SUMMARY

Heart Failure (HF) is a heterogeneous and multifactorial clinical syndrome resulting from structural and/or functional cardiac abnormalities caused by primary cardiomyopathies and/or by secondary aetiologies (e.g. coronary artery disease, valvular disease or hypertension). Left ventricular ejection fraction (LVEF) remains the cornerstone within the recently published universal classification of HF to classify this syndrome\(^1\). The rationale behind this relates back to the early trials in the 80s and 90s of the previous century, in which LVEF was used as a predominant tool to select patients at increased risk for hard study endpoints for enrichment purposes\(^2-4\). While categorising HF based on LVEF provided us with valuable insights into the pathophysiology of HF at the outer ends of the spectrum\(^4,5\), and LVEF currently remains an important and easy to assess clinical marker used for the initiation of evidence-based HF therapies\(^1,6\), it results in an enormous oversimplification of a complex syndrome\(^2-4\). As a result, numerous experts recently proposed that LVEF based categorisation of HF should not drive the future of HF research and that the nomenclature of HF and cardiomyopathies should be driven by science and not the other way around\(^2-4,7\).

Large scale registries with real-world data will play a pivotal to move the current HF field forward\(^4,8\). In the last years, our Maastricht Cardiomyopathy Registry (mCMP-registry) team created a future-proof foundation for a multidisciplinary (early) cardiomyopathy and HF registry. Establishing such a large-scale registry is time-consuming and requires in-depth insights into the local (logistic) hurdles in performing HF research. During the last years, we therefore performed cardiomyopathy and HF-related research across the LVEF spectrum of which some examples are provided in Part I (Chapters 2-8) of this thesis. Our team tackled the (logistic) hurdles faced during these studies to improve the way HF registry-based research is performed at our institution, ultimately leading to the mCMP-registry, founded in 2021 and presented in Chapter 9. These studies have also yielded new scientific insights. An overview of the results of the studies presented in Part I (chapters 2-8) of this thesis is summarised below:

Chapters 2-5 of this thesis focus on a specific subgroup of HF patients, namely DCM patients. In Chapter 2, we showed that the LVEF-trajectory of DCM patients with truncating variants in titin (TTNtv, which has a prevalence up to 25% in DCM\(^9\)\(^-\)\(^11\)) has a concave shape. The LVEF-trajectory shows a steep increase until an apex at two years after baseline, immediately followed by a slow decline of the LVEF. Patients without TTNtv had comparable recovery of LVEF in the first two years, but their
LVEF remained stable during follow-up. In the study presented in Chapter 3, we observed that TTNtv DCM patients have more severe LA dysfunction compared to DCM patients without a TTNtv. Using computational modelling we showed that while the observed LV dysfunction partially explains the observed LA dysfunction, both intrinsic LV and LA dysfunction are likely present in patients with and without a TTNtv, highlighting LA failure as a significant contributor to DCM.

Inter-atrial block (IAB) is a well-known entity associated with atrial failure\textsuperscript{12,13}, and has already been associated with supraventricular arrhythmias, cardiovascular and all-cause mortality\textsuperscript{12,14,15}, and even life-threatening arrhythmias (LTA) in the general population\textsuperscript{16}. In Chapter 4, the first study is presented that provides insights into the prognostic association between IAB and LTAs in ambulant DCM patients. In both the derivation and external validation cohort used for this study, the presence of IAB at baseline was significantly associated with incident LTAs.

In Chapter 5, the first randomised clinical trial is presented that studied the effect of intravenous immunoglobulin (IVIg) on systolic cardiac function and cardiac parvovirus B19 (B19V) presence in patients with idiopathic chronic DCM and cardiac B19V persistence. We showed that IVIg did not improve cardiac function, functional capacity, and quality of life in these patients.

The studies presented in Chapters 6-8 included subjects with a normal LVEF. The HFA-PEFF diagnostic algorithm was recently developed to optimise (early) recognition of HF patients with a normal LVEF, also known as HFpEF\textsuperscript{17}. In the pilot study present in Chapter 6, we aimed to: 1) identify distinct “early-HFpEF” phenogroups by cluster analysis of the recently published HFA-PEFF domain scores in subjects that present with HF-like symptoms, a normal LVEF, and without a medical history of HF; and 2) study whether these phenogroups may be associated with distinct blood proteome profiles. We found four distinct phenogroups within this pilot study. In total, 32 out of the 93 studied Olink protein biomarkers significantly differed between these phenogroups. Whether the identified phenogroups have incremental value in predicting incident HFpEF and its progression and whether the associated biomarkers have any (incremental) diagnostic/prognostic value must be determined in longitudinal multi-centre trials.

The study presented in Chapter 7 shows that most diagnostic HFpEF biomarker studies have a high risk of bias, reducing the reproducibility and the potential for clinical care. Methodological well-designed studies with a uniform reference diagnosis are urgently needed to determine the incremental value of circulating biomarkers for diagnosing HFpEF.
A promising non-circulating prognostic biomarker in heart failure and cardiomyopathy-related research is the global longitudinal strain (GLS), which is studied in a pilot study presented in Chapter 8 of this thesis. The aim of this study was to determine a cut-off value of GLS that indicates an increased risk of adverse outcomes in individuals without diagnosed HF and with a normal LVEF. In this study, we found that the risk for cardiac hospitalisation and cardiovascular mortality was doubled in patients with a GLS of -21% and higher. Noteworthy, this value is lower than the previously reported lower limit of normal in men and women (-17% and -18%, respectively)\(^{18}\).

In Chapter 9 (Part II of this thesis), the mCMP-Registry design paper is presented. This registry is the result of a multi-disciplinary team effort and years of work to optimise the way registry-based HF and cardiomyopathy-related research is performed at our centre. The aim of the mCMP-registry is to improve (early) diagnosis, risk-stratification, and management of cardiomyopathies and HF. The registry enables a unique opportunity to achieve this by: 1) The broad inclusion criteria; 2) The standardised electronic medical record forms, allowing semi-automatic data-collection within the electronic case report forms (eCRF) of the mCMP-registry; 3) The extensive study-related data collection, including the annual automatic sending of questionnaires over a period of 15 years to, among other things, make it easier to detect the occurrence of events outside the hospital, to follow up complaints and quality of life longitudinally, and to be able to perform cost-benefit analysis; 4) The multi-disciplinary approach within and beyond our centre, including both pre-clinical and clinical researchers from multiple departments (including the department of immunology, pathology, clinical genetics, medical microbiology, and cardiology) and supporting staff (including research nurses, lab technicians, bio-statisticians and IT support). The infrastructure even allows to (semi-)automatically contact subjects that gave explicit permission to inform them about other cardiovascular-related research. This option is, e.g. used to inform participants about the existence of the Netherlands Heart Tissue bank (NHTB). The design paper of the NHTB is presented in Chapter 10 of this thesis. The NHTB aims to boost a wide range of cardiac disease-related fundamental and translational studies. The NHTB does this by strengthening the cardiovascular research infrastructure with an open-access non-profit biobank. The NHTB will include cardiac tissue and related clinical data from donors with and without known cardiovascular diseases, which will increase our understanding of cardiac diseases during early and advanced disease development.
Summary

This thesis describes the past, present (Part I), and future (Part II) of registry-based HF and cardiomyopathy studies across the LVEF spectrum. The discussion of this thesis (Chapter II) aims to put the results of the studies presented in Part I in perspective and to provide an outlook for the future of (early) HF and/or cardiomyopathy research that can be performed due to the solid mCMP-registry foundation.