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Novel Aspects of Heart Failure Biomarkers

Focus on Inflammation, Obesity and Sex Differences

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the decision by the College of Deans.

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TABLE OF CONTENTS

	Introduction and Aims	9
Chapter 1	From Inflammation to Fibrosis – Molecular and Cellular Mechanisms of Myocardial Tissue Remodelling and Perspectives on Differential Treatment Opportunities. <i>Curr Heart Fail Rep.</i> (2017)	17
Chapter 2	Galectin-3 Activation and Inhibition in Heart Failure and Cardiovascular Disease: An Update. <i>Theranostics.</i> (2018)	47
Chapter 3	Heart Failure and Inflammation-related Biomarkers as Predictors of New-onset Diabetes in the General Population. <i>Int J Cardiol.</i> (2018)	81
Chapter 4	Relationship between Body-mass Index, Cardiovascular Biomarkers and Incident Heart Failure. <i>Submitted</i>	103
Chapter 5	Sex-specific Associations of Obesity and NT-proBNP levels in the General Population. <i>Eur J Heart Fail.</i> (2018)	119
Chapter 6	Sex-related differences in contemporary biomarkers for heart failure: a review. <i>Eur J Heart Fail.</i> (2020)	145
Chapter 7	High-sensitivity Troponin-T and Cardiovascular Outcomes in the General Population: Differences between Men and Women. <i>Mayo Clin Proc.</i> (2020)	177
Chapter 8	Sex-specific Associations of Cardiovascular Risk Factors and Biomarkers with Incident Heart Failure. <i>J Am Coll Cardiol.</i> (2020)	199
Chapter 9	Being in two minds – the challenge of HFpEF diagnosis with a single biomarker. <i>Clin Chem.</i> (2020) <i>Accepted</i>	227
	General Discussion and Future Perspectives	237

Appendices

Dutch Summary Nederlandse Samenvatting	245
Acknowledgements	251
List of Academic Degrees and Selected Publications	254

INTRODUCTION AND AIMS

Novel Aspects of Heart Failure Biomarkers

Heart Failure (HF) is a clinical syndrome resulting from structural or functional abnormality of the heart, along with disruption of cardiovascular homeostatic mechanisms. Based on left ventricular ejection fraction (LVEF), HF is broadly classified into two distinct disorders: HF with reduced ejection fraction (HFrEF, LVEF <40%) and HF with preserved ejection fraction (HFpEF, LVEF >50%).^{1,2} HF with mid-range ejection fraction (HFmrEF or simply HFmEF) is an intermediate clinical profile between HFrEF and HFpEF.³⁻⁵ Although at present, the LVEF construct remains the cornerstone of classification of HF patients, a contemporary view calls for a continuous HF spectrum that moves beyond an LVEF-based classification.^{6,7}

HF patients usually present with symptoms of dyspnoea, fatigue or reduced exercise tolerance and exhibit signs such as elevated jugular venous pressure, S3 gallop, laterally displaced left ventricular impulse, pulsus alternans, hepatojugular reflux, ankle oedema, pulmonary congestion, ascites and muscle wasting.⁸ HF is estimated to affect at least 25-30 million individuals worldwide.^{9,10} Latest data from the United States indicate that HF prevalence continues to rise over time: around 6.2 million Americans ≥20 years of age had HF between 2013 and 2016, compared with an estimated 5.7 million between 2009 and 2012.¹¹ Similar trends were also reported in a UK-based population study enrolling more than 4 million individuals: the estimated absolute number of prevalent HF cases increased by 23% (from 750,127 to 920,616) between 2002 and 2014.¹²

With the increasing number of people diagnosed with HF, and a 5-year survival lower than most cancers,¹³⁻¹⁵ HF *will* become the most important public health concern worldwide.¹⁶ HF severely affects the quality of life and contributes to approximately 30% of all disability cases.^{14,17} It is also an expensive disorder: according to data from 197 countries, the overall cost of HF in 2012 was estimated at \$108 billion per annum.¹⁸ The economic burden imposed by HF on health care services is predicted to increase severalfold,¹⁹ and will mirror the increase in HF prevalence rates.

The American College of Cardiology/American Heart Association (ACC/AHA) classify HF into four stages (A, B, C and D)² which are listed below. Unlike the New York Heart Association (NYHA) functional classification, progression from a lower HF stage to a higher HF stage is unilateral i.e., once HF has progressed to stage C, it cannot regress back to stages B or A. In this context, an ounce of prevention is worth a pound of cure, and it is of crucial importance that healthcare professionals are able to identify patients in Stage A of HF, and initiate necessary and effective preventative strategies so as to prolong progression to higher stages.

- **Stage A:** Patients at risk for HF who have not yet developed structural cardiac changes i.e. those with diabetes mellitus or those with coronary artery disease without prior myocardial infarction.
- **Stage B:** Patients with structural heart disease (i.e. reduced LVEF, left ventricular hypertrophy, chamber enlargement) who have not yet developed symptoms of HF.
- **Stage C:** Patients who have developed clinical HF
- **Stage D:** Patients with refractory HF requiring advanced intervention (i.e. biventricular pacemakers, left ventricular assist device, cardiac transplantation)

Major cardiovascular risk factors and conditions leading to HF, as well as comorbidities frequently accompanying HF are summarized in **Figure 1**. Due to dramatic changes in global food consumption patterns, and an increasing number of individuals adopting a sedentary lifestyle, HF developing secondary to metabolic disorders such as type-2 diabetes mellitus and obesity²⁰ has become increasingly relevant.

Figure 1. Heart failure risk factors and precursors. Abbreviations: COPD, chronic obstructive pulmonary disease; OSAS, obstructive sleep apnoea syndrome.

HEART FAILURE BIOMARKERS

HF biomarkers are usually circulating proteins that are relatively inexpensive to measure, and are used in routine clinical care to predict HF risk, diagnose HF, and to prognosticate outcomes in HF patients.^{21,22} They also provide objective information on cardiac and systemic pathophysiological processes associated with HF and cardiovascular disease.²³ For instance, natriuretic peptides reflect cardiac stretch, cardiac troponins indicate myocardial injury, C-reactive protein (CRP) reflects systemic inflammation, and galectin-3 indicates ongoing tissue fibrosis. An overview of major HF biomarkers, and the pathophysiological processes represented by them is provided in **Figure 2**.

AIMS AND OUTLINE OF THIS THESIS

- To highlight that inflammation and fibrosis are key pathophysiological mechanisms operating in HF, and may be amenable to therapy.
- To use biomarkers to identify pathophysiological mechanisms linking type-2 diabetes mellitus and obesity with HF.
- To understand the overlapping effects of obesity and sex on HF biomarker levels, and to investigate the extent to which obesity and sex affect the interpretation of these biomarkers in HF risk prediction.

In **Chapter 1** of this *Thesis*, we provide a detailed overview of major molecular and cellular mechanisms contributing to cardiac inflammation and fibrosis, and how uncontrolled activation of the fibro-inflammatory axis leads to adverse myocardial tissue remodelling. We also discuss potential therapeutic options including selective modulation of myocardial fibro-inflammatory activation. In **Chapter 2**, we focussed on the fibrosis biomarker Galectin-3, and describe in detail how this molecule has emerged as a potentially attractive biotarget for treating HF. We discuss novel aspects of galectin-3 binding which may facilitate the development of targeted anti-galectin-3 therapeutics.

Recent trends suggest that type-2 DM and obesity have become common HF-related comorbidities.²⁰ Therefore, in **Chapter 3**, we studied pathophysiological mechanisms linking HF to type-2 DM by evaluating associations of multiple HF-related biomarkers with incident DM using data from the Prevention of Renal and Vascular End-stage Disease (PREVEND) cohort.

Figure 2. ANP indicates atrial natriuretic peptide; APO, apolipoprotein; BNP, B-type natriuretic peptide; CK-MB, creatinine kinase-muscle/brain; CRP, C-reactive protein; FAS, Fas cell surface death receptor; GDF, growth differentiation factor; hsTnI, high-sensitivity troponin; IL, interleukin; LDL, low-density lipoprotein; LP-PLA2, lipoprotein-associated phospholipase A2; MMP, matrix metalloproteinases; MPO, myeloperoxidase; MR-proADM, midregional proadrenomedullin; MR-proBNP, midregional pro-B-type natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sFAS, soluble Fas cell surface death receptor; sST2, soluble ST2; sTRAIL, soluble TNF-related apoptosis-inducing ligand; TIMP, tissue inhibitors of metalloproteinases; TNF, tumor necrosis factor; TnI, troponin I; and TnT, troponin T. Figure reproduced with permission from Januzzi et al.²³

In **Chapter 4**, we examined associations of multiple cardiovascular biomarkers with body-mass index (BMI), and investigated whether these biomarkers had a differential predictive value for incident HF in lean, overweight and obese individuals.

Obesity affects cardiac endocrine function, and obesity is considered to be a natriuretic peptide deficient state.^{24,25} Fat distribution patterns, however, are substantially different among men and women.^{26,27} Therefore, in **Chapter 5**, we studied whether associations of BMI, waist circumference and bodyweight with circulating NT-proBNP levels differed between community-dwelling men and women. An accompanying editorial entitled “*The paradox of low B-type natriuretic peptide levels in obesity revisited: Does sex matter?*” was written by Clerico and colleagues.²⁸ In **Chapter 6**, we proceeded along the lines of the editorial, and conducted a literature review focussing on the overlapping effects of sex and obesity on HF biomarkers. We formulated several clinical pointers and potential research questions – which may particularly be of interest to cardiology residents and students interested in HF research.

In **Chapters 7 and 8**, we explored sex-related differences in the association between cardiovascular risk factors, biomarkers, and the risk of incident HF using data from the PREVEND cohort, as well as from three longitudinal observational cohorts from the United States: Framingham Heart Study (FHS), Multi-Ethnic Study of Atherosclerosis (MESA) and Cardiovascular Health Study (CHS). In **Chapter 9**, we highlight the inadequacy of cardiac natriuretic peptides in HFpEF diagnosis, and propose a hypothetical HFpEF diagnostic algorithm that also incorporates multimarker testing along with clinical risk stratification, echocardiographic evaluation and invasive haemodynamic testing.

This *Thesis* ends with a **General Discussion** that also includes **Future Perspectives**.

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