sousa A, Pinho T, Silva-Cardoso J, Maciel MJ. Prevalence, predictors and prognosis of ventricular reverse remodeling in idiopathic dilated cardiomyopathy. *Rev Port Cardiol* 2016;**35**:253–260.
101. Givertz MM, Mann DL. Epidemiology and natural history of recovery of left ventricular function in recent onset dilated cardiomyopathies. *Curr Heart Fail Rep* 2013;**10**:321–330.
102. de Groote P, Fertin M, Duva Pentiah A, Goeminne C, Lamblin N, Bauters C. Long-term functional and clinical follow-up of patients with heart failure with recovered left ventricular ejection fraction after beta-blocker therapy. *Circ Heart Fail* 2014;**7**:434–439.
103. Merken J, Brunner-La Rocca HP, Weerts J, Verdonschot J, Hazebroek M, Schummers G, Schreckenberg M, Lumens J, Heymans S, Knackstedt C. Heart failure with recovered ejection fraction. *J Am Coll Cardiol* 2018;**72**:1557–1558.
104. Halliday BP, Wassall R, Lota AS, Khalique Z, Gregson J, Newsome S, Jackson R, Rahneva T, Wage R, Smith G, Venneri L, Tayal U, Auger D, Midwinter W, Whiffin N, Rajani R, Dungu JN, Pantazis A, Cook SA, Ware JS, Baksi AJ, Pennell DJ, Rosen SD, Cowie MR, Cleland JGF, Prasad SK. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. *Lancet* 2019;**393**:61–73.
105. Adamo L, Perry A, Novak E, Makan M, Lindman BR, Mann DL. Abnormal global longitudinal strain predicts future deterioration of left ventricular function in heart failure patients with a recovered left ventricular ejection fraction. *Circ Heart Fail* 2017;**10**:e003788.
106. Gulati G, Udelson JE. Heart failure with improved ejection fraction: is it possible to escape one's past? *JACC Heart Fail* 2018;**6**:725–733.
107. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, McDonagh T, Sechtem U, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012;**14**:803–869.
108. Kober L, Thune JJ, Nielsen JC, Haarbo J, Videbaek L, Korup E, Jensen G, Hildebrandt P, Steffensen FH, Bruun NE, Eiskjaer H, Brandes A, Thogersen AM, Gustafsson F, Egstrup K, Videbaek R, Hassager C, Svendsen JH, Hofsten DE, Torp-Pedersen C, Pehrson S; DANISH Investigators. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med* 2016;**375**:1221–1230.
109. Klem I, Weinsaft JW, Bahnson TD, Hegland D, Kim HW, Hayes B, Parker MA, Judd RM, Kim RJ. Assessment of myocardial scarring improves risk stratification in patients evaluated for cardiac defibrillator implantation. *J Am Coll Cardiol* 2012;**60**:408–420.
110. Halliday BP, Gulati A, Ali A, Guha K, Newsome S, Arzanauskaite M, Vassiliou VS, Lota A, Izgi C, Tayal U, Khalique Z, Stirrat C, Auger D, Pareek N, Ismail TF, Rosen SD, Vazir A, Alpendurada F, Gregson J, Frenneaux MP, Cowie MR, Cleland JGF, Cook SA, Pennell DJ, Prasad SK. Association between midwall late gadolinium enhancement and sudden cardiac death in patients with dilated cardiomyopathy and mild and moderate left ventricular systolic dysfunction. *Circulation* 2017;**135**:2106–2115.
111. Barison A, Aimo A, Ortalda A, Todiere G, Grigoratos C, Passino C, Camici PG, Aquaro GD, Emdin M. Late gadolinium enhancement as a predictor of functional recovery, need for defibrillator implantation and prognosis in non-ischemic dilated cardiomyopathy. *Int J Cardiol* 2018;**250**:195–200.
112. Pascual-Figal DA, Ordonez-Llanos J, Tornel PL, Vazquez R, Puig T, Valdes M, Cinca J, de Luna AB, Bayes-Genis A. Soluble ST2 for predicting sudden cardiac death in patients with chronic heart failure and left ventricular systolic dysfunction. *J Am Coll Cardiol* 2009;**54**:2174–2179.
113. Lupón J, Cediel G, Moliner P, de Antonio M, Domingo M, Zamora E, Núñez J, González B, Santiago-Vacas E, Santesmases J, Troya MI, Díez-Quevedo C, Boldó M, Barallat J, Bayes-Genis A. A bio-clinical approach for prediction of sudden cardiac death in outpatients with heart failure: the ST2-SCD score. *Int J Cardiol* 2019;**293**:148–152.
114. White JA, Yee R, Yuan X, Krahn A, Skanes A, Parker M, Klein G, Drangova M. Delayed enhancement magnetic resonance imaging predicts response to cardiac resynchronization therapy in patients with intraventricular dyssynchrony. *J Am Coll Cardiol* 2006;**48**:1953–1960.
115. Chen Z, Sohal M, Sammut E, Child N, Jackson T, Claridge S, Cooklin M, O'Neill M, Wright M, Gill J, Chiribiri A, Schaeffter T, Carr-White G, Razavi R, Rinaldi CA. Focal but not diffuse myocardial fibrosis burden quantification using cardiac magnetic resonance imaging predicts left ventricular reverse modeling following cardiac resynchronization therapy. *J Cardiovasc Electrophysiol* 2016;**27**:203–209.
116. Massoullié G, Sapin V, Ploux S, Rossignol P, Mulliez A, Jean F, Marie PY, Merlin C, Pereira B, Andronache M, Motreff P, Chabin X, Sellal JM, Citron B, Lusson JR, Vorilhon C, Clerfond G, Bordachar P, Zannad F, Eschalier R. Low fibrosis biomarker levels predict cardiac resynchronization therapy response. *Sci Rep* 2019;**9**:6103.
117. García-Bolao I, López B, Macías A, Gavira JJ, Azcárate P, Díez J. Impact of collagen type I turnover on the long-term response to cardiac resynchronization therapy. *Eur Heart J* 2008;**29**:898–906.
118. Stolen CM, Adourian A, Meyer TE, Stein KM, Solomon SD. Plasma galectin-3 and heart failure outcomes in MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy). *J Card Fail* 2014;**20**:793–799.
119. Lam CS, Rienstra M, Tay WT, Liu LC, Hummel YM, van der Meer P, de Boer RA, Van Gelder IC, van Veldhuisen DJ, Voors AA, Hoendermis ES. Atrial fibrillation in heart failure with preserved ejection fraction: association with exercise capacity, left ventricular filling pressures, natriuretic peptides, and left atrial volume. *JACC Heart Fail* 2017;**5**:92–98.
120. Richards M, Di Somma S, Mueller C, Nowak R, Peacock WF, Ponikowski P, Mockel M, Hogan C, Wu AH, Clopton P, Filippatos GS, Anand I, Ng L, Daniels LB, Neath SX, Shah K, Christenson R, Hartmann O, Anker SD, Maisel A. Atrial fibrillation impairs the diagnostic performance of cardiac natriuretic peptides in dyspneic patients: results from the BACH Study (Biomarkers in ACute Heart Failure). *JACC Heart Fail* 2013;**1**:192–199.
121. Reddy YNV, Obokata M, Gersh BJ, Borlaug BA. High prevalence of occult heart failure with preserved ejection fraction among patients with atrial fibrillation and dyspnea. *Circulation* 2018;**137**:534–535.
122. Inciardi RM, Giugliano RP, Claggett B, Gupta DK, Chandra A, Ruff CT, Antman EM, Mercuri MF, Grosso MA, Braunwald E, Solomon SD; ENGAGE AF-TIMI 48 Investigators. Left atrial structure and function and the risk of death or heart failure in atrial fibrillation. *Eur J Heart Fail* 2019;**21**:1571–1579.
123. Reddy YNV, Obokata M, Verbrugge FH, Lin G, Borlaug BA. Atrial dysfunction in patients with heart failure with preserved ejection fraction and atrial fibrillation. *J Am Coll Cardiol* 2020;**76**:1051–1064.
124. Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. *J Am Coll Cardiol* 2009;**53**:1119–1126.
125. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol* 2017;**14**:591–602.
126. Reddy YNV, Rikhi A, Obokata M, Shah SJ, Lewis GD, AbouEzzedine OF, Dunlay S, McNulty S, Chakraborty H, Stevenson LW, Redfield MM, Borlaug BA. Quality of life in heart failure with preserved ejection fraction: importance of obesity, functional capacity, and physical inactivity. *Eur J Heart Fail* 2020;**22**:1009–1018.
127. Reddy YNV, Lewis GD, Shah SJ, Obokata M, Abou-Ezzedine OF, Fudim M, Sun JL, Chakraborty H, McNulty S, LeWinter MM, Mann DL, Stevenson LW, Redfield MM, Borlaug BA. Characterization of the obese phenotype of heart failure with preserved ejection fraction: a RELAX trial ancillary study. *Mayo Clin Proc* 2019;**94**:1199–1209.
128. Aimo A, Januzzi JL Jr, Vergaro G, Clerico A, Latini R, Meessen J, Anand IS, Cohn JN, Gravning J, Ueland T, Nymo SH, Brunner-La Rocca HP, Bayes-Genis A, Lupón J, de Boer RA, Yoshihisa A, Takeishi Y, Egstrup M, Gustafsson I, Gaggin HK, Eggers KM, Huber K, Tentzeris I, Ripoli A, Passino C, Emdin M. Revisiting the obesity paradox in heart failure: per cent body fat as predictor of biomarkers and outcome. *Eur J Prev Cardiol* 2019;**26**:1751–1759.
129. Gentile F, Sciarrone P, Zamora E, De Antonio M, Santiago E, Domingo M, Aimo A, Giannoni A, Passino C, Codina P, Bayes-Genis A, Lupon J, Emdin M, Vergaro G. Body mass index and outcomes in ischaemic versus non-ischaemic heart failure across the spectrum of ejection fraction. *Eur J Prev Cardiol* 2021;**28**:948–955.

130. Madamanchi C, Alhosaini H, Sumida A, Runge MS. Obesity and natriuretic peptides, BNP and NT-proBNP: mechanisms and diagnostic implications for heart failure. *Int J Cardiol* 2014;**176**:611–617.
131. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. *Circulation* 2017;**136**:6–19.
132. Singh S, Pandey A, Neeland IJ. Diagnostic and prognostic considerations for use of natriuretic peptides in obese patients with heart failure. *Prog Cardiovasc Dis* 2020;**63**:649–655.
133. Bayes-Genis A, Lloyd-Jones DM, van Kimmenade RR, Lainchbury JG, Richards AM, Ordoñez-Llanos J, Santaló M, Pinto YM, Januzzi JL Jr. Effect of body mass index on diagnostic and prognostic usefulness of amino-terminal pro-brain natriuretic peptide in patients with acute dyspnea. *Arch Intern Med* 2007;**167**:400–407.
134. Scrutinio D, Passantino A, Guida P, Ammirati E, Oliva F, Sarzi Braga S, La Rovere MT, Lagioia R, Frigerio M, Di Somma S. Relationship among body mass index, NT-proBNP, and mortality in decompensated chronic heart failure. *Heart Lung* 2017;**46**:172–177.
135. Pandey A, Berry JD, Drazner MH, Fang JC, Tang WHW, Grodin JL. Body mass index, natriuretic peptides, and risk of adverse outcomes in patients with heart failure and preserved ejection fraction: analysis from the TOPCAT trial. *J Am Heart Assoc* 2018;**7**:e009664.
136. Horwich TB, Hamilton MA, Fonarow GC. B-type natriuretic peptide levels in obese patients with advanced heart failure. *J Am Coll Cardiol* 2006;**47**:85–90.
137. van Kimmenade RR, Januzzi JL, Jr, Baggish AL, Lainchbury JG, Bayes-Genis A, Richards AM, Pinto YM. Amino-terminal pro-brain natriuretic peptide, renal function, and outcomes in acute heart failure: redefining the cardiorenal interaction? *J Am Coll Cardiol* 2006;**48**:1621–1627.
138. van Kimmenade RR, Januzzi JL, Jr, Bakker JA, Houben AJ, Rennenberg R, Kroon AA, Crijns HJ, van Dieijen-Visser MP, de Leeuw PW, Pinto YM. Renal clearance of B-type natriuretic peptide and amino terminal pro-B-type natriuretic peptide a mechanistic study in hypertensive subjects. *J Am Coll Cardiol* 2009;**53**:884–890.
139. Schaub JA, Coca SG, Moledina DG, Gentry M, Testani JM, Parikh CR. Amino-terminal pro-B-type natriuretic peptide for diagnosis and prognosis in patients with renal dysfunction: a systematic review and meta-analysis. *JACC Heart Fail* 2015;**3**:977–989.
140. Ureche C, Sascău R, Ţăpoi L, Covic A, Moroşanu C, Voroneanu L, Burlacu A, Stătescu C, Covic A. Multi-modality cardiac imaging in advanced chronic kidney disease. *Echocardiography* 2019;**36**:1372–1380.
141. Pressman GS, Seetha Rammohan HR, Romero-Corral A, Fumo P, Figueredo VM, Gorcsan J 3rd. Echocardiographic strain and mortality in Black Americans with end-stage renal disease on hemodialysis. *Am J Cardiol* 2015;**116**:1601–1604.
142. Ravera M, Rosa GM, Fontanive P, Bussalino E, Dorighi U, Picciotto D, Di Lullo L, Dini FL, Paoletti E. Impaired left ventricular global longitudinal strain among patients with chronic kidney disease and end-stage renal disease and renal transplant recipients. *Cardiorenal Med* 2019;**9**:61–68.
143. Iles L, Pfluger H, Phrommintikul A, Cherayath J, Aksit P, Gupta SN, Kaye DM, Taylor AJ. Evaluation of diffuse myocardial fibrosis in heart failure with cardiac magnetic resonance contrast-enhanced T1 mapping. *J Am Coll Cardiol* 2008;**52**:1574–1580.
144. Bull S, White SK, Piechnik SK, Flett AS, Ferreira VM, Loudon M, Francis JM, Karamitsos TD, Prendergast BD, Robson MD, Neubauer S, Moon JC, Myerson SG. Human non-contrast T1 values and correlation with histology in diffuse fibrosis. *Heart* 2013;**99**:932–937.
145. Chin CWL, Everett RJ, Kwiecinski J, Vesey AT, Yeung E, Esson G, Jenkins W, Koo M, Mirsadraee S, White AC, Japp AG, Prasad SK, Semple S, Newby DE, Dweck MR. Myocardial fibrosis and cardiac decompensation in aortic stenosis. *JACC Cardiovasc Imaging* 2017;**10**:1320–1333.
146. Chin KM, Rubin LJ, Channick R, Di Scala L, Gaine S, Galiè N, Ghofrani HA, Hoeper MM, Lang IM, McLaughlin VV, Preiss R, Simonneau G, Sitbon O, Tapson VF. Association of N-terminal pro brain natriuretic peptide and long-term outcome in patients with pulmonary arterial hypertension. *Circulation* 2019;**139**:2440–2450.
147. Eindhoven JA, van den Bosch AE, Ruys TP, Opić P, Cuypers JA, McGhie JS, Witsenburg M, Boersma E, Roos-Hesselink JW. N-terminal pro-B-type natriuretic peptide and its relationship with cardiac function in adults with congenital heart disease. *J Am Coll Cardiol* 2013;**62**:1203–1212.
148. Schuuring MJ, van Riel AC, Vis JC, Duffels MG, van Dijk AP, de Bruin-Bon RH, Zwinderman AH, Mulder BJ, Bouma BJ. New predictors of mortality in adults with congenital heart disease and pulmonary hypertension: midterm outcome of a prospective study. *Int J Cardiol* 2015;**181**:270–276.
149. Geenen LW, Baggen VJM, van den Bosch AE, Eindhoven JA, Cuypers J, Witsenburg M, Boersma E, Roos-Hesselink JW. Prognostic value of soluble ST2 in adults with congenital heart disease. *Heart* 2019;**105**:999–1006.
150. Pradhan NM, Mullin C, Poor HD. Biomarkers and right ventricular dysfunction. *Crit Care Clin* 2020;**36**:141–153.
151. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Muñoz D, Rosenhek R, Sjögren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;**38**:2739–2791.
152. Pizarro R, Bazzino OO, Oberti PF, Falconi ML, Arias AM, Krauss JG, Cagide AM. Prospective validation of the prognostic usefulness of B-type natriuretic peptide in asymptomatic patients with chronic severe aortic regurgitation. *J Am Coll Cardiol* 2011;**58**:1705–1714.
153. Bergler-Klein J, Klaar U, Heger M, Rosenhek R, Mundigler G, Gabriel H, Binder T, Pacher R, Maurer G, Baumgartner H. Natriuretic peptides predict symptom-free survival and postoperative outcome in severe aortic stenosis. *Circulation* 2004;**109**:2302–2308.
154. Clavel MA, Malouf J, Michelena HI, Suri RM, Jaffe AS, Mahoney DW, Enriquez-Sarano M. B-type natriuretic peptide clinical activation in aortic stenosis: impact on long-term survival. *J Am Coll Cardiol* 2014;**63**:2016–2025.
155. Nakatsuma K, Taniguchi T, Morimoto T, Shiomi H, Ando K, Kanamori N, Murata K, Kitai T, Kawase Y, Izumi C, Miyake M, Mitsuoka H, Kato M, Hirano Y, Matsuda S, Inada T, Nagao K, Mabuchi H, Takeuchi Y, Yamane K, Toyofuku M, Ishii M, Minamino-Muta E, Kato T, Inoko M, Ikeda T, Komasa A, Ishii K, Hotta K, Higashitani N, Kato Y, Inuzuka Y, Maeda C, Jinnai T, Morikami Y, Saito N, Minatoya K, Kimura T; CURRENT AS Registry Investigators. B-type natriuretic peptide in patients with asymptomatic severe aortic stenosis. *Heart* 2019;**105**:384–390.
156. Enriquez-Sarano M, Tajik AJ, Schaff HV, Orszulak TA, Bailey KR, Frye RL. Echocardiographic prediction of survival after surgical correction of organic mitral regurgitation. *Circulation* 1994;**90**:830–837.
157. Clavel MA, Tribouilloy C, Vanoverschelde JL, Pizarro R, Suri RM, Szymanski C, Lazam S, Oberti P, Michelena HI, Jaffe A, Enriquez-Sarano M. Association of B-type natriuretic peptide with survival in patients with degenerative mitral regurgitation. *J Am Coll Cardiol* 2016;**68**:1297–1307.
158. Pizarro R, Bazzino OO, Oberti PF, Falconi M, Achilli F, Arias A, Krauss JG, Cagide AM. Prospective validation of the prognostic usefulness of brain natriuretic peptide in asymptomatic patients with chronic severe mitral regurgitation. *J Am Coll Cardiol* 2009;**54**:1099–1106.
159. Alashi A, Mentias A, Patel K, Gillinov AM, Sabik JF, Popović ZB, Mihaljevic T, Suri RM, Rodriguez LL, Svensson LG, Griffin BP, Desai MY. Synergistic utility of brain natriuretic peptide and left ventricular global longitudinal strain in asymptomatic patients with significant primary mitral regurgitation and preserved systolic function undergoing mitral valve surgery. *Circ Cardiovasc Imaging* 2016;**9**:e004451.
160. Yoon CH, Zo JH, Kim YJ, Kim HK, Shine DH, Kim KH, Kim KB, Ahn H, Sohn DW, Oh BH, Park YB. B-type natriuretic peptide in isolated severe tricuspid regurgitation: determinants and impact on outcome. *J Cardiovasc Ultrasound* 2010;**18**:139–145.
161. Emdin M, Aimo A, Rapezzi C, Fontana M, Perfetto F, Seferović PM, Barison A, Castiglione V, Vergaro G, Giannoni A, Passino C, Merlini G. Treatment of cardiac transthyretin amyloidosis: an update. *Eur Heart J* 2019;**40**:3699–3706.
162. Vergaro G, Aimo A, Barison A, Genovesi D, Buda G, Passino C, Emdin M. Keys to early diagnosis of cardiac amyloidosis: red flags from clinical, laboratory and imaging findings. *Eur J Prev Cardiol* 2020;**27**:1806–1815.
163. Falk RH, Plehn JF, Deering T, Schick EC Jr, Boinay P, Rubinow A, Skinner M, Cohen AS. Sensitivity and specificity of the echocardiographic features of cardiac amyloidosis. *Am J Cardiol* 1987;**59**:418–422.
164. Phelan D, Collier P, Thavendiranathan P, Popović ZB, Hanna M, Plana JC, Marwick TH, Thomas JD. Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis. *Heart* 2012;**98**:1442–1448.
165. Baccouche H, Maunz M, Beck T, Gaa E, Banzhaf M, Knayer U, Fogarassy P, Beyer M. Differentiating cardiac amyloidosis and hypertrophic cardiomyopathy by use of three-dimensional speckle tracking echocardiography. *Echocardiography* 2012;**29**:668–677.
166. Ternacle J, Bodez D, Guellich A, Audureau E, Rappeneau S, Lim P, Radu C, Guendouz S, Couetil JP, Benhaiem N, Hittinger L, Dubois-Randé JL, Plante-Bordeneuve V, Mohty D, Deux JF, Damy T. Causes and consequences of longitudinal LV dysfunction assessed by 2D strain echocardiography in cardiac amyloidosis. *JACC Cardiovasc Imaging* 2016;**9**:126–138.
167. Nicol M, Baudet M, Brun S, Harel S, Royer B, Vignon M, Lairez O, Lavergne D, Jaccard A, Attias D, Macron L, Gayat E, Cohen-Solal A, Arnulf B, Logeart D. Diagnostic score of cardiac involvement in AL amyloidosis. *Eur Heart J Cardiovasc Imaging* 2020;**21**:542–548.

168. Castiglione V, Franzini M, Aimo A, Carecci A, Lombardi CM, Passino C, Rapezzi C, Emdin M, Vergaro G. Use of biomarkers to diagnose and manage cardiac amyloidosis. *Eur J Heart Fail* 2021;**23**:217–230.
169. Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, Fu M, Heliö T, Heymans S, Jahns R, Klingel K, Linhart A, Maisch B, McKenna W, Mogensen J, Pinto YM, Ristic A, Schultheiss HP, Seggewiss H, Tavazzi L, Thiene G, Yilmaz A, Charron P, Elliott PM. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2013;**34**:2636–2648.
170. Friedrich MG, Sechtem U, Schulz-Menger J, Holmvang G, Alakija P, Cooper LT, White JA, Abdel-Aty H, Gutberlet M, Prasad S, Aletras A, Laissy JP, Paterson I, Filipchuk NG, Kumar A, Pauschinger M, Liu P. Cardiovascular magnetic resonance in myocarditis: a JACC White Paper. *J Am Coll Cardiol* 2009;**53**:1475–1487.
171. Costanzo MR, Dipchand A, Starling R, Anderson A, Chan M, Desai S, Fedson S, Fisher P, Gonzales-Stawinski G, Martinelli L, McGiffin D, Smith J, Taylor D, Meiser B, Webber S, Baran D, Carboni M, Dengler T, Feldman D, Frigerio M, Kfoury A, Kim D, Kobashigawa J, Shullo M, Stehlik J, Teuteberg J, Uber P, Zuckermann A, Hunt S, Burch M, Bhat G, Canter C, Chinnock R, Crespo-Leiro M, Delgado R, Dobbels F, Grady K, Kao W, Lamour J, Parry G, Patel J, Pini D, Towbin J, Wolfel G, Delgado D, Eisen H, Goldberg L, Hosenpud J, Johnson M, Keogh A, Lewis C, O'Connell J, Rogers J, Ross H, Russell S, Vanhaecke J. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. *J Heart Lung Transplant* 2010;**29**:914–956.
172. Streeter RP, Nichols K, Bergmann SR. Stability of right and left ventricular ejection fractions and volumes after heart transplantation. *J Heart Lung Transplant* 2005;**24**:815–818.
173. Hammerer-Lercher A, Mair J, Antretter H, Ruttmann E, Poelzl G, Laufer G, Puschendorf B, Hangler H. B-type natriuretic peptide as a marker of allograft rejection after heart transplantation. *J Heart Lung Transplant* 2005;**24**:1444.
174. Sun JP, Abdalla IA, Asher CR, Greenberg NL, Popović ZB, Taylor DO, Starling RC, Thomas JD, Garcia MJ. Non-invasive evaluation of orthotopic heart transplant rejection by echocardiography. *J Heart Lung Transplant* 2005;**24**:160–165.
175. Mena C, Wencker D, Krumholz HM, McNamara RL. Detection of heart transplant rejection in adults by echocardiographic diastolic indices: a systematic review of the literature. *J Am Soc Echocardiogr* 2006;**19**:1295–1300.
176. Mingo-Santos S, Moñivas-Palomero V, Garcia-Lunar I, Mitroi CD, Goirigolzarri-Artaza J, Rivero B, Oteo JF, Castedo E, González-Mirelis J, Cavero MA, Gómez-Bueno M, Segovia J, Alonso-Pulpón L. Usefulness of two-dimensional strain parameters to diagnose acute rejection after heart transplantation. *J Am Soc Echocardiogr* 2015;**28**:1149–1156.
177. Ruiz Ortiz M, Peña ML, Mesa D, Delgado M, Romo E, Santisteban M, Puentes M, López Granados A, Castillo JC, Arizón JM, de Lezo JS. Impact of asymptomatic acute cellular rejection on left ventricle myocardial function evaluated by means of two-dimensional speckle tracking echocardiography in heart transplant recipients. *Echocardiography* 2015;**32**:229–237.
178. Butler CR, Thompson R, Haykowsky M, Toma M, Paterson I. Cardiovascular magnetic resonance in the diagnosis of acute heart transplant rejection: a review. *J Cardiovasc Magn Reson* 2009;**11**:7.
179. Butler CR, Savu A, Bakal JA, Toma M, Thompson R, Chow K, Wang H, Kim DH, Mengel M, Haykowsky M, Pearson GJ, Kaul P, Paterson I. Correlation of cardiovascular magnetic resonance imaging findings and endomyocardial biopsy results in patients undergoing screening for heart transplant rejection. *J Heart Lung Transplant* 2015;**34**:643–650.
180. Usman AA, Taimen K, Wasielewski M, McDonald J, Shah S, Giri S, Cotts W, McGee E, Gordon R, Collins JD, Markl M, Carr JC. Cardiac magnetic resonance T2 mapping in the monitoring and follow-up of acute cardiac transplant rejection: a pilot study. *Circ Cardiovasc Imaging* 2012;**5**:782–790.
181. Bonnemains L, Villemin T, Escanye JM, Hossu G, Odille F, Vanhuyse F, Felblinger J, Marie PY. Diagnostic and prognostic value of MRI T2 quantification in heart transplant patients. *Transpl Int* 2014;**27**:69–76.