Summary

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 left ventricular (LV) systolic (contractility) and/or diastolic (filling/relaxation property) function. Heart failure is more prevalent in individuals with type 2 diabetes, and co-existence of these conditions has a worse prognosis. This thesis comprises a number of epidemiological studies that are aimed at identifying potential predictors of heart failure and of worsening LV systolic and diastolic dysfunction. 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.

Study populations
For the studies described in this thesis, data from 2 populations have been used: the Hoorn Study and the Australian Diabetes, Obesity and Lifestyle Study (AusDiab). Both studies are population-based prospective cohort studies and thus provided us with the 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 with 2484 participants aged 50-75 years. Follow-up examinations took place in 1996-1998 (n=1513), 1999-2001 (n=648, all individuals with, and random samples of individuals without diabetes were invited and n=188 individuals with diabetes from the Hoorn Screening Study were added to the cohort), and 2007-2009 (n=441). Results from several Hoorn Study examinations are discussed in Chapters 2 and 4-8. AusDiab began in 1999-2000. Initially, 11247 adults aged ≥ 25 years, drawn from 42 randomly selected census collector districts across Australia, participated at baseline. Of the 10788 participants eligible for testing in 2004-2005, 6537 (60.6%) attended the follow-up examination. Results of AusDiab are discussed in Chapter 3.

Main findings
Associations of glucose status and arterial distensibility coefficients (as a measure of arterial stiffness) with LV systolic and diastolic dysfunction in the Hoorn Study are described in Chapter 2. The presence of type 2 diabetes and lower arterial distensibility coefficients were both independently associated with more severe LV diastolic dysfunction and with deterioration of LV diastolic dysfunction. This indicates that type 2 diabetes and arterial stiffness may relate to LV diastolic dysfunction through different pathways.
The contribution of another measure of arterial stiffness, namely pulse pressure, to changes in renal function was investigated in AusDiab in Chapter 3. Pulse pressure was shown to be significantly associated with estimated glomerular filtration rate (GFR) decline and incident chronic kidney disease over a 5-year period. These associations were significantly stronger in individuals with, as compared to those without type 2 diabetes. This implies that, especially in individuals with type 2 diabetes, pulse pressure is an important risk factor for chronic kidney disease.

In Chapter 4 we assessed courses of cardiovascular risk factors over 17 years of the Hoorn Study in relation to the presence or absence of LV diastolic dysfunction in 2007-2009. Elevated cardiovascular risk factors around the age of 58 years, in particular glycaemic levels, lipid levels, and blood pressure, were independently associated with the presence of LV diastolic dysfunction 17 years later. With passing time, differences in cardiovascular risk factors became smaller according to the ultimate presence or absence of LV diastolic dysfunction. Therefore, early identification and treatment of high-risk individuals may be of value for prevention or postponement of developing LV diastolic dysfunction.

In Chapters 5 and 6, we studied cross-sectional and prospective associations of B-type natriuretic peptide (BNP) with LV systolic and diastolic dysfunction. BNP is predominantly secreted in the LV in response to volume expansion and pressure overload and is therefore used as a marker for heart failure. Cross-sectionally (Chapter 5), higher BNP was associated with higher LV mass, worse LV systolic function and higher markers of LV diastolic function, and the association of BNP with the latter appeared to be particularly strong in individuals with type 2 diabetes. Prospectively (Chapter 6), higher BNP was associated with deterioration in markers of LV systolic and diastolic dysfunction. Higher BNP was also associated with increasing LV mass, but only in individuals with type 2 diabetes. This implies that the presence or absence of type 2 diabetes should be taken into account if BNP levels are used to assess the risk of heart failure or LV diastolic dysfunction.

In Chapter 7, we developed a prediction model for 8-year incident heart failure in the Hoorn Study population. Unlike existing prediction models, this study was the first to screen for heart failure rather than using clinical diagnoses. At present, heart failure often remains undetected, but screen-detected heart failure was already associated with lower quality of life. Intensive treatment of risk factors, combined with lifestyle changes might prevent development of heart failure in those with elevated risk of heart failure. We used an extensive set of predictors including BNP, which was not available in existing models to predict heart failure. This model provides a tool to estimate the risk of future heart failure and identify individuals for preventive interventions.

Associations of heart failure and markers of LV systolic and diastolic dysfunction with cognitive functioning were investigated in Chapter 8. We showed that worse cognitive functioning could already be observed in early stages of LV dysfunction and heart failure. BNP levels appeared to be the strongest indicator of cognitive functioning. BNP is therefore a target for further investigations on risk stratification and early prevention of both heart failure and cognitive impairment.

In Chapter 9, the main findings presented in this thesis are discussed, and implications for future research are given. Firstly, we discussed methodological considerations of the study populations, measurements, and statistical methods. We then described potential mechanistic pathways for our findings, and discussed clinical relevance of the results. Finally, we described implications for future research to investigate consequences of mild forms of heart failure, how to identify individuals at high risk of heart failure, and finally how to prevent or delay the onset of heart failure by intervening in individuals at high risk.
In conclusion, this thesis emphasizes the complex interplay between several risk factors that underlie and result from the development of LV systolic and diastolic dysfunction. Type 2 diabetes, arterial stiffening, renal dysfunction, BNP levels and cognitive function are all closely related to each other and to LV systolic and diastolic dysfunction. Arterial stiffness, high cholesterol, and high blood pressure do not seem to explain the link between diabetes and heart failure, but are independently associated with LV diastolic dysfunction. Furthermore, individuals who developed LV diastolic dysfunction, appeared to have elevated risk factors up to 17 years in advance. Early treatment of these risk factors might reduce the risk of LV diastolic dysfunction and heart failure. Effectiveness of early detection and treatment to prevent heart failure needs to be investigated in future studies.