CHAPTER 1

General introduction
Life expectancy in developed countries is rising continuously. Individuals seem to live longer with less disability and less chronic diseases. However, despite these improvements, the prevalence of type 2 diabetes and of heart failure are still rising. Type 2 diabetes is a disease characterised by elevated blood glucose levels, which involves an elevated risk of developing cardiovascular disease. The worldwide number of patients with diabetes was estimated to be 171 million (2.8%) in the year 2000, and expected to more than double to 366 million (4.4%) in 2030. Heart failure is characterised by impaired contraction and/or relaxation properties of the left ventricle (LV). The LV pumps oxygen-rich blood into the aorta, from where it is distributed throughout the body. Impairments in LV systolic function (contraction), or in LV diastolic function (relaxation) may hamper blood supply to the body’s tissues. Type 2 diabetes and heart failure are related to each other and prevalences increase with ageing. Both also share common risk factors and comorbidities. For example, increased body weight, stiffer arteries, and worse functioning of kidneys, the heart and the brain. This thesis comprises a number of epidemiological studies that are aimed at identifying potential predictors of heart failure and of deteriorating LV systolic and diastolic function. Interactions between type 2 diabetes and heart failure, and potential predictors including body weight, blood pressure, blood glucose and lipid levels, arterial stiffness, renal function, and cognitive function are of particular interest in these studies.

**Type 2 diabetes**

Type 2 diabetes is a metabolic disease characterized by elevated blood glucose levels, or hyperglycaemia. Type 2 diabetes has since long time been established as a major risk factor for cardiovascular complications. Despite overall reductions in cardiovascular mortality in the past 50 years, individuals with type 2 diabetes still have a 2-fold higher risk of cardiovascular disease compared to individuals without type 2 diabetes. A major complication of type 2 diabetes is heart failure, which occurs 2-5 times more often in individuals with compared to those without type 2 diabetes.

**Heart failure**

Heart failure is defined as an inability of the heart to supply sufficient blood to the body’s tissues and it is characterized by abnormalities of LV systolic and/or diastolic function. Diagnosis of heart failure is based on the presence of symptoms, including dyspnoea, fatigue, fluid retention, or breathlessness, evidence of systolic and/or diastolic LV dysfunction, and response to therapy. Heart failure can develop secondary to other cardiovascular diseases, like arrhythmias, coronary artery disease, valvular disease, LV hypertrophy, or dilated cardiomyopathy. Because of its progressive nature and high mortality, heart failure is often referred to as the final pathway of any structural or functional cardiac disorder. Heart failure prevalence is rising along with the ageing and increasingly overweight population in the western world. In the Rotterdam Study, the prevalence of diagnosed heart failure ranged from 0.9% in subjects aged 55-64 years to 17.4% in individuals aged 85 years and older. Almost 1 in 3 individuals aged 55 years or older will eventually develop heart failure and 5-year survival after diagnosis is 35%. In addition to the increased risk associated with type 2 diabetes, each % higher HbA1c in diabetes patients was shown to increase heart failure risk with 8%. Furthermore, heart failure prognosis is even worse with co-existing type 2 diabetes.
Properties of 2 distinct types of heart failure

About half of all heart failure patients have LV systolic dysfunction, most commonly with coexisting LV diastolic dysfunction. LV systolic function is the ability of the LV to contract and eject blood into the aorta. LV ejection fraction is the fraction of blood pumped out of the LV with each heartbeat and is therefore a measure of LV systolic function. LV ejection fraction can be determined using echocardiography by dividing the stroke volume by the LV end-diastolic volume (Figure 1.1). Heart failure with LV systolic dysfunction, defined as a LV ejection fraction below 50%, is referred to as “heart failure with reduced ejection fraction” (HFREF).

The other approximate half of heart failure patients have “heart failure with normal ejection fraction” (HFNEF), characterized by LV diastolic dysfunction. LV diastolic function refers to relaxation properties of the LV, when it recoils to fill itself with blood from the left atrium. The prevalence of LV diastolic dysfunction and HFNEF have been rising along with their predisposing factors: older age, hypertension, obesity and type 2 diabetes. Although HFNEF might be preventable, appropriate treatment is still lacking. In fact, while prognosis for HFREF has been improving, that of HFNEF has remained unchanged. This emphasizes the importance of identification of new risk factors for HFNEF. LV diastolic dysfunction is present when there is evidence of an increased passive stiffness or impaired relaxation of the LV. This evidence is more difficult to obtain than evidence of LV systolic dysfunction, and generally a combination of several echocardiographic measurements is used. These markers of LV diastolic dysfunction include the ratio of early (E) mitral valve flow velocity and early (e') diastolic lengthening velocity (E/e'), left atrial volume index, LV mass index, and the product of LV mass index and left atrial volume. Despite some debate on its use in patients with other cardiac disorders, the estimate to measure LV diastolic dysfunction that is currently considered most reliable is E/e', measured with pulsed wave and tissue Doppler echocardiography (Figure 1.2). E/e' provides an estimate of LV filling pressure and left atrial pressure, because it increases with higher LV inflow velocity (E) and/or delayed LV tissue reextension (e'). A second marker of LV diastolic function is left atrial volume index, since elevated LV filling pressures can lead to dilation of the left atrium (Figure 1.3). LV mass index, an indicator of LV hypertrophy, is associated with impaired LV relaxation, and is therefore another marker of LV diastolic dysfunction. LV mass indexed by height has been identified as a predictor of heart failure in individuals without coronary artery disease, but is also a diagnostic criterion for the diagnosis of HFNEF (Figure 1.4). Finally, the fourth marker of LV diastolic dysfunction is the product of LV mass index and left atrial volume, which makes a good distinction between LV hypertrophy and HFNEF.

Plasma B-type natriuretic peptide (BNP) is a neurohormone primarily secreted from the cardiac ventricles in response to increased volume and pressure. BNP is used as a marker for heart failure, but its specificity is very low. BNP levels are elevated in both LV systolic and diastolic dysfunction, but also in case of renal failure, valvular disease, myocardial infarction, and older age. Its use for prediction of LV systolic and diastolic dysfunction remains to be elucidated.
**Figure 1.1.** Assessment of Left ventricular (LV) ejection fraction by measuring LV end-diastolic (left, EDV) and end-systolic (right, ESV) volumes in apical 4-chamber view. LV ejection fraction = (EDV - ESV) / EDV.

**Figure 1.2.** Assessment of the ratio of early diastolic mitral inflow velocity (E, cm/sec) and early diastolic myocardial lengthening velocity (e’, cm/sec) using pulsed wave and tissue Doppler, respectively.
Figure 1.3. Assessment of end-systolic left atrial volume in apical 4-chamber view.

Figure 1.4. Assessment of left ventricular (LV) mass by measuring interventricular septum thickness (IVST), posterior wall thickness (PWT), and LV diameter (EDD) in end-diastole using M-mode echocardiography. LV mass = 0.8*(1.04*(EDD+PWT+IVST)^3 - (EDD)^3) + 0.6
Backgrounds on type 2 diabetes and heart failure

Type 2 diabetes and arterial stiffness are both recognised contributors to LV stiffness and LV systolic and diastolic dysfunction. Type 2 diabetes and arterial stiffness also are highly interconnected. Another factor that has repeatedly been linked to heart failure is chronic kidney disease. Both diseases share common risk factors, including diabetes, hypertension and arterial stiffness. Type 2 diabetes might cause arterial stiffening, for instance due to alterations in arterial wall collagen, increased oxidative stress and chronic low-grade inflammation. Arterial stiffness reduces the cushioning capacity of arteries, necessary to smooth flow pulsations to an almost steady stream through organs and tissues. Furthermore, stiff arteries increase wave reflections in peripheral branching sites. Therefore arterial stiffness is hypothesized to lead to microvascular damage, increased LV afterload and decreased coronary perfusion. Arterial stiffness might therefore be an important factor linking type 2 diabetes to chronic kidney disease and heart failure.

Higher plasma BNP in a non-heart failure range predicts heart failure and cardiovascular disease mortality in the general population. Associations of BNP to LV mass and function in individuals with a different glucose status have not been compared. These might be different, since type 2 diabetes is associated with heart failure, but also with relatively low BNP levels. This might be due to a decreased secretion and/or increased clearance of BNP in individuals who are obese.

In 1999, the Framingham Study developed a model to assess 4-year heart failure risk in individuals predisposed by coronary disease, hypertension, or valvular heart disease. More recently, a 5-year heart failure prediction score has been developed in elderly participants of the Health ABC study. Both studies defined the presence of heart failure based on hospital records. Therefore it is possible that these risk scores poorly identify persons whose heart failure would not be diagnosed and treated in clinical practice. Furthermore, both risk scores did not include BNP measurements. Although its positive predictive values are too low to use BNP levels alone for diagnosis of heart failure, elevated BNP levels indicate a higher risk and may thus be a very important component in a prediction model for heart failure.

Heart failure has a high impact on quality of life and also on cognitive function. Cognitive impairment can be detected in approximately one third of hospitalised heart failure patients and transplant candidates and is associated with a reduced survival in these patients. Heart failure is hypothesised to cause or contribute to cognitive impairment by mechanisms including cerebral hypoperfusion, silent cerebral infarction, atrial fibrillation and endothelial dysfunction. Cardiac transplantations and resynchronisation therapy are often followed by improvements in cognitive functioning, which suggests that cognitive impairment is a result from impaired LV function rather than the other way around. Cognitive impairments may include memory functions, or planning, organising and monitoring of behaviour and may therefore hamper day to day functioning. Modest cognitive decrements impact daily functioning and will, in a proportion of the individuals, progress to dementia. However, so far studies on markers of LV function in relation to cognitive function in the general population are scarce. Previous studies on heart failure-associated cognitive impairment mainly relied on relatively brief neuropsychological assessments, or cognitive screening instruments. In addition, assessment of LV function in previous studies was predominantly based on a clinical diagnosis of heart failure rather than standardised echocardiographic examinations.
**Study populations**

For the studies described in this thesis, data from two large population-based studies have been used: the Hoorn Study and the Australian Diabetes, Obesity and Lifestyle Study (AusDiab). Both studies are prospective cohort studies and thus provided us with a perfect opportunity to study the processes we were interested in, over a longer period of time.

The Hoorn Study is a study on glucose metabolism and cardiovascular disease, which started in 1989-1991 (visit 1, Figure 1.5). Briefly, 3553 men and women, aged 50–74 years, were randomly selected from the population register of the medium-sized Dutch town of Hoorn, of whom 2484 (70%) participated. In 1996-1998 (visit 2), 1513 (73%) of all surviving participants agreed to participate in the first follow-up. In 1999-2001 (visit 3), all those who were diagnosed as having diabetes during the previous examinations (n=176), and random samples of individuals with normal glucose metabolism (n=705) and impaired glucose metabolism (n=193) were invited, of whom 648 (60%) participated. In addition, we invited 217 individuals with type 2 diabetes from the Hoorn Screening Study, a population-based targeted type 2 diabetes screening study, of whom 188 (87%) participated. Visit 3 included the first standardised echocardiographic examinations. For follow-up examinations in 2007-2009 (visit 4), we excluded 40 (5%) individuals of whom no satisfactory echocardiography data were measured at visit 3, and 12 (1%) individuals who were mentally incompetent to participate; 129 (15%) individuals died. Of the remaining 655 individuals, 441 (67%) participated in examinations including echocardiography at visit 4. Results from the Hoorn Study will be discussed in Chapters 2 and 4-8.

AusDiab began in 1999-2000 (Figure 1.6). Initially, 11247 adults aged ≥ 25 years, drawn from 42 randomly selected census collector districts across Australia, participated at baseline (response rate 55.3% of those completing a household questionnaire). Of the 10788 participants eligible for testing in 2004-2005, 6537 (60.6%) attended the follow-up examination. Results of AusDiab will be discussed in Chapter 3.
Figure 1.5. Flowchart of Hoorn Study examinations and the chapters in which these examinations are discussed (numbers in squares, connected with dashed lines).

Figure 1.6. Flowchart of Australian Diabetes, Obesity and Lifestyle Study (AusDiab) examinations and the chapter in which these examinations are discussed (number in square, connected with dashed lines).
Outline of this thesis (Figure 1.7)

In Chapter 2, we describe relative contributions of glucose status and arterial stiffness to LV systolic and diastolic dysfunction. Furthermore we investigated whether glucose status and arterial stiffness were associated with changes in markers of LV systolic and diastolic dysfunction. In Chapter 3 we investigated whether pulse pressure, as a marker of arterial stiffness, was associated with 5-year changes in renal function and incident chronic kidney disease (CKD) in the AusDiab Study. We also describe whether type 2 diabetes modified these associations. We then show longitudinal analyses in Chapter 4, that assessed courses of cardiovascular risk factors over 17 years of the Hoorn Study in relation to the presence or absence of LV diastolic dysfunction at visit 4. In Chapters 5 and 6 we report on cross-sectional and 8-years prospective associations of BNP with markers of LV systolic and diastolic dysfunction and effect modification from glucose status. We then consider potential predictors of heart failure in Chapter 7, in which we developed a prediction model for 8-year incident heart failure. In Chapter 8 we investigated whether the presence of heart failure and variations in LV systolic and diastolic dysfunction were associated with cognitive performance. Finally in Chapter 9, we provide a discussion of the main findings and implications of the above studies.

Figure 1.7. Associations investigated in the present thesis (solid lines), investigated interactions (dashed lines) and the chapters in which these associations are discussed (numbers in squares, connected with dashed lines). 'Type 2 diabetes' also includes glucose and HbA1c levels. In chapter 7 (prediction model) we re-assessed associations of all potential predictors, therefore this chapter has been excluded from the Figure. LV=left ventricular.
References


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