CHAPTER 1

Introduction and Aims

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Heart failure is one of the great global public health crises of the 21st century. One in every five men or women will develop heart failure during their lifetime (1). Unfortunately, the survival rates of heart failure patients are poor and 50% of patients die within five years after the diagnosis of heart failure is established (2). Diagnosis of heart failure is based on the presence of specific symptoms of heart failure, such as shortness of breath on exertion or in rest and fatigue, as well as signs including pulmonary rales, elevated jugular pressure and ankle edema. In addition, positive diagnosis requires patients to have functional and/or structural abnormalities of the heart, which results in a reduced cardiac output (3).

Two types of heart failure can be distinguished: acute heart failure and chronic heart failure. Acute heart failure patients are characterized by the acute onset of severe signs and symptoms of heart failure requiring immediate treatment. In contrast, chronic heart failure patients have signs and symptoms which slowly develop over time and gradually become worse (3). Heart failure is often subdivided according to the left ventricular ejection fraction (LVEF); heart failure with a reduced ejection fraction (HFrEF; LVEF <40%); heart failure with a mid-range ejection fraction (HFmrEF; LVEF 40-49%); and heart failure with a preserved ejection fraction (HFpEF, LVEF ≥50%). Over the years, several novel treatment modalities, including angiotensin converting enzyme inhibitors (ACE-inhibitors), beta-blockers and mineralocorticoid receptor antagonists (MRA), have greatly improved patient outcomes for heart failure with HFrEF (2, 3). Unfortunately, these treatment options have not proven effective in patients with HFpEF (4–7).

The heart failure syndrome is highly heterogenous. We currently recognize a plethora of etiologies underlying heart failure including ischemic heart disease, valvular heart disease, hypertensive heart disease as well as dilates and hypertrophic cardiomyopathies, characterized by a distinct geographic distribution (Figure 1). These different etiologies of heart failure all share a final common presentation, which includes a reduced cardiac output and increased filling pressures (3, 8). While treatment of patients with HFpEF has not proven effective, there currently is a one-size-fits all approach in the treatment of HFrEF with ACE-inhibitors, beta-blockers and mineralocorticoid receptor antagonists (3). This has proven problematic as it has become increasingly clear that even between patients with HFrEF there is considerable heterogeneity in response to guideline-directed treatment. An important example is the recent finding that patients with both HFrEF and atrial fibrillation might not derive a treatment benefit from beta-blockers (9). This suggests that a more comprehensive classification of patients with HFrEF is needed to tailor treatment to the individual patient.

Patients with HFmrEF have recently been recognized as a novel subgroup of heart failure patients. It remains unclear whether these patients can benefit from current guideline treatment recommendations including ACE-inhibitors, beta-blockers and MRAs (3, 10). Recent evidence has suggested that the etiology of HFmrEF is closer to HFrEF (11, 12). Additionally, several post-hoc analyses of important clinical trials including the CHARM program have suggested that patients with HFm-
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rEF might benefit from RAAS-inhibition (13). Nevertheless, the pathophysiological background of HFmrEF remains unclear. Furthermore, additional more advanced clinical tools are needed to distinguish patients with HFmrEF who might benefit from guideline directed treatment.

Current guideline treatment recommendations for patients with HFrEF have not proven effective in patients with HFpEF (2, 4–7). Patients with HFpEF constitute approximately 50% of all patients with heart failure and, despite having better outcomes than patients with HFrEF, they are still subject to dismal outcomes (14). Treatment options for these patients remain one of the greatest unmet needs in heart failure. Patients with HFpEF are usually elderly, female, and have high rates of comorbidities such as hypertension, diabetes mellitus, obesity and atrial fibrillation (16). Unfortunately, the underlying pathophysiology of patients with HFpEF remains poorly understood. The dominant present-day paradigm suggests that multimorbidity causes a pro-inflammatory state, which in turn causes stiffening of the heart muscle, thereby increasing filling pressures and reducing cardiac output (17). Nevertheless, the HFpEF syndrome in itself is considered to be highly heterogenous (18). It remains unclear what specific disease mechanisms play a role in the pathophysiology of HFpEF. A more personalized medicine approach is needed to target specific subtypes of HFpEF with their respective disease mechanisms.

BIOMARKERS IN HEART FAILURE

The International Programme on Chemical Safety, led by the World Health Organization (WHO), together with the United Nations and the International Labor Organization, has defined a biomarker as “any substance, structure, or process that can be measured in the body or its products and influence or predict the...
incidence of outcome or disease” (19). The National Institutes of Health Biomarkers Definitions Working Group defines a biomarker 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.” (20). Within cardiovascular research, biomarkers are generally considered to be blood circulating biomarkers (21). These could be either proteins, microRNAs or even genetic markers (22, 23).

Biomarkers have several clinical and empirical applications. An important clinical application is diagnosis: a biomarker can be used to identify patients with a certain disease. Within heart failure, particularly B-type natriuretic peptide (BNP) and its N-terminal form N-terminal pro-BNP (NT-proBNP) are of key importance for diagnosis. BNP and NT-proBNP have been widely used in clinical practice to identify patients with heart failure among patients with (acute) shortness of breath who present at an out-patient clinic or the emergency department (24).

Another important function of biomarkers is monitoring treatment response. Here, biomarkers can be used to assess the effectiveness of treatment. An important example of this is the usage of HbA1C in diabetes mellitus treatment. In heart failure research, BNP and NT-proBNP are used as an alternative study endpoints to monitor treatment with a novel drug (25). This is of particular importance in early stages of drug development, where pharmacodynamic biomarkers can be used to assess a pharmacological response in dose-finding studies. Unfortunately, trials using BNP and/or NT-proBNP as a guide for therapy, have come out neutral. This suggests that using NT-proBNP for guiding treatment decisions might not be the way forward (26). Results from the CHAMPION trials, which compared the use of an implantable wireless pulmonary artery hemodynamic monitoring system as a guide for treatment to standard of care, greatly reduced hospitalizations for HF (27).

One of the most well studied applications of biomarkers is that of outcome prediction. Here, biomarkers are used to predict future adverse disease outcomes such as death or unplanned hospitalizations. Within heart failure, blood urea nitrogen (BUN) and sodium are the strongest predictors of outcome (28). While a great number of studies have been performed in search of novel predictive biomarkers that might have additional predictive value on top of BNP/NT-proBNP, few have succeeded (29). Potential novel biomarkers with clinical utility include: ST2, a remodeling and inflammation marker, and growth-differentiation factor 15 (GDF-15), which is involved in coronary inflammation and arteriosclerosis (30, 31). Additionally, several studies have employed multi-marker-based approaches to improve outcome prediction. Here, investigators have used multiple biomarkers from different pathophysiological domains (e.g. inflammation, cardiac stretch) to improve outcome prediction (32). While interesting from an empirical perspective, the results of these studies have been disappointing. This suggests that the usage of single biomarkers for predicting outcome in HF as a whole is limited to NT-proBNP, urea and sodium (28).

The last and also more novel application is the usage of biomarkers for disease characterization. Biomarkers can be used to identify possible pathophysiological processes associated with a disease or syndrome. An early example of this is a study in chronic heart failure patients that investigated a large panel biomarker in patients with HFrEF and HFrEF. The authors found that levels of renal damage markers were relatively higher in patients with HFrEF compared to patients with
HFrEF (33). Other studies have shown that biomarkers can be used to identify mutually exclusive subgroups of patients: an early study published in 2002 identified mutually exclusive subgroups of ovary cancer patients based on proteomic signatures (34). This particular subfield of biomarker application might lead to a more personalized approach in treatment of heart failure.

**Biomarkers in personalized and precision medicine**

The concept of personalized medicine is relatively novel and is often considered the next frontier in human medicine. The overall goal of the personalized medicine approach is to provide better tailored treatment options to individual patients in accordance with their individualized disease profile. The individualization of a disease profile comes from drawing on information on the collective burden of an individual’s genetic background, biomarker profile, relevant clinical characteristics such as sex, age, and past as well as present comorbidities (Figure 2). Within personalized medicine, the concept of precision medicine is of particular importance. The term precision medicine refers to using computational network knowledge that summarizes information from (heart failure) patients, healthy individuals, and experimental systems to identify key disease mechanisms which can lead to therapies that more precisely target pathophysiological mechanisms in heart failure (35).

Recently, the American Heart Association (AHA) created a precision medicine platform for cardiovascular research. This research platform was accompanied by a guideline for opportunities in precision medicine in cardiovascular research (36). Within heart failure, some early adoption studies used multi-marker scores to identify patients with heart failure at risk for adverse outcomes such as mortality or an unplanned hospitalization for heart failure (32, 37). In addition, risk calculators have been developed to identify individuals with heart failure who are at risk for adverse cardiac remodeling (38). While relatively successful, these early studies are still far from clinical application.

**Aims and outline of this thesis**

Heart failure is a heterogeneous syndrome and the empirical literature indicates that a one-size-fits-all approach is ineffective. While previous early adoption studies have helped to tailor treatment to the needs of patients, more comprehensive approaches are needed. Therefore, the main aims of this thesis are as follows:

1) To use biomarker profiles to better understand pathophysiological differences between patients with HFrEF and HFpEF;

2) To distinguish clinically relevant subgroups using biomarkers as a first step in a personalized medicine approach.

To address these aims we used a novel approach to identify differences between HFrEF and HFpEF based on precision medicine. Subsequently we identify clinically relevant subgroups of heart failure patients using a personalized medicine approach (Figure 2).

In Chapter 2 we investigate syndecan-1 in chronic heart failure. Syndecan-1 is a fibrosis marker, which is associated with cardiac remodeling and inflammation following myocardial injury (39–41). This suggests that syndecan-1 may be able to differentiate between patients with HFrEF and HFpEF.
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In this chapter, we focus in specific on the differential association of syndecan-1 with outcomes in HFrEF and HFpEF. Furthermore, we investigate the association of syndecan-1 with other markers relevant to heart failure pathophysiology, to establish a possible rationale for the differential association of syndecan-1 with outcomes between HFrEF and HFpEF.

Next, we investigate differences in biomarker profiles between chronic patients with HFrEF and HFpEF in Chapter 3. Here, we study differences in levels of biomarkers as well as differences in predictive power of biomarkers between patients with HFrEF and HFpEF. In doing so we use network analysis, a novel precision medicine-based approach, to investigate differences in biomarker profiles between HFrEF and HFpEF.

In Chapter 4 we study biomarker profiles in acute heart failure patients. Here, we will specifically investigate the biomarker profiles of patients with HFmrEF. It is unclear whether patients with
HFmrEF are closer to patients with HFrEF or HFpEF and thus might benefit from guideline directed therapy. This chapter will study whether patients with HFmrEF are closer to patients with HFrEF or HFpEF.

While the usage of network analysis in Chapters 3 and 4 represents the first step towards an improved practice of precision medicine, techniques that are more sophisticated are needed. Therefore, we will identify key differences in biomarker profiles and biological mechanisms between patients with HFrEF and HFpEF in a large multi-centre European cohort of patients with worsening heart failure in Chapter 5. The results of this study are validated in a large contemporary validation cohort. In this chapter we move beyond conventional techniques and examine possible differences in disease mechanics between patients with HFrEF and HFpEF.

In Chapter 6 we use a personalized medicine based approach to identify mutually exclusive endotypes of heart failure patients based on their biomarker profiles. We will investigate differences in outcomes and clinical characteristics between endotypes. Also, we study the association between up titration of ACE-inhibitors and beta-blockers as well as the treatment benefit of these critical medications across endotypes.

In Chapter 7, we will discuss the possible implications of a personalized medicine approach in predicting heart failure and point to possible ways forward in improving heart failure prediction based on personalized medicine approaches.

Finally, we discuss the main findings and conclusions of this thesis, as well as possible steps for future research, in Chapter 8.
REFERENCES

CHAPTER 2
The fibrosis marker syndecan-1 and outcome in heart failure patients with reduced and preserved ejection fraction

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