Introduction

INTRODUCTION

Burden of cardiovascular disease

Although their treatment has drastically improved in the past decades, cardiovascular diseases (CVD), or diseases of the circulatory system (ICD-10 code I00-I99), still remain the most common cause of death worldwide, with more than 4 million people dying in Europe every year (1). This may in part be attributed to the ageing of the general population, for which reason mortality rates due to CVD are expected to rise even further in the future (2). With 37,795 (24.6%) deaths, CVD / diseases of the circulatory system were the second cause of mortality in The Netherlands in 2018 (Figure 1). Taking a closer look, within the class of CVD, coronary artery disease (CAD; ICD-10 I20-I25) and heart failure (HF; ICD-10 I50-I51) caused 8,268 and 7,564 deaths, respectively (3), whereas CAD and HF were responsible for 67,607 and 30,405 hospital admissions (4). These numbers underscore the burden of CVD on Dutch society, in particular CAD/HF, and call for continuing action.

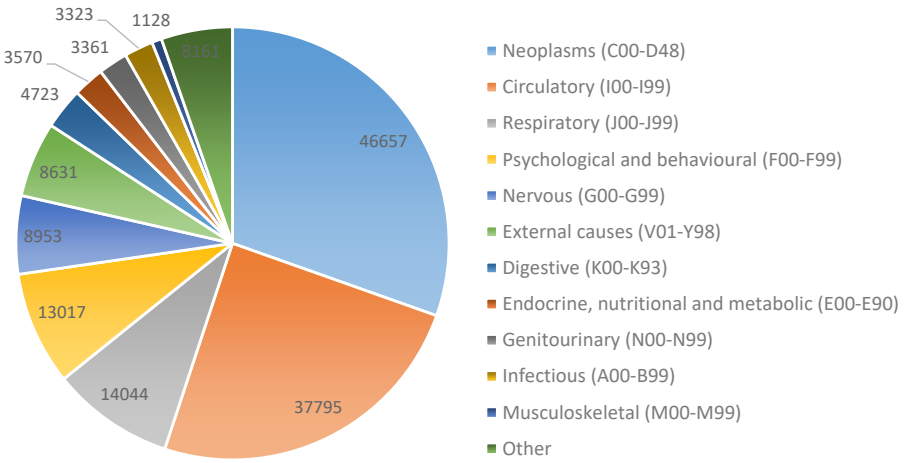

Figure 1 - Causes of mortality in The Netherlands in 2018 according to the ICD-10 classification (source: https://opendata.cbs.nl)

Understanding the disease course in individuals with acquired heart disease

In order to reduce the burden of CAD/HF on patients and society, a combination of public prevention campaigns with a personalized approach is required. In order to fully utilize the opportunities of a personalized medicine model, obviously, our understanding of the disease should be improved, in particular the prediction of

an adverse disease course in individual patients. This thesis aimed to investigate if and to what extent serum biomarkers and intracoronary imaging may contribute to these goals in patients with established CAD (Part I) and HF (Part II).

Part I - Coronary artery disease

In the first part of this thesis we focus on patients with established CAD, and study:

the relation between the anatomic Syntax score (SXscore), based on coronary angiography (CAG), and coronary plaque characteristics as assessed by radiofrequency intravascular ultrasound (RF-IVUS) and near-infrared spectroscopy (NIRS) imaging; the relation between serum markers of inflammation, renal function and lipid metabolism, and the NIRS-derived coronary lipid core burden index (LCBI); changes in serum CRP levels in relation to changes in blood lipids and coronary plaque characteristics in patients receiving high-intensity statin treatment; the association between biomarkers of inflammation, renal function and lipid metabolism with the occurrence of major adverse cardiac events (MACE) during long-term follow-up.

The outline of this section is as follows:

In **Chapter 2** we study 680 CAD patients, and examine the association between the atherosclerotic burden derived from all three coronary arteries, as assessed by the CAG-based SXscore, and the atherosclerotic burden as assessed by RF-IVUS and NIRS in a single, non-culprit segment. The SXscore is a well-established anatomical scoring tool that grades the complexity of the luminal coronary obstruction and is also used for short- and long-term prediction of MACE in patients undergoing revascularization (5, 6). This score takes into account the number of significant lesions and their location, as well as the complexity of each lesion independently. We investigate whether information derived with this established tool is correlated with information on the extent and phenotype of coronary atherosclerosis as provided by the intracoronary imaging modalities RF-IVUS and NIRS. RF-IVUS is capable of identifying thin-cap fibroatheroma (TCFA) lesions, which are predictive for the occurrence of MACE, particular death and acute coronary syndrome (ACS) (7). NIRS is capable of identifying plaques in the coronary wall with a lipid rich core, which are vulnerable for rupture (8, 9).

In CAD patients, NIRS and FR-IVUS derived plaque characteristics contain prognostic information. Circulating biomarkers are also useful to identify CAD patients who are prone to an adverse disease course. Moreover, serum biomarkers may be

capable to detect vulnerable coronary plaques in an early stage and in a non-invasive manner. Investigating blood biomarkers in relation to intravascular imaging findings could help bridge the gap between known biological pathways and clinical characteristics of atherosclerosis, and could provide further insights into prognostication. Thus, in the **chapters 3, 4, and 5** we study circulating biomarkers of inflammation and renal function, and lipid metabolism, in 581 CAD patients who participated in the ATHEROREMO study. We investigate the relationship between these biomarkers and NIRS-derived LCBI, as well as their association with the occurrence of MACE during longer-term follow-up.

In **chapter 6** we focus further on inflammation, which is known to play a major role in the initiation, progression, and instability of atherosclerotic plaques (10, 11). Among all inflammatory biomarkers, C-reactive protein (CRP) in particular, has been extensively investigated and proven as a prognostic biomarker of CVD (12). Here, we examine the associations between serially measured serum CRP levels with changes in cholesterol levels and changes in intracoronary plaque characteristics as assessed by RF-IVUS and NIRS in a series of 164 patients who received intensive statin therapy for 1 year.

Finally, in **chapter 7**, we move to the clinical practice of treating CAD patients. Here our focus is on patients presenting with chest pain suggestive of myocardial infarction (MI). In pre-hospital settings handled by paramedics, appropriate triage of MI patients remains challenging when automated electrocardiogram (ECG) interpretation is inconclusive. We aimed to identify those patients in order to get them on the right track to primary percutaneous coronary intervention (PCI). For that purpose, In the Rotterdam-Rijnmond region, automated ECG devices on all ambulances were supplemented with a modem, enabling transmission of ECGs for online expert interpretation. The diagnostic protocol for acute chest pain was modified accordingly. We monitored the performance of this system during 1 year, and report on a total of 1,076 patients.

Part II - Heart failure

For HF patients several multivariable prognostic risk scores have been developed. These scores mostly rely on clinical characteristics, and leave room for improvement. In the past years a large body of research has emerged showing that many circulating biomarkers are involved in heart failure (13, 14). However, previous studies on this topic 'classically' related single biomarker measurements at study baseline with adverse events occurring over the years thereafter. Thus, disease dynamics

might easily have been missed. We hypothesized that temporal biomarker patterns contain additional prognostic information that may help improve individualized risk assessment.

In the second part of this thesis we focus on patients with established HF. We investigate temporal patterns of a broad range of serum biomarkers, including markers of inflammation, myocardial ischemia, myocardial stress, microRNAs, and glomerular and tubular renal markers; and relate these temporal patterns with the clinical (adverse) disease course.

The outline of this section is as follows:
In the **chapters 8 and 9** we study a series of 263 ambulant HF patients who had blood sampling at enrolment and subsequently every 3 months. We examine the associations between repeatedly measured N-terminal pro-B-type natriuretic (NT-proBNP), high-sensitivity troponin T (Hs-TnT), C-reactive protein (CRP), which are established prognostic biomarkers in HF patients (13), and New York Heart Association (NYHA) class, which classifies symptom severity of HF. We also examine the association between the temporal evolution of these biomarkers and occurrence of adverse events, including cardiovascular (CV) mortality and HF hospitalisation.

Several studies have suggested that circulating microRNAs (miRs) are associated with HF, but these studies were small, and limited to single miR measurements. In **chapter 10** we examine 7 miRs that were previously linked to heart failure, and test whether their temporal expression level predicts the incidence of CV mortality or HF hospitalisation in the above-mentioned prospective cohort of ambulant HF patients.

Heart failure patients often have impaired renal function (13, 15), whereas renal (dys)function itself is an important determinant of adverse clinical outcome. Single assessments of renal function fail to reflect clinically silent progression of HF. Therefore, in **chapter 11**, we again studied the 263 ambulant HF patients, and now evaluated the temporal evolutions of creatinine/estimated glomerular filtration rate (eGFR) and cystatin C (CysC), which are markers of glomerular function, as well as urinary N-acetyl-beta-D-glucosaminidase (NAG), kidney injury molecule (KIM)-1, and plasma and urinary neutrophil gelatinase-associated lipocalin (NGAL), which are markers of tubular function. We also aimed to determine if the patient-specific evolutions of these biomarkers can predict (adverse) clinical outcome in patients with clinically stable heart failure.

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