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Biomarkers in heart failure clinical trials. A review from the Biomarkers Working Group of the Heart Failure Association of the European Society of Cardiology

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The approval of new heart failure (HF) therapies has slowed over the past two decades in part due to the high costs of conducting large randomized clinical trials that are needed to adequately power major clinical endpoint studies. Several biomarkers have been identified reflecting different elements of HF pathophysiology, with possible applications in diagnosis, risk stratification, treatment monitoring, and even in the design of clinical trials. Biomarkers could potentially be used to refine study inclusion criteria to enable enrolment of patients who are more likely to respond to a therapeutic intervention, despite being at sufficient risk to meet pre-determined study endpoint rates. When there is a close relationship between biomarker levels and clinical endpoints, changes in biomarker levels after a given treatment can act as a surrogate endpoint, potentially reducing the duration and cost of a clinical trial. Natriuretic peptides have been widely used in clinical trials with a variable amount of added value, which such variation being probably due to the absence of a close pathophysiological connection to the study drug. Notable exceptions to this include sacubitril/valsartan and vericiguat. Future studies should seek to adopt unbiased approaches for discovery of true companion diagnostics; with -omics-based tools, biomarkers might be more precisely selected for

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Cardiovascular disorders remain the leading cause of morbidity and mortality worldwide, but the pace of drug and device development is considerably slower than for other conditions such as neoplastic disorders. A possible reason is the high cost of clinical trials adequately powered for hard clinical endpoints. Problems with trial design might be another issue, as 20% of drugs completing the phase 3 stage are not approved by the United States (U.S.) Food and Drug Administration (FDA), and only 6% of all novel cardiovascular drugs entering phase 1 are ultimately approved. It has been noted that clinical development programmes selecting patients through biomarker-based criteria have higher success rates at each phase of development. Indeed, biomarkers might facilitate the enrolment of patients who are most likely to respond to therapeutic intervention, despite still having the sufficient number of events to meet the trial endpoints.

A biomarker (from ‘biological marker’) has been defined as ‘a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention’. The analysis of circulating substances is the most common form of biomarker measurement, and has become widespread in clinical research. A 2019 FDA guidance document indicates that biomarkers have potential utility to enrol heart failure (HF) patients with a greater event risk, stratify patients based on their predicted prognosis, and allow early proof of concept and dose selection studies. Despite the almost exclusive focus on B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP), many biomarkers reflecting different elements of HF pathophysiology exist, and the identification of specific biomarkers for each drug has been proposed.

Building on the FDA document and some authoritative papers, this review article provides specific suggestions for biomarker use in HF clinical trials.

### Possible applications of heart failure biomarkers

Many biomarkers have been proposed to guide the diagnosis and management of HF (Figure 1). Ibrahim and Januzzi summarized in five points the characteristics of an ideal HF biomarker: (1) the method by which a biomarker is judged should be thorough; (2) the assays used to measure the biomarker should be robust; (3) the biomarker should reflect an important pathophysiological pathway involved in the HF disease process; (4) the biomarker should provide information other than what is already available by routine physical exam and laboratory evaluation; (5) the biomarker should add to clinical judgment for understanding diagnosis, prognosis, or management of HF. Biomarkers can predict the development of signs and symptoms, identify patients with subclinical disease, help diagnose HF, predict disease trajectories, guide therapeutic management, or serve as surrogate endpoints.

The BNP and NT-proBNP >80th percentile predict a higher risk of new-onset HF at 5 years in the general population. Two randomized controlled trials (St Vincent’s Screening TO Prevent Heart Failure [STOP-HF] and NT-proBNP Selected Preventin of Cardiac Events in a Population of Diabetic Patients Without a History of Cardiac Disease [PONTIAC]) evaluated a BNP- or NT-proBNP-guided approach in individuals with risk factors for HF. The STOP-HF trial enrolled subjects aged >40 years with at least one risk factor or cardiovascular comorbidity, while the PONTIAC trial enrolled diabetic patients. The positive results of these trials informed the American College of Cardiology/American Heart Association/HF Society of America (ACC/AHA/HFSA) guideline recommendation of a natriuretic peptide (NP)-based screening in patients at risk for HF (IIa B-R recommendation).

In symptomatic patients, BNP or NT-proBNP are recommended to diagnose chronic HF by both the European Society of Cardiology (ESC; I B recommendation) and ACC/AHA/HFSA (I A recommendation) guidelines. BNP or NT-proBNP are also recommended to diagnose acute HF. High NP levels are also essential components of the universal definition of HF. A large number of biomarkers have proven useful for the prediction of disease trajectories in patients with acute decompensated or ambulatory HF. The most studied are again NPs, and their use as prognostic tools in outpatient care is recommended by the ACC/AHA/HFSA guidelines (1 A), as well as on admission (1 A) and at discharge (2a B-NR). Additionally, current evidence suggests that sex modulates cardiovascular biomarker biology. However, the biological mechanisms are still poorly defined, with limited translation into clinical practice. In detail, there are limited sex-specific trials, with consistent underrepresentation of women as a standard or special population and limited inclusion of biological sex in research study design. This ultimately results in a general uncertainty regarding different tailoring of clinical care for men and women, starting from specific biomarker thresholds. Future approaches should include a sex-specific approach, from recruitment to study design and reporting.
Regarding biomarker integration in diagnostic, prognostic and therapeutic settings, circulating biomarkers and imaging techniques provide independent and complementary information to guide management of HF. A recent consensus document by the Heart Failure Association (HFA) of the ESC recently presented evidence-based indications relevant to the integration of imaging techniques and biomarkers in HF. These include screening, diagnosis, risk stratification, treatment guidance, and monitoring. An individually tailored approach includes a deep characterization of cardiac dysfunction, age, gender, and comorbidities. Circulating biomarkers associated with different pathways are an ideal complement of multi-modal imaging techniques in patient-centred and condition-specific approaches to HF assessment and management.

Several studies tried to find biomarkers able to guide therapeutic management in HF, with disappointing results. The Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) trial enrolled patients with left ventricular ejection fraction <40%, an HF episode within the prior 12 months, and elevated NPs within the previous month (BNP >400 ng/L or NT-proBNP >2000 ng/L), who were randomized to an NT-proBNP-guided strategy (target NT-proBNP <1000 ng/L) or the standard of care. The study was discontinued prematurely for futility after 894 patients out of the planned 1100 were enrolled, because there was no significant difference in the risk of cardiovascular death or HF hospitalization over a median of 15 months (hazard ratio [HR] 0.98, 95% confidence interval [CI] 0.79–1.22; p = 0.88), with the neutral results most likely caused by similar treatment.

Finally, biomarkers could serve as surrogate endpoints that could be reached in a shorter time than hard endpoints, thus reducing the follow-up time, the size of the study group and overall cost of clinical trials. The prerequisite is a close relationship between biomarker change and a clinical endpoint. At present, such relationship has not emerged for any biomarker. In the Prospective Comparison of ARNI (Angiotensin Receptor–Neprilysin Inhibitor) with ACEI (Angiotensin-Converting-Enzyme Inhibitor) to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, an early decrease in NT-proBNP predicted fewer clinical endpoints, but it did not predict the superior...
treatment effect of the experimental therapy. Nonetheless, the perfect alignment of biology and pharmacology (NT-proBNP changes due to drug effects) led to the FDA utilizing changes in NT-proBNP in paediatric studies of sacubitril/valsartan as a bridge to approval.

**Biomarkers in heart failure clinical trials**

Biomarkers have many possible applications in HF trials (Table 1). BNP and NT-proBNP have been by far the most commonly evaluated biomarkers, and have been employed usually for patient selection or as surrogate endpoints (Figure 2).

**Inclusion criteria**

The use of biomarkers as inclusion criteria has become standard practice in HF clinical trials, encouraging enrolment of patients with a level of risk that allows to design adequately powered trials that are still economically viable.

Natriuretic peptides have several characteristics that make their use ideal for patient selection for clinical trials. Most notably, they are inexpensive, reproducible, reliable, sensitive and specific to diagnose HF, and have strong prognostic value. Given their significant associations with the presence and severity of HF, NP-based inclusion criteria might allow to accurately identify patients with HF. This is particularly important in patients with HF and preserved ejection fraction (HFrEF) because the potential for misdiagnosis of HF is greater in this population, which might in turn dilute the observed benefit of the investigational treatment. Most of the major recent trials used NP-based inclusion criteria.

In the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial (TOPCAT), patients could be enrolled based on clinical suspicion of HF plus either elevated

<table>
<thead>
<tr>
<th>Table 1 Possible applications of biomarkers in heart failure clinical trials</th>
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<tr>
<td><strong>Phase 2</strong></td>
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<tr>
<td>• Development of mechanistic hypotheses</td>
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<td>• Inclusion criteria</td>
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<td>• Safety monitoring</td>
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**Figure 2** Use of natriuretic peptides in heart failure clinical trials. This analysis refers to all studies registered in ClinicalTrials.gov up to July 2019. Reprinted with permission from Ibrahim et al.
BNP or NT-proBNP or a recent HF hospitalization. While no significant benefit from spironolactone was found for the primary outcome, a significant benefit was seen in patients enrolled based on elevated NPs (HR 0.65; 95% CI 0.49–0.87; p = 0.003). Furthermore, patients enrolled without meeting the biomarker entry requirement had a lower event rate, suggesting misdiagnosis of HF. A recent analysis of the Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction (PARAGON-HF) trial focused on the 193 patients (4.0%) not meeting the final NP-based enrolment criteria (NT-proBNP >300 ng/L for patients in sinus rhythm or >900 ng/L for those in atrial fibrillation/flutter). These patients had lower rates of the primary endpoint of total HF hospitalizations and cardiovascular death as compared with patients meeting final enrolment criteria (8.6 [6.7–11.2] events per 100 patient-years vs. 14.0 [13.4–14.7] events per 100 patient-years; p = 0.01). The rate ratio for the treatment effect comparing sacubitril/valsartan with valsartan was 0.85 (95% CI 0.74–0.99; p = 0.04) in those who met final criteria.

In 2020, a search on the ClinicalTrials.gov dataset identified 3446 trials, with 10.6% using BNP or NT-proBNP as inclusion criteria. Among these trials, 43% used both NPs, 33% used only NT-proBNP, and 24% used only BNP in determining eligibility. Significant variations existed across trials in terms of BNP and NT-proBNP cut-off values used as inclusion criteria (online supplementary Table Appendix S1). Only some trials (10% in patients with decompensated HF; 20% in ambulatory outpatients with HF) employed adjusted cut-offs for at least some patient populations, although NP levels are known to be lower in black, obese, or patients with HFrEF, and higher in elderly patients or those with atrial fibrillation. Ibrahim et al. went on to propose recommendations for the use of NPs for patient selection in HF clinical trials (online supplementary Table 2).

Elevated NPs predict a higher risk of adverse outcomes, including death and rehospitalization. The value of NPs for risk prediction seems similar in patients with HFrEF or HF with reduced ejection fraction (HFrEF) despite lower concentrations of both BNP or NT-proBNP in patients with HFrEF. The possibility to predict future disease trajectories is particularly useful for enriching the study population with patients who have higher event rates to minimize the risk for type II error in underpowered studies. In the PARADIGM-HF trial, patients were required to have a BNP ≥150 ng/L or NT-proBNP ≥600 ng/L, or a BNP ≥100 ng/L or NT-proBNP ≥400 ng/L if they had been hospitalized for HF within the previous 12 months. The resulting high event rates allowed for more timely completion of this event-driven study. Higher concentrations of selected predictive biomarkers may enrich a trial with study participants at high risk, which usually benefit the most from a certain treatment. On the other hand, an excessively high biomarker threshold could lead to enrol patients who are unlikely to respond to therapy because of their excessive risk. An example of this may be provided by a post hoc analysis of the Vericiguat Global Study in Patients With Heart Failure and Reduced Ejection Fraction (VICTORIA) trial, which demonstrated a significant benefit in the primary composite endpoint only in subjects with NT-proBNP levels up to 8000 ng/L.

### Table 2 Possible natriuretic peptide-based cut-offs in heart failure clinical trials

<table>
<thead>
<tr>
<th>Goal</th>
<th>NP Cut-offs</th>
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<tbody>
<tr>
<td>To enrich a study population for risk in advanced/morbid chronic HF clinical trials:</td>
<td></td>
</tr>
<tr>
<td>- BNP ≥300 ng/L or NT-proBNP ≥1000 ng/L</td>
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<tr>
<td>Special circumstances:</td>
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<tr>
<td>1. Atrial fibrillation</td>
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<tr>
<td>- BNP and NT-proBNP: consider an increase of enrolment threshold by ≥30%</td>
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<tr>
<td>2. Black patients</td>
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<tr>
<td>- BNP and NT-proBNP: consider lowering enrolment threshold by ≥30%</td>
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<tr>
<td>3. Elderly patients (&gt;75 years)</td>
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<tr>
<td>- BNP: consider raising enrolment threshold by at least 20–30%</td>
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<tr>
<td>- NT-proBNP: ≥1800 ng/L</td>
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<tr>
<td>4. Chronic kidney disease</td>
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<td>- Exclude patients with ESRD or receiving RRT from enrolment by NPs</td>
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<tr>
<td>5. Neprilysin inhibition</td>
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<tr>
<td>- Avoid BNP use for monitoring response to neprilysin inhibition until more data are available regarding response of the various BNP assays to therapy. BNP should be used for study population enrichment, however</td>
<td></td>
</tr>
<tr>
<td>- No adjustment needed for NT-proBNP</td>
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<tr>
<td>6. Obesity</td>
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</tr>
<tr>
<td>- BNP and NT-proBNP: consider lowering enrolment threshold by at least 20–30% for patients with BMI ≥30 kg/m²</td>
<td></td>
</tr>
</tbody>
</table>

BMI, body mass index; BNP, B-type natriuretic peptide; ESRD, end-stage renal disease; HF, heart failure; HFrEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NP, natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RRT, renal replacement therapy.

Modified with permission from Ibrahim et al.
Assessment of response to treatment

In the non-randomized Effects of Sacubitril/Valsartan Therapy on Biomarkers, Myocardial Remodeling and Outcomes (PROVE-HF) study, early changes in NT-proBNP were associated with a subsequent reverse remodelling in patients with HFrEF receiving sacubitril/valsartan. The drop in NT-proBNP was reported to precede a decrease in high-sensitivity cardiac troponin T (hs-cTnT), and the combination of these biomarker changes predicted reverse remodelling more accurately than each biomarker alone. Besides sacubitril/valsartan, several drug classes, proven to be beneficial in HFrEF, have been shown to reduce NPs. For example, treatment with spironolactone and empagliflozin were associated with a decrease in NT-proBNP. With the notable exception of sacubitril/valsartan, biomarker changes are usually not a direct effect of therapy, but rather reflect an amelioration of HF severity. In the case of sodium–glucose cotransporter 2 inhibitors, our incomplete understanding of the drug effects on cardiomyocytes does not allow us to define with certainty whether NT-proBNP changes partially represent a direct manifestation of the mechanism of action of the drug.

Regardless of the lack of a biological link between specific therapies and NP changes, when a reduction in BNP or NT-proBNP occurs after a therapy is applied, it is more often than not accompanied by a temporal shift in prognosis. Often, the prognostic meaning of NP lowering may be significantly greater than other risk markers: for example, despite an unclear association between sodium–glucose cotransporter 2 inhibitor effects and the biology determining NT-proBNP and hs-cTnT release, reduction of both markers were the strongest predictors of outcome in the recent EMPEROR programme focused on empagliflozin in HF. However, NPs remain surrogate measurements whose relationship with outcomes remains indirect. It must be tested whether they may actually substitute outcome for drug approval whereas outcome, as well as quality of life, remain major endpoints that need direct assessment.

The use of a biomarker to monitor response to therapy in clinical trials need to be carefully assessed for each drug–biomarker combination. In particular, (i) the biomarker should be affected by a specific treatment in a manner that indicates how effective the treatment is; (ii) changes in the biomarker levels should reflect the benefit of the therapy; (iii) the biomarker should be sampled with a specific treatment in a manner that indicates how effective the benefit of the therapy; (iv) a pre-specified threshold to assess treatment response should be chosen, based either on percent or absolute changes. For most biomarkers, these points remain unclear, and more work in this area is needed as it might lead to their use as a surrogate endpoint for expedited regulatory approval of promising therapies. The optimal conditions to choose a surrogate biomarker are summarized in Table 3.

Biomarkers as elements of composite endpoints

Despite their relative strength as indicators of prognosis, changes in biomarker concentrations may nonetheless be insufficient to represent the entire clinical effect of a given treatment. Indeed, biomarker changes, as well as symptom resolution, and clinical events should be considered together as a measure of treatment benefit. A ranking approach allows to incorporate both events and quantitative measures of functional status (e.g. quality of life assessment, 6-min walking distance, or cardiac biomarkers), and to assess them based on a pre-specified hierarchical system. A pre-specified hierarchical ranking system can overcome the discrepancies often found between phase 2 and 3 trials, where the phase 2 trial shows an improvement in symptoms or congestion (surrogate endpoints), but these positive findings do not translate into a significant benefit in terms of hard clinical outcomes in the subsequent phase 3 trial. Indeed, the combination of continuous biomarker data and clinical endpoints in a hierarchical system in a phase 2 study might provide a more reliable indicator of the success or failure of the treatment in the following phase 3 study. The global rank endpoint of Felker and Maisel is an example of hierarchical approach that is based on the occurrence of death, the relief of dyspnoea at 24 h, and changes in three biomarkers (cardiac troponin, creatinine, and BNP/NT-proBNP). A limitation of this approach is that if we consider the low percentage of in-hospital death and the very high likelihood of meaningful symptom improvement at 24 h, this endpoint can be simplified as a comparison of biomarkers to test the efficacy of a new drug. However, since there is no established relationship between changes in cardiac troponin or BNP and outcomes in acute HF, this approach is not considered a valid surrogate for regulatory review. The win ratio is a novel method of incorporating morbidity, mortality, health-related quality of life and NPs in HF studies in a hierarchical fashion. Nonetheless, the more complex the ranking approach, the less easy it is for physicians to understand the benefit of a certain treatment and to carry out cost-effectiveness analyses.

Subgroup analyses

Biomarkers may be used to provide insight into specific subgroups of patients included in clinical trials, generating novel hypotheses. This may provide insight into the mechanism of drug action, the benefits of a drug, or the identification of subgroups or specific phenotypes of patients that report a differential benefit. Notably, although NPs are recognized biomarkers in many different settings, including HfPEF, we should highlight its limitations, as recently shown by Verbrugge et al. In particular,
while patients with HFpEF and normal NP display in general mild functional alterations, with more favourable clinical outcomes, there remains an increased residual risk of events, emphasizing the importance of a phenotype potentially poorly tracked by a biomarker only-based strategy in large clinical trials in this specific setting.

**Surrogates for safety**

Numerous types of cardiac toxicity have been revealed throughout drug development, and interest in using biomarkers as an early system for toxicity detection has increased. In pre-clinical studies, biomarkers may be used to identify hazards, generate hypotheses, and guide patient monitoring in clinical trials. In phase 2–4 trials, it is critical to have effective tools to monitor cardiac toxicity for innovative therapies to ensure patient safety. When biomarkers are used to detect potentially toxic effects of HF drugs, it is critical to establish a solid biological link between the biomarker and therapy toxicity, and any risk estimated from the change in biomarker levels over time should be rigorously validated, including knowledge of the minimum amount of change required to predict risk. One should not assume a rise in biomarker is necessarily a sign of toxicity: the importance of clear understanding of how therapies may cause unexpected rise in biomarkers is illustrated in the increase of NPs following treatment with drugs from the neuregulin class or increase in hs-cTn following myosin activator therapy with omecamtiv mecarbil. In both cases, no increase in risk was observed with the rise in biomarker levels.

Cardiac troponin is an indicator of cardiomyocyte damage, and its measurement through high-sensitivity assays may be used in HF trials to assess the toxicity of treatment strategies. Nonetheless, several hs-cTnI tests exist, each with its own reference range, and there are no specific guidelines establishing hs-cTn cut-offs above which concentrations would signal an abnormality. It is then difficult to say, for example, if a 4 ng/L higher median change in hs-cTnI in patients on a novel drug versus placebo is clinically relevant. Changes in hs-cTn should be interpreted considering the clinical setting and other laboratory data. If hs-cTn is employed in clinical trials as a toxicity monitor without a clear grasp of how to interpret concentration changes, it may jeopardize an otherwise beneficial medication.

**When might biomarkers not be used?**

The use of biomarkers in the development of cardiovascular therapies is particularly attractive when assessing slowly progressive cardiovascular diseases, patients with little or no symptoms, subclinical cardiovascular diseases, populations with low rates of clinical events, or therapeutic options requiring accelerated approval. Studies on patients with clinical HF usually do not meet these criteria, unless specific aetiologies are considered (e.g. hypertrophic cardiomyopathy or cardiac amyloidosis).

Biomarkers are not strictly required when clinically relevant measures can be assessed, such as patient-reported outcomes, physical performance, and mortality. Biomarkers should not be utilized when they have not been completely validated, or when they have not been evaluated in the patient demographic or disease state being researched. This is not trivial: intra-individual variability between biomarkers differs greatly, and the origin of most biomarkers is not the cardiac muscle but rather other organs such as fatty tissue, liver, and kidney. Therefore, changes over time of most biomarkers reflect changes in the entire organism, not changes of the cardiac muscle. Furthermore, short-term biomarker changes in patients with HF treated with a brief treatment exposure should not be viewed as conclusive for a longer-term benefit if the therapy in question does not have long-lasting effects.

**Proposals for the use of biomarkers in future clinical trials**

Based on the considerations above, we may formulate several suggestions for the future use of biomarkers in clinical trials (Table 4). As a first point, the use of biomarkers in HF clinical trials requires standardization of analytical aspects, which is now less relevant for NPs, but is a significant issue for other biomarkers, such as hs-cTn. Patient enrolment in HF trials is now commonly based on NP levels, but there is a lack of consensus on the specific cut-offs to be employed. In addition, factors affecting NP values (including age, gender, ejection fraction, atrial fibrillation, or chronic kidney disease) are not given sufficient consideration. Recently proposed cut-offs (Table 2) are in agreement with a previous position paper by the ESC, and might represent the first step toward standardized NP-based inclusion criteria. A relevant filed of application is represented by valvular heart disease. The recent ESC/EACTS guidelines emphasize the central role of cardiac biomarkers in valvular patients, in particular NPs, especially...
in asymptomatic patients or to better tailor the follow-up. However, biomarker use should be adopted selectively and, at present, starting from trial guidance in percutaneous setting,22 their standardization should be almost completely addressed along all trial phases.

Instead of focusing on NPs in every trial, future studies could try to identify specific biomarkers for each drug. These patterns could be employed for risk enrichment and to assess the response to treatment. A panel of biomarkers reflecting different cardiac alterations, such as collagen peptides or sST2 associated with fibrosis, C-reactive protein and interleukins with inflammation, endothelin or adrenomedullin with endothelial dysfunction, antigen carbohydrate 125 or bio-adrenomedullin with fluid overload, urinary sodium for monitoring decongestion, or direct renin for renin–angiotensin–aldosterone system activation could provide additional useful information regarding the pathophysiological impact on cardiac remodelling features.23 In addition, an unbiased -omic approach could be more accurate than the simple evaluation of biomarkers more closely associated with specific disease mechanisms24–26 (Figure 3). The heterogeneous setting of HFrEF seems particularly well-suited for this kind of approach.27

The main priorities for cardiac safety biomarkers are to define the strengths and limitations of in vitro models, and the relative advantages of human- versus animal-derived models for specific questions. Appropriate applications need assessment of study duration (acute vs. chronic effects), resource availability, the value of single versus multiparametric outcomes, and overall translational fidelity. Additionally, unbiased -omics may help identify safety markers before phase 3 studies.28

Finally, future clinical trials in HF should systematically include a plan for the collection, storage, and management of laboratory samples, to warrant the adequate quality of the aliquots and to ensure the possibility to test novel biomarkers.

**Supplementary Information**

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

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