ESC European Society of Cardiology

European Journal of Heart Failure (2024)
doi:10.1002/ejhf.3357

INVITED EDITORIAL

Identifying reliable biomarkers for pulmonary congestion: Toward a close yet sustainable heart failure follow-up

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This article refers to 'Serial cardiac biomarkers, pulmonary artery pressures and traditional parameters of fluid status in relation to prognosis in patients with chronic heart failure: Design and rationale of the BioMEMS study' by Y. Allach *et al.*, published in this issue on pages xxx.

Heart failure (HF) affects over 64 million people worldwide, and its burden is expected to increase over the next few years.[1] Hospital admissions due to HF not only impact the patients' quality of life and prognosis, but also impose a great burden on healthcare systems. Early detection of impending decompensation may allow for changes in therapeutic strategy and potentially prevent a hospitalization due to worsening HF.[2] Haemodynamic congestion is a primary cause of HF hospitalizations, underscoring the need for reliable markers of congestion. The biomarkers used in clinical practice are B-type natriuretic peptides (NPs), which have several limitations. First, several comorbidities (i.e. atrial fibrillation, chronic kidney disease, and obesity) may affect NP values regardless of congestion status.[3] Second, measurement intervals during follow-up have not been standardized and typically range from 6 to 12 months. Third, no validated protocols for therapy adjustment based on NP changes exist because of the little evidence on the prognostic efficacy of treatment strategies guided by NP values.[4]

Pulmonary artery (PA) pressure reflects pulmonary congestion. Direct, invasive monitoring of PA pressure allows for timely therapy adjustments and the prevention of HF exacerbations. The use of remote PA pressure monitoring to guide treatment of patients with HF reduces episodes of worsening HF and subsequent hospitalizations.[5] Possible drawbacks of this approach are its costs, the need for a platform integrating data and providing alerts, as well as dedicated healthcare professionals to monitor information flow and provide instructions. For these reasons, PA pressure monitoring might not be feasible on a large scale.[6]

An alternative approach is decentralization of care through periodic measurements of congestion biomarkers, possibly either at home or in a general practitioner's office, and referral to an outpatient visit only when there is a clinically significant increase in the biomarker. This requires a biomarker that accurately reflects worsening congestion, is measurable through point-of-care testing, and whose values can be easily interpreted. The first step in this direction is identifying such a biomarker, looking for possible alternatives to NPs, which have the problems discussed above.

The BioMEMS study, whose design is presented in this issue of the Journal,[7] is a first step in this direction. BioMEMS is a biobank substudy of the MONITOR-HF trial, an open-label multicentre randomized clinical trial enrolling 348 patients with chronic HF, New York Heart Association (NYHA) class III, who had experienced at least one HF hospitalization or urgent visit necessitating intravenous diuretics within 12 months prior to enrolment.[8] Patients were enrolled regardless of their left ventricular ejection fraction. Those with HF with reduced ejection fraction (HFrEF) were to be on optimal or maximally tolerated guideline-directed medical therapy. At baseline, beta-blockers, renin–angiotensin–aldosterone system inhibitors, mineralocorticoid receptor antagonist, and sodium–glucose cotransporter 2 inhibitors (SGLT2i) were prescribed in 85%, 90%, 86%, and 11% of patients with HFrEF, respectively. Patients were randomized in a 1:1 ratio to PA pressure monitoring (CardioMEMS-HF system, $n = 176$ [51%]) or standard care ($n = 172$ [49%]).[8] When allocated to the treatment group, patients underwent sensor implantation and were instructed to take daily readings.[8,9] A study operating procedure helped clinicians guide HF therapy following a significant rise in PA pressure over time, also avoiding hypovolaemia.[8] Follow-up visits were scheduled at 3, 6, and 12 months, with laboratory assessments performed during these visits. The primary endpoint was the mean difference

The opinions expressed in this article are not necessarily those of the Editors of the *European Journal of Heart Failure* or of the European Society of Cardiology. doi: 10.1002/ejhf.3303.

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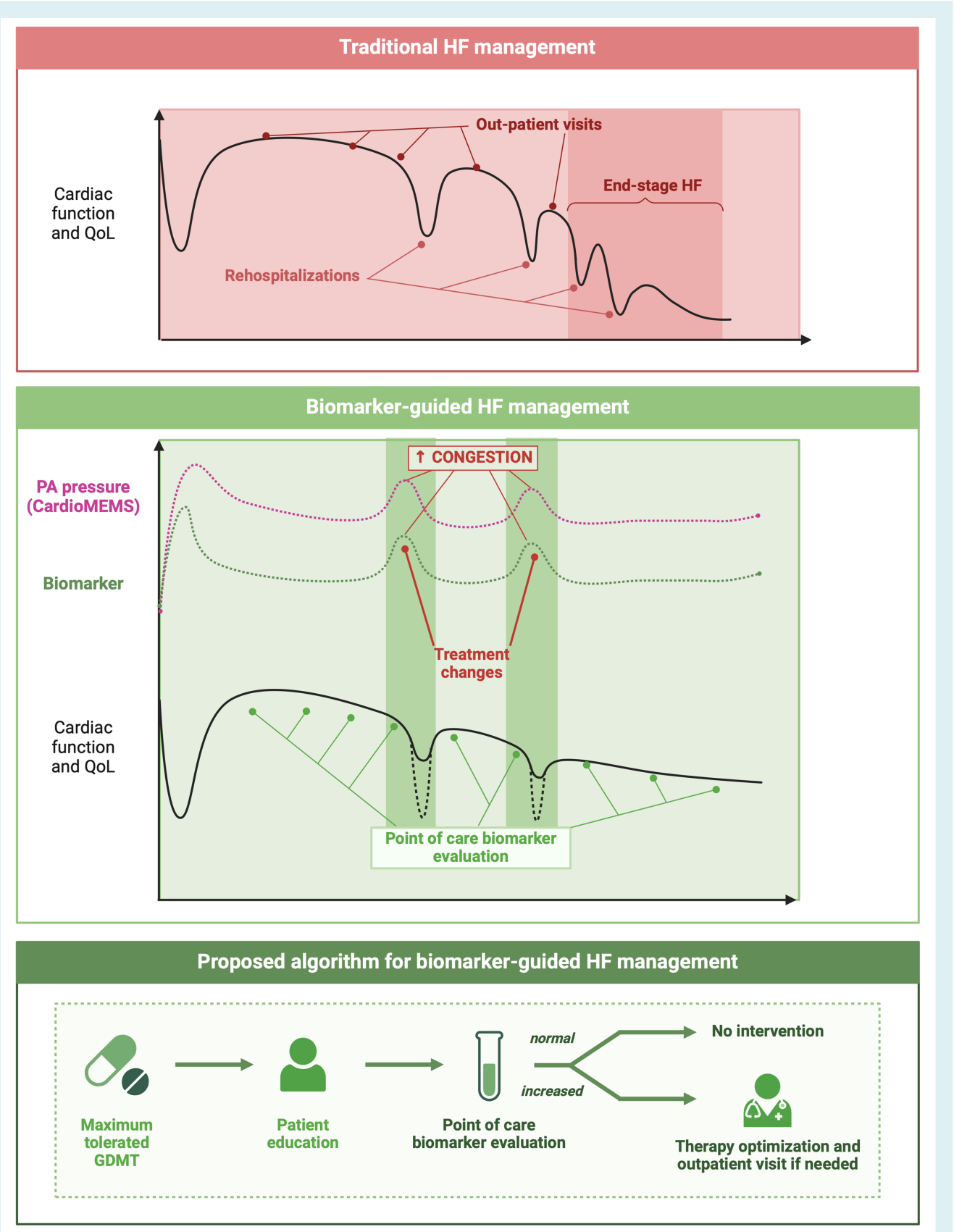

Figure 1 Traditional versus biomarker-guided heart failure (HF) monitoring. GDMT, guideline-directed medical therapy; QoL, quality of life; PA, pulmonary artery.

in the Kansas City Cardiomyopathy Questionnaire overall summary score (KCCQ-OSS) at 12 months. Haemodynamic monitoring substantially improved quality of life, with a mean change in KCCQ-OSS of 7.13 (95% confidence interval 1.51–12.75; $p = 0.013$) between groups.[8]

The BioMEMS study involves the collection of additional blood samples from 340 participants (98% of the MONITOR-HF cohort) during 3-, 6-, and 12-month follow-up visits.[7] Samples are analysed using the Olink Cardiovascular III panel, which measures 92 cardiovascular disease-related human protein biomarkers. The first goal is to evaluate the relationship between PA pressures and different biomarkers and to identify biomarkers that can serve as surrogate indicators of PA pressure changes, thereby predicting an exacerbation of HF or cardiovascular death. The long-term goal is to derive data that can be used to design trials on home management of HF patients guided by biomarkers.[7]

To our knowledge, the BioMEMS project is the first study to correlate serial biomarkers to PA pressures. The integration of laboratory and haemodynamic data enhances our understanding of temporal patterns that could be used to predict and prevent HF decompensation. A possible limitation of BioMEMS is the lack of serial echocardiographic data preventing their correlation with biomarkers, and the lack of information on possible factors influencing biomarker values beyond congestion, e.g. atrial fibrillation episodes or infections, that are also well recognized precipitating factors for HF admissions. Furthermore, most patients were enrolled before the release of the 2021 ESC guidelines on HF,[10] which explains the low rates of SGLT2i prescription[7]; this could limit the translatability of the results to a contemporary real-world cohort. Additionally, the panel provides normalized protein expression values instead of standard concentration units,[8] complicating comparisons with clinically applied cut-off values, and includes only known biomarkers associated with cardiovascular disease. Last, the focus on patients with moderate to severe HF may limit the generalizability of the findings to other HF phenotypes. The inclusion of patients with different stages and aetiologies of HF in future studies could provide a more comprehensive understanding of the potential applications of biomarker and haemodynamic data in HF management.

What characteristics should an ideal biomarker have for effective monitoring of HF patients? Firstly, it should be directly related to HF pathophysiology, such as being released in response to cardiac stress or pulmonary and/or systemic congestion. It should accurately reflect the severity and progression of HF without being influenced by other confounding factors (e.g. age and sex, diet, comorbidities, renal dysfunction), and exhibit low intrinsic variability, meaning its levels should remain relatively stable in the absence of changes in HF status. NPs, such as N-terminal pro-B-type NP (NT-proBNP), may not be ideal biomarkers in this context due to their many confounding factors and high intrinsic variability, which can be as high as 30%.[11] The ideal biomarker should be obtainable through non-invasive or minimally invasive methods, also being easy to measure using standardized, reliable, and widely available laboratory techniques. Finally, the biomarker should not be a mere outcome predictor but also serve as a tool with proven clinical usefulness. This means that there should be strong evidence supporting the biomarker's utility in guiding clinical decision-making, predicting outcomes, improving patient management and preventing HF events.

Several biomarkers beyond NPs seem promising. Soluble suppression of tumorigenesis-2 is released in response to vascular congestion and inflammatory and pro-fibrotic stimuli, with a biological variability significantly lower than that of NT-proBNP in patients with chronic HF.[12] Inflammation markers, such as galectin-3, myeloperoxidase or metalloproteinases, may reflect the adverse mechanisms of angiogenesis, fibrosis, and oxidative stress seen in HF, namely HF with preserved ejection fraction.[13] Additionally, insulin-like growth factor binding protein-7 has recently shown to predict adverse cardio-renal outcomes in HF patients, even in models adjusted for conventional biomarkers.[14]

Further research should focus on validating these biomarkers in diverse HF populations and exploring their potential in routine clinical practice. The development of risk stratification models based on serial biomarker patterns and haemodynamic data could inform the intensity and frequency of outpatient visits, allowing for more personalized and effective HF management. Additionally, the integration of remote monitoring technologies with biomarker data has the potential to transform HF care by enabling early detection of worsening HF and timely interventions. This approach could reduce the burden on healthcare systems by preventing hospitalizations and improving patient quality of life.

A biomarker-based management strategy could make follow-up of these patients much more decentralized, manageable, and economically sustainable. After a first HF hospitalization, the patient could be discharged with lifestyle recommendations to manage key modifiable cardiovascular risk factors. The patient could also be re-evaluated in an outpatient setting within a month of discharge to reassess the fluid overload status and potentially optimizing therapy. At this point, a remote monitoring plan could be established with periodic biomarker measurements at the general practitioner's office or even at home (if point-of-care methods are available), with time intervals varying based on biomarker values (*Figure 1*). The patient would be instructed on situations that warrant seeking assistance from their primary care physician or cardiologist, such as worsening signs and symptoms or an increase in the value of a specific biomarker. If the patient remains asymptomatic and the biomarkers remain stable, continued follow-up could be conducted remotely. Remote PA pressure monitoring could be reserved to patients with more advanced HF requiring a more accurate control of PA pressures.

To summarize, the BioMEMS study paves the way for an innovative approach to follow-up based on serial biomarker management. By capturing the dynamic progression of HF and providing early indications of decompensation, these approaches offer the promise of more effective and personalized therapy. This proactive approach promises not only to improve patient outcomes and quality of life, but also to create a more efficient and sustainable healthcare system for managing HF.

Conflict of interest: none declared.

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