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STUDY DESIGN

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

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Aims Heart failure (HF), a global pandemic affecting millions of individuals, calls for adequate predictive guidance for improved therapy. Congestion, a key factor in HF-related hospitalizations, further underscores the need for timely interventions. Proactive monitoring of intracardiac pressures, guided by pulmonary artery (PA) pressure, offers opportunities for efficient early-stage intervention, since haemodynamic congestion precedes clinical symptoms.

Methods The BioMEMS study, a substudy of the MONITOR-HF trial, proposes a multifaceted approach integrating blood biobank data with traditional and novel HF parameters. Two additional blood samples from 340 active participants in the MONITOR-HF trial were collected at baseline, 3-, 6-, and 12-month visits and stored for the BioMEMS biobank.

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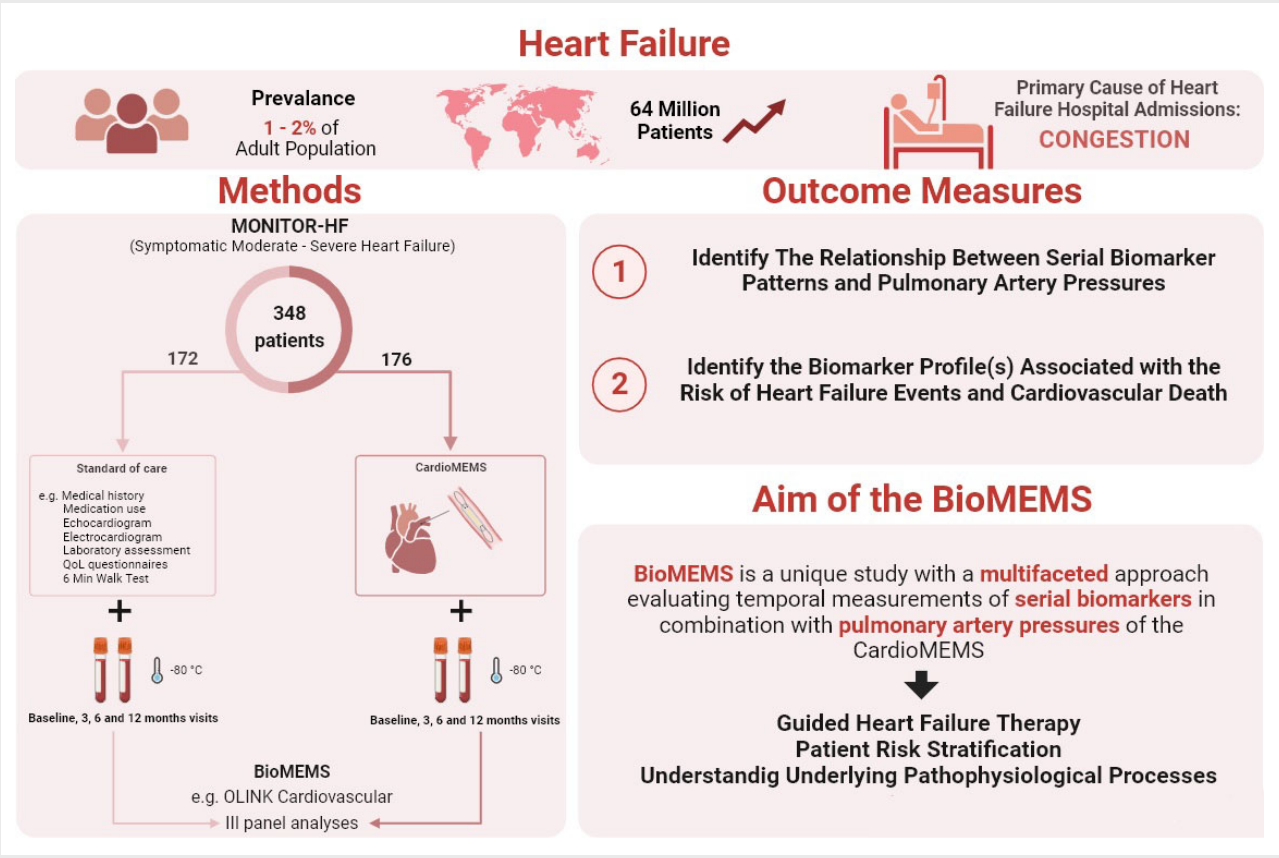
The main aims are to identify the relationship between temporal biomarker patterns and PA pressures derived from the CardioMEMS-HF system, and to identify the biomarker profile(s) associated with the risk of HF events and cardiovascular death.

Conclusion Since the prognostic value of single baseline measurements of biomarkers like N-terminal pro-B-type natriuretic peptide is limited, with the BioMEMS study we advocate a dynamic, serial approach to better capture HF progression. We will substantiate this by relating repeated biomarker measurements to PA pressures. This design rationale presents a comprehensive review on cardiac biomarkers in HF, and aims to contribute valuable insights into personalized HF therapy and patient risk assessment, advancing our ability to address the evolving nature of HF effectively.

Graphical Abstract



Design and rationale of the BioMEMS study. QoL, quality of life. Graphical abstract is created with BioRender.com

Keywords Biomarkers • Heart failure • Haemodynamic monitoring • Repeated measurements • Risk stratification • Intracardiac pressures

Introduction

Over the past few decades, heart failure (HF) has emerged as a global pandemic, affecting 64 million patients worldwide.[1,2] Considering the high number of hospital admissions and the increasing life expectancy of the global population, it is anticipated that HF will continue to pose a significant public health challenge and impose a burden on hospital resources.[2,3]

Haemodynamic congestion stands as the primary cause of hospital admissions for HF.[4,5] There is a pressing clinical need for

improved prediction of the risk of decompensation, and for appropriate parameters that enable adequate therapy guidance for HF patients. Previous attempts at guided therapy utilizing biomarkers such as N-terminal pro B-type natriuretic peptide (NT-proBNP) have encountered considerable challenges. These were partly investigated by the use of a single biomarker approach, as well as the use of absolute cut-off values instead of individual, temporal biomarker patterns. Accordingly, biomarker studies employing the right combination of biomarkers and novel techniques that study serial biomarker measurements in relation to anticipated events, have recently shown promising results.[6–8] Moreover, emerging technologies such as the CardioMEMS-HF system, which measures pulmonary artery (PA) pressures, can provide more detailed, subclinical information about the course of the HF disease processes by haemodynamic feedback.[9] Ensuing PA pressure-guided therapy can provide improved and personalized care for HF patients. Implementation of this system has shown enhanced quality of life and reduced HF-related hospitalizations.[10–12] Given that haemodynamic congestion precedes the manifestation of clinical congestion symptoms such as oedema and dyspnoea, proactive monitoring of PA pressures may serve as an efficient means of guiding therapy in HF patients, enabling timely interventions for decongestion during the early stages.[13] To the best of our knowledge, no previous studies have investigated the correlation between serial biomarker patterns and invasive PA pressures obtained from a remote PA pressure sensor. Nonetheless, several studies have previously reported correlations between increases in natriuretic peptides and haemodynamic parameters such as left ventricular filling pressures and PA wedge pressures, as determined by Doppler echocardiography or measured using Swan–Ganz catheters. Finally, NT-proBNP-guided therapy is a clinically intuitive approach to tailor therapy, but studies have not yet consistently shown an improvement in prognosis in patients with HF and reduced ejection fraction (EF).[14–19]

We hypothesize that temporal biomarker patterns associated with PA pressures can provide new, non-invasive targets for guided therapy, and can further inform us about congestive processes in HF. The utilization of congestion-related biomarkers further holds significant practical value, because it provides assessment of individual risk for deterioration of disease in a more accessible and comprehensive manner.

In this paper, we present the design and rationale of a biomarker substudy related to invasive haemodynamic monitoring, along with a relevant review on HF biomarker pathways. The rationale aims for adopting a multifaceted and dynamic approach that incorporates novel and distinct characteristics represented by multiple serial biomarkers in the management of HF. While a single baseline biomarker measurement is relatively straightforward to implement in a clinical setting, it falls short in accurately capturing the dynamic progression of HF.[6,20,21]

Moreover, we describe how these components are studied in the BioMEMS study, which serves as a substudy within the MONITOR-HF randomized clinical trial, which compares remote haemodynamic monitoring with the CardioMEMS device to standard of care. The MONITOR-HF trial includes a blood biobank comprising serial patient visits, along with traditional congestion parameters assessed through physical examination, echocardiography, and intracardiac pressures measured by the sensor during follow-up. The objective of this study is to evaluate the utility of temporal patterns derived from serial measurements of multiple biomarkers, in relation to haemodynamic PA pressures and clinical events as displayed in the *Graphical Abstract*.

Study design

Study population and design

The BioMEMS study is a biobank substudy of the MONITOR-HF trial. A detailed description of the MONITOR-HF study design has been published previously.[22] Briefly, the MONITOR-HF was an investigator-initiated, multicentre randomized clinical trial of 348 patients diagnosed with chronic HF (≥3 months), New York Heart Association (NYHA) class III, who had at least one HF hospitalization (within 12 months prior to enrolment) or urgent visit with necessity of intravenous diuretics. Patients with an HF diagnosis according to the European Society of Cardiology (ESC) HF guidelines were eligible for inclusion independent of left ventricular EF. A detailed overview of the inclusion and exclusion criteria is described elsewhere.[22] Study participants had moderate to severe HF in NYHA class III and a previous HF hospitalization with a median age of 69 years (interquartile range 61–75), median EF of 30% (23–40) and 24.4% were female. Written informed consent was obtained (including the biobank), and the study was approved by the Medical Ethical Committee (ErasmusMC, MEC 2018–1563) and registered under clinical trial registration number NTR7672.

The MONITOR-HF trial comprised a minimum follow-up period of 12 months. The follow-up visits were scheduled at 3, 6, and 12 months and every 6 months thereafter. The last patient included was followed for at least 12 months per protocol. As part of standard care, during the study, laboratory assessments were performed, which consisted of renal function and NT-proBNP. Patients with the CardioMEMS PA pressure monitor were instructed to take measurements early in the morning, after a period of rest, typically upon awakening at the start of the day. At baseline and 3-, 6-, and 12-month visits, two blood (EDTA plasma and serum) samples from each patient in the MONITOR-HF trial were collected during scheduled outpatient clinic visits, and were centrally stored for the BioMEMS biobank which was situated at the Durrer Research Institute, Amsterdam, The Netherlands (*Figure 1*). For this particular analysis using the Olink Cardiovascular III panel, all the samples were analysed by the Olink core facility of Utrecht Medical Centre, The Netherlands, together in a single batch.

Blood sample collection and storage

The trial provided a structured logistic approach and a high-quality framework for the construction of the biobank. Of the 348 patients randomized, 176 were allocated to CardioMEMS and 172 allocated to standard of care. In the group of patients randomized to CardioMEMS, 168 patients received their allocated treatment. Thus, a total of 340 patients from 25 Dutch hospitals with baseline and serial blood samples are available for the current analysis.

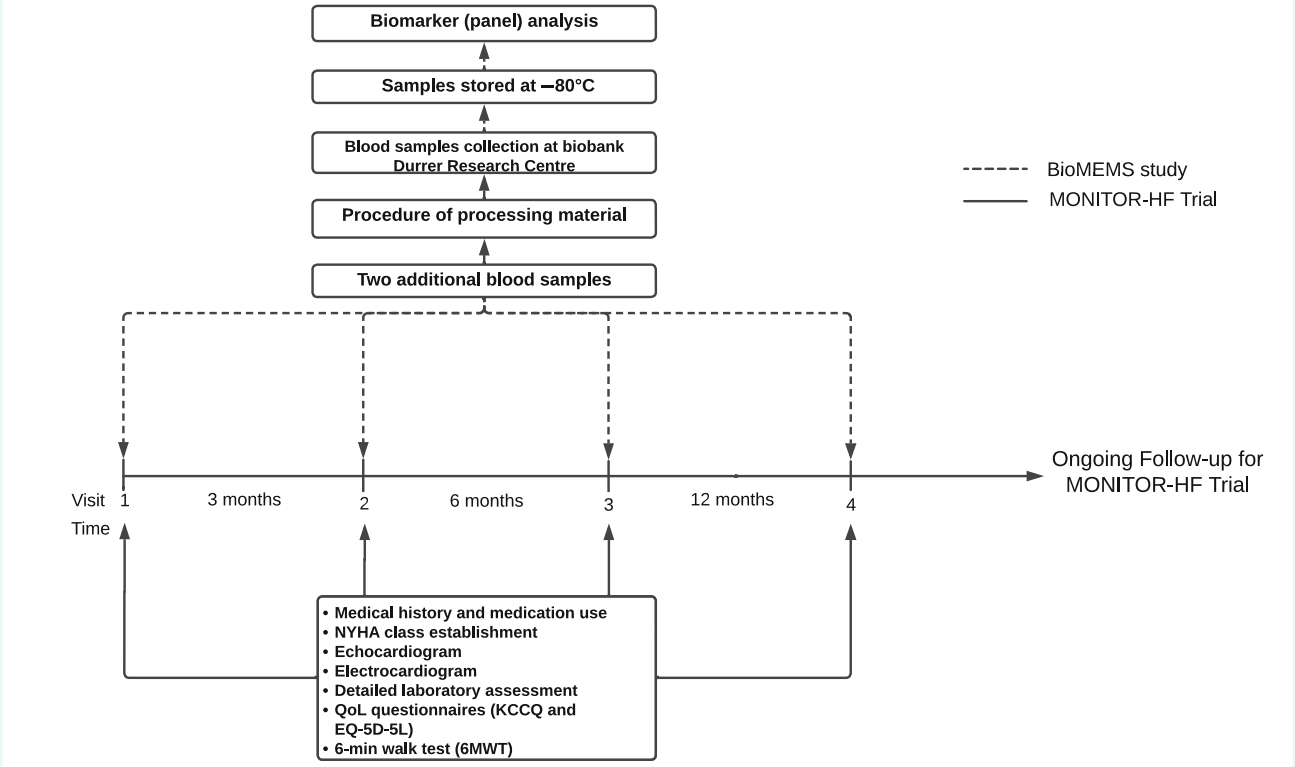


Figure 1 Flowchart of the BioMEMS study design. EQ-5D-5L, five-level EuroQol five-dimension; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; QoL, quality of life.

Blood samples from these patients were stored at the Durrer Research Centre's Biobank (Amsterdam UMC, The Netherlands) according to standardized validated protocols in −80°C freezers. In short, of each patient two samples (EDTA plasma and serum) were collected, centrifuged and subdivided into eight 1 ml vials which were subsequently frozen. The blood samples were labelled and kept for short-term storage at the local hospital at −80°C. Samples were subsequently transported under controlled conditions to Durrer Research Centre's Laboratory to be positioned, registered, and again stored at −80°C. Theoretically, a maximum of 1360 repeated patient samples will be available according to the number of included patients and visits (340 patients × 4 visits = 1360 repeated samples, of each sample we store 8 vials of 1 ml = 10 880 vials). The actual number of available patient samples after correction for missing data, quality checks and/or patients that died during follow-up will be available upon first analyses.

Quality assessment

Participating centres followed the uniform biobank protocol at all local labs for sample preparation and management, and correctly filled in the labelling forms for all samples and vials with specific bar codes for each tube stored in a local and central data file. Moreover, centres were requested to check if the registered blood samples on the collection forms matched with the information in the registration file, to ensure that each blood sample corresponds with the right study number and moment of the study visit. All datasets underwent a standardized quality assessment for completeness and inconsistencies. In case of inconsistencies, local principal investigators were contacted for re-evaluation of their data.

Aims and outcome measures

The main aims of the BioMEMS study are (i) to identify the relationship between serial biomarker patterns and PA pressures, and (ii) to identify the serial biomarker profile(s) associated with the risk of HF events and cardiovascular death.

Statistical analyses

Data will be summarized using univariable statistics (mean and, standard deviation, median with 25th–75th percentile) or frequency (number, percentage), as appropriate. For baseline characteristics, stratified data of subgroups will be compared using the chi-square or Fisher exact test for categorical variables and the Mann–Whitney U or Kruskal–Wallis test for continuous variables, as appropriate.

We will conduct a comprehensive evaluation of biomarkers in relation to haemodynamic (PA) pressures and clinical events (HF hospitalization and mortality rates), both univariably and multivariably, and considering both single measurements and serial measurements. To enable direct comparisons between

biomarkers, a z-score of the NPX biomarker values (which are provided on the log scale) will be utilized. The average mean PA pressure during the week preceding blood sample collection will be considered as the (trend) measurement of PA pressure at the time of blood sample collection, and will be used as the clinical endpoint. Regarding lag time, additional sensitivity analyses will be performed for the average PA measurement over 3 and 14 days prior to blood sample collection.

We will examine the associations between serially measured biomarker levels and serially measured PA pressures in MONITOR-HF patients who have received a PA pressure sensor implant by using univariable and multivariable linear mixed-effects (LME) models. These models aim to uncover the connections between changes in biomarker profiles and the evolving temporal patterns of PA pressures. Utilizing LME allows us to incorporate random slopes and intercepts, which are essential when dealing with longitudinal data. To identify the multivariable subset of biomarkers that is most informative for PA pressure, we will use penalized LME models in which the 92 repeatedly measured biomarkers, entered together, will serve as the independent variables. The dependent variables will consist of haemodynamic measurements, consecutively including mean PA pressures, systolic PA pressures, diastolic PA pressures, and heart rate. Models will be corrected for multiple testing, when appropriate.

We will examine the relationships between serial biomarker levels and clinical events in the complete study population of MONITOR-HF using joint modelling, which combines linear mixed models for the temporal biomarker patterns, with relative risk models for the time-to-event analysis. These models will account for covariates like age and sex. We will use the framework of joint models for longitudinal and survival data. In these joint models, a LME (longitudinal) model provides estimates of the individual temporal trajectories of the biomarkers. These estimated trajectories will be combined with a relative risk model, to study their association with the risk of the study primary endpoint. However, it is important to note that missing measurements of PA pressure or biomarker levels will not be imputed in our analysis. We refrain from imputing data on our main endpoints due to concerns about maintaining the integrity of our results, particularly as the missingness pattern may be influenced by unobserved variables, rendering it inappropriate for multiple imputation methods according to Rubin's rules.

To identify the multivariable subset of biomarkers that offers the most valuable information for predicting the endpoint, we will employ a penalized model. To achieve this, we will use a time-dependent Cox regression in combination with a penalized approach.[23,24] All analyses will be performed using IBM SPSS Statistics, version 25.0 (IBM Corp., Armonk, NY, USA) and R Statistical Software.

Established heart failure biomarkers

Numerous novel and established biomarkers have lately been described to carry prognostic value in the course of HF disease, and research in the area of HF biomarkers has received extensive attention and obtained promising results in the past two decades.[25–27] A recent review summarized the current evidence on the association of several promising and established primary targets of biomarkers to HF hospitalization and mortality, with regard to prognosis, risk stratification, and haemodynamics. Additionally, the authors emphasized several pathological pathways that contribute to our in-depth understanding of HF disease.[26] Another review of Núñez *et al.*[27] provided an overview of circulating biomarkers of congestion with clear potential in prognostication and risk stratification of HF. The most well-known and widely used biomarkers in HF are the natriuretic peptides, which are released in response to volume or pressure overload, as commonly seen in patients with HF. Therefore, natriuretic peptide such as (NT-pro)BNP constitute a crucial component of biomarker research for HF prognostication and risk stratification. Also, several new and relatively unexplored biomarkers such as growth differentiation factor-15 and galectin (Gal)-3 are of interest to investigate their association with fluid status. For instance, Gal-3, a component of the Olink Cardiovascular III panel, has demonstrated increased relevance in the development of HF. When released by macrophages and other inflammatory cells, Gal-3 triggers the release of additional inflammatory cytokines and growth factors. This cascade of events eventually leads to alterations in the cellular and molecular components of the heart, a crucial and recognized process termed myocardial remodelling.[26] The list of candidate biomarkers ensures a comprehensive coverage of biomarkers to identify the relation between serial biomarker patterns, fluid status and haemodynamics, consequently this will enhance our understanding of the fundamental processes underlying HF. In this study, the Olink Cardiovascular III panel will serve as the initial exploratory biomarker panel evaluated in our study population, allowing us to identify potential associations.

Olink Target 96 Cardiovascular III panel

The patient samples will be utilized to first conduct the Cardiovascular Target 96 Panel III, Olink Proteomics AB, Uppsala, Sweden (92 cardiovascular disease-related human protein biomarkers) (online supplementary *Table S1*). These 92 high abundance proteins were selected for the Olink panel, because they had been shown to play a pathophysiological role in cardiovascular disease or because they had shown promise in this area but had not yet been fully studied in this setting. The Olink panel is the first biomarker panel selected for the BioMEMS study and provides biomarkers that offer a broad selection of proteins associated with biological functions linked to the underlying causes of cardiovascular diseases, including HF.[27,28] The Olink panel assay is based on proximity extension assay technology, wherein the specific biomarker protein target is bound by a matching pair of antibodies that have been coupled to unique oligonucleotides.[29] The blood samples were distributed over a 96-well PCR plate and randomized in accordance with the sample preparation protocol of Olink. Eventually, a PCR reporter sequence is generated through a proximity-dependent DNA polymerization process. After amplification, the biomarker sequence can be quantified by using high throughput real-time qPCR. All of the analysed samples will be subjected to both internal and external controls, which were specifically designed by Olink for the purpose of data normalization and quality control. These controls serve

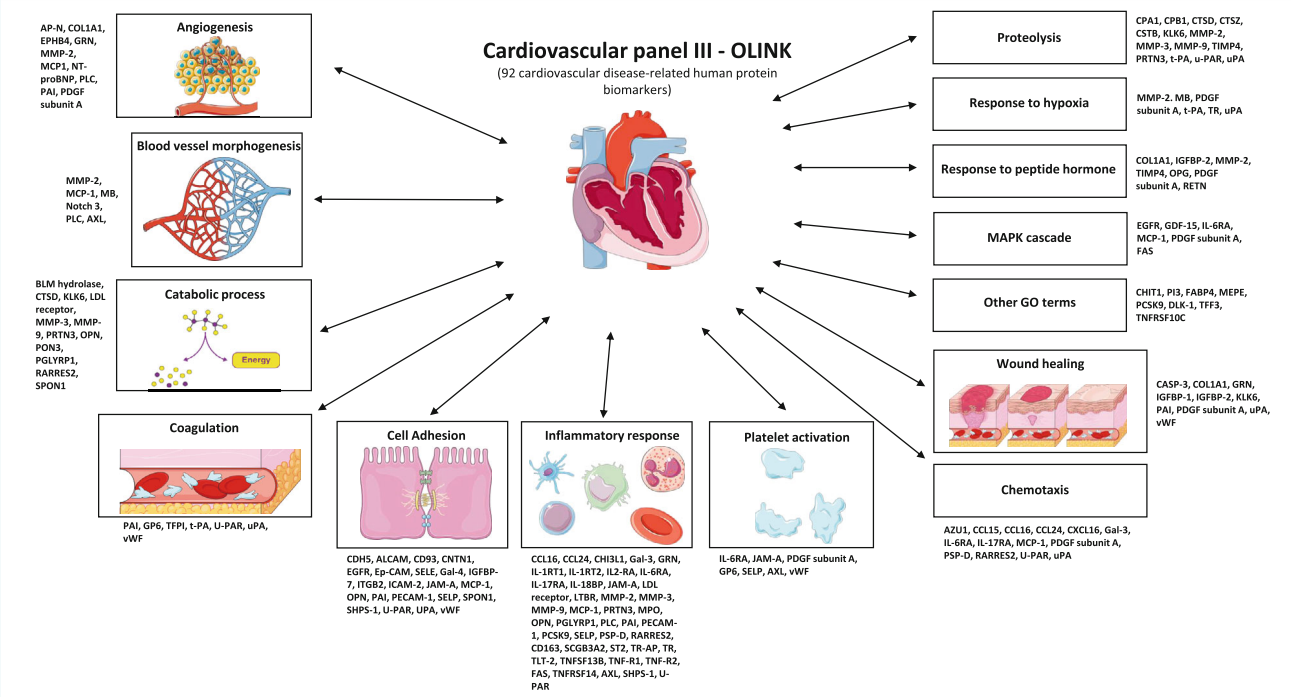


Figure 2 Classification of biomarker proteins included in the Olink Cardiovascular III panel based on biological process. Parts of the figure were created using pictures from Servier Medical Art licensed under a Creative Commons Attribution 3.0 unported license.

the dual function of allowing the monitoring of technical assay performance and assessing the quality of individual samples.[30] In this study, samples in which one or more of the internal control values fall outside a predefined range (>0.3 or <−0.3) will be flagged and excluded from the statistical analysis. Furthermore, each plate incorporates an external inter-plate control, which enhances the precision between assays and enables effective comparison of data obtained from multiple runs. As a result, Olink data will be presented in the form of normalized protein expression (NPX) values, using Olink Proteomics' arbitrary unit on a log2 scale, where a greater value indicates an increased protein level in the sample.

The Olink Cardiovascular III panel features a variety of novel biomarkers that could offer valuable insights into the pathobiological pathways affected by HF. The pathophysiology of HF is closely connected to several established biological processes such as neurohormonal activation, myocardial necrosis, myocardial remodelling, and inflammation. A graphical classification of protein biomarker included in the Cardiovascular III panel based on biological process is provided in *Figure 2*. These biomarkers may offer thorough insights into the complex interactions within these important pathways.

The importance of temporal patterns of biomarker levels

Numerous biomarker studies have explored the association between baseline biomarker levels and clinical events or disease progression. However, these baseline measurements are typically obtained during stable periods of the disease state. Limited longitudinal data are currently available for patients who have undergone multiple biomarker assessments throughout the course of their HF progression and their response to therapy. Moreover, to the best of our knowledge, no studies exist that relate repeatedly measured biomarkers to repeatedly measured intracardiac pressures. The duration of data collection is often relatively short, resulting in limited and underpowered descriptions of the serial, temporal dynamics of potential biomarkers during the transition from early stages to advanced HF. We believe that repeated measurements of biomarkers carry potential to provide more comprehensive diagnostic and prognostic information throughout the progression of HF and could be valuable in guided therapy. Notably, biomarker values that exhibit improvement during medical interventions have shown promise in predicting a more favourable prognosis.[6,20,21,31] Therefore, we highlight the significance of serial biomarker measurements, which offers longitudinal insights to guide HF therapy effectively. In the BioMEMS study, we correlate the biomarker levels as measured in the available samples at baseline, 3, 6, and 12 months with PA pressures and clinical events during this 12-month period in which biomarker data are available.

Discussion

Heart failure admissions represent a significant concern, occur frequently, and one of the main determinants is congestion.[32,33] Therefore, early surveillance of symptoms and fluid status is crucial for effective monitoring and management of HF. However, it is

important to recognize that subclinical haemodynamic congestion precedes the clinical manifestation of congestion. Considering this, haemodynamic data can provide valuable insights into the progression of HF. Among the available devices, the CardioMEMS sensor emerges as a promising tool for remote monitoring of haemodynamics, specifically PA pressures, in patients with chronic HF.[11] This device is both safe and reliable, offering diagnostic capabilities that enable proactive treatment interventions at the appropriate time, ultimately preventing HF hospitalizations driven by congestion.[10,11,22] To assess the relation between intracardiac pressures (haemodynamics) and serial biomarker levels, we propose the BioMEMS study as a novel and unique approach to link the haemodynamic sensor data with serial biomarker levels. This study will not only enhance our understanding of worsening HF, but it will also explore the relationship with traditional parameters obtained through physical examinations and echocardiograms during regular trial visits where biomarkers could have a practical role. We advocate for using the diagnostic information provided by these sensors to further refine the prognostic value of serial biomarkers to obtain a further in-depth understanding of worsening HF. This unique opportunity within the MONITOR-HF trial allows for the integration of multiple biomarker and haemodynamic information, paving the way for comprehensive insights into HF management.

According to the most recent ESC guidelines for the diagnosis and treatment of acute and chronic HF, patients with HF still need to be monitored even if their symptoms are under control and stable in order to continue optimizing their therapy and catch asymptomatic progression of the condition.[34] However, because the results of studies evaluating the potential of biomarkers in the direction of HF therapy were inconsistent, the use of biomarkers (such as NT-proBNP) to guide therapy for HF patients has not yet been included in the guidelines. However, traditional indicators such as weight or blood pressure are inadequate for accurately monitoring fluid status. Reliance on these simple indicators alone can lead to delayed recognition of decompensation, resulting in less effective therapy and a higher likelihood of hospitalization.[35–38] (Invasive) devices are promising because interpretation of their results is straightforward and, intuitive, and they are easy to use. PA pressures are being provided to physicians to assist them to understand and monitor the success of HF treatment. In order to recognize the early signs of (a)symptomatic congestion in HF patients, the BioMEMS study combines the integration of intracardiac pressures, serial circulating biomarkers, remote monitoring of symptoms and indicators, and echocardiography to intervene early in the course of HF. We believe that the haemodynamic data provided by remote sensors can further improve and enrich current biomarker models. Additionally, these data will help discover new relevant biomarker pathways, especially related to (pre-clinical) congestion that could possibly be used to guide treatment in HF patients in the future. Elevations in biomarkers detected during episodes of acute decompensation are linked to a higher risk of adverse clinical outcomes, such as HF hospitalization.[26,39] Hence, it would be beneficial to regularly assess biomarkers associated with elevated PA pressures to closely monitor HF patients. This approach offers an alternative risk stratification method for impeding worsening HF based upon the biomarker level variation, which can aid in reducing HF-related morbidity effectively. Considering the associated costs, it is unlikely that invasive remote sensors can be used to monitor all HF patients. These sensors will likely be targeted towards the higher-risk group of moderate to severe HF patients in more advanced stages of the disease at high risk of HF admissions. However, there is a pressing need for an easy accessible biomarker model that can facilitate monitoring and counselling for the overall stable HF population. For example, performing blood tests in the patients' own environment and sending the samples to the hospital can potentially reduce the burden on hospitals and the resources required for check-ups. In this context, linking blood biomarkers to PA pressure measurements can contribute to the development of a risk stratification model that detects pre-clinical haemodynamic congestion in HF patients. Thereby, distinguishing between low- and high-risk patients for decompensation and informing the clinician about the appropriate intensity of outpatient visits.

Limitations

Although the BioMEMS study benefits from a detailed, unique data collection, in a well-phenotyped cohort of patients, it is important to acknowledge its limitations. Firstly, haemodynamic changes may be attributed to factors beyond HF where we lack detailed clinical information. However, we expect that external influences will be limited and comparable between patients, and more importantly we seek for direct numerical associations between a biomarker level and a mean PA pressure trend. Sample collection occurred uniformly during regularly scheduled outpatient clinic visits for all patients. Secondly, we cannot consider serial echo measurements to track gradual changes in EF due to the absence of these data during the 3- and 6-month follow-up periods. We expect that an improvement in EF will likely coincide with a change in the biomarker or mean PA pressure that is already reflected in the numerical association. We do have serial echo measurements available at the 12-month follow-up visit which could be used to correct for any EF changes, if applicable. Another limitation is that Olink's proteomic assay does not offer standard concentration units, which complicates comparisons with clinically applied cut-off values. Moreover, the Olink panel primarily focuses on biomarkers associated with cardiovascular disease. This cannot rule out the presence of other clinically relevant biomarkers excluded from this panel, which can be part of biomarker panels assessed in future analyses. Finally, our study involves symptomatic patients with moderate to severe HF, this may impact the generalizability of our findings to other HF phenotypes.

Future perspectives and potential avenues for future research

The main goals of HF management are to maintain euvolaemia and detect symptoms of worsening HF as early as possible. Physicians may monitor HF patient health and disease progression outside of the clinical setting with the use of biomarkers. Clinical monitoring of biomarkers that are directly associated with fluid balance and intracardiac filling pressures such as natriuretic peptides is anticipated to be beneficial for predicting HF risk and

therapy response in HF patients. This approach offers an alternative risk stratification method for impeding worsening HF based upon the biomarker level variation. Therefore, discovering a potential biomarker capable of predicting or correlating with changes in PA pressures could be an effective surrogate and alternative management strategy for HF patients with an unique opportunity to learn from the BioMEMS data correlations between haemodynamics and biomarker levels. Especially considering the costs associated with invasive sensors, this tool may not be feasible for all HF patients in all countries. Biomarkers, if easily accessible and at a lower cost, could serve as an alternative for patients who are not eligible or lack the access to invasive remote monitoring strategies. This also allows for tailored decision-making regarding follow-up (timing, frequency, and intensity) to each individual patient. Optimizing the use of biomarkers could identify high-risk patients with poor prognosis, allowing for focused intervention to patient needs. These data might also provide a more comprehensive understanding of the worsening HF condition and gain deeper insights into its underlying dynamic pathological processes.

Conclusion

Accurately assessing congestion remains a challenge in the management of HF. However, with the advancement of continuous and consistent monitoring of HF patients, including their fluid status and biomarker levels, clinicians nowadays have the ability to identify early signs of HF decompensation. The cardiac biomarkers mentioned in this paper hold potential for monitoring early signs of congestion or worsening HF which can improve risk stratification of HF patients, albeit that the results should be interpreted in light of the included study population of MONITOR-HF with strict inclusion and exclusion criteria. Nevertheless, incorporating temporal patterns of biomarkers into research can enrich our understanding of prognosis and risk stratification in HF. This is now enhanced by using the haemodynamic data provided by the PA pressure sensor and linkage of serial biomarker patterns to the ensuing data which represent pre-clinical signs of congestion. Furthermore, the ongoing development of haemodynamic remote sensors should be used to deepen our understanding of the dynamic pathophysiological processes in (worsening) HF and maximally utilize the diagnostic information provided by biomarkers. The identification of significant biomarker profiles associated with pre-clinical congestion and intracardiac pressures can be the next step in the prospective evaluation of biomarker-guided therapy in HF, as well as new trials on this topic.

Supplementary Information

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

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