The burden of myocardial infarction
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Chapter 1
General introduction
INTRODUCTION

Cardiovascular disease: no. 1 cause of death worldwide
In 2012, 17.5 million people died of cardiovascular disease of which around 7 million died of ischemic heart disease\(^1\). With almost one third of all deaths cardiovascular disease is the number 1 cause of death worldwide. In Europe 1.9 million people every year die of cardiovascular disease. Together with a decline in overall mortality\(^1\), cardiovascular death in Western Europe declined with 12.8% between 1990 and 2013\(^2\). The reduction in cardiovascular death can be partially attributed to progress made in controlling risk factors, such as the decline in tobacco smoking and primary prevention, and the improvements in treatment of cardiovascular disease. However, the absolute number as well as the proportion of cardiovascular deaths compared to other causes of death has further increased during the last decade (coronary artery disease from 6 million in 2000 to 7.4 million in 2012; stroke 5.7 million to 6.7 million). Along with mortality, cardiovascular disease also leads to significant morbidity with a yearly hospitalization rate of 2,500 on 100,000 persons\(^3\). The burden of cardiovascular disease will continue to increase with 23.6 million deaths in 2030\(^4\). Cardiovascular risk factors such as hypertension and diabetes are expected to rise as well by 2030. A global health program, Horizon 2020, focuses on tackling this major threat to healthy ageing by improving primary prevention and treating these risk factors\(^5\).

Coronary artery disease
Cardiovascular diseases are comprised of several disorders of the blood vessels and the heart, of which the most common type is coronary artery disease. Clinical symptoms of coronary artery disease can be classified into stable angina, unstable angina, myocardial infarction, and sudden coronary death. In this thesis, the focus will be on myocardial infarction. ST-segment elevation myocardial infarction (STEMI) is clinically differentiated from non-ST segment elevation myocardial infarction (NSTEMI), the two subtypes of myocardial infarction. The current treatment of STEMI is immediate reperfusion therapy as can be accomplished by percutaneous coronary intervention (PCI) with concomitant thrombus aspiration and placement of (a) drug-eluting stent(s) in the infarct-related artery\(^6\). Periprocedural antithrombotic medication is indicated and comprises antiplatelets and anticoagulants. Before patient discharge of STEMI hospitalization, echocardiographic evaluation of left ventricular function and infarct size is recommended\(^6\). Secondary prevention focuses on lifestyle interventions and drug therapies (under which antithrombotic therapy, lipid-lowering therapy, beta-blockers, angiotensin-converting enzyme inhibitors and aldosterone antagonists) to prevent new ischemic events, stent thrombosis, hospitalization for cardiovascular events, and cardiovascular mortality. Since the introduction of reperfusion therapy, mortality rates decreased substantially
in STEMI patients. However, despite the current treatment strategy, 5-year mortality in a Belgian-United Kingdom cohort including patients hospitalized for STEMI was approximately 20% and the majority of deaths occurred after hospitalization of the index event. Apart from mortality, a substantial part of patients with myocardial infarction have persistent chest pain symptoms or develop heart failure and are re-hospitalized. In the previous study, more than half of the patients were readmitted to the hospital within 5 years of follow-up. Incidence of acute decompensated heart failure in a study including 593 STEMI patients undergoing primary PCI was 4.9% after 3 years of follow-up. Both remarks reflect the increased morbidity after acute coronary syndrome, which also has its impact on quality of life. Heart failure for example is associated with impaired quality of life, in patients as well as their partners. Apart from personal health, coronary artery disease has a major economic impact. It brings along high costs for society, short-term and long-term. To improve cost-effectiveness, several initiatives have been undertaken, such as a chest pain unit for acute coronary syndrome, which indeed has been proven successful. Incidence of myocardial infarction is expected to increase in the near future and despite these initiatives, healthcare costs will probably rise further. To conclude, the burden of myocardial infarction on personal health, family health and society is high and current treatment has its shortcomings. First, in order to reduce incidence of myocardial infarction we have to improve our primary prevention. A second challenge is to cut both the morbidity and mortality rates with better risk assessment, better understanding and new treatments as part of the secondary prevention concerning cardiac dysfunction after myocardial infarction.

Aim of this thesis
In an attempt to further optimize primary and secondary prevention thus reducing the burden caused by myocardial infarction I evaluated risk of myocardial infarction in the general population, especially in the northern part of the Netherlands. Second, I aimed to better understand predictors of cardiac dysfunction and outcome after myocardial infarction. Third, I studied new therapies in adjunction to PCI aimed at reducing cardiac dysfunction and improved outcome after myocardial infarction.

PART I
In part I insights in cardiovascular risk in the general population are handled. Due to changes in lifestyle, the ageing society, and other factors, the prevalence of cardiovascular disease is expected to increase substantially in the near future. Epidemiologic studies are essential to further our understanding of the interacting genetic, behavioral, and environmental determinants associated with cardiovascular disease and its risk factors.
A contemporary population-based cohort study which can improve our knowledge on (cardiovascular) healthy ageing in the northern part of The Netherlands is the LifeLines Cohort Study. In chapter 2 the prevalence of cardiovascular disease, its risk factors and utilization of primary prevention by drug treatment in the LifeLines Cohort Study are presented. In chapter 3 we studied individuals who had electrocardiographic signs of myocardial infarction but were unaware of this. We studied the predictors of unrecognized myocardial infarction with a matched case-control set of LifeLines Cohort Study participants.

**PART II**

In part II we focused on assessing risk of left ventricular (LV) dysfunction after myocardial infarction. Many studies in the past studied various clinical, biochemical and angiogenic factors in relation to left ventricular ejection fraction (LVEF) and infarct size after STEMI. Interestingly, many of the previous studies ignored the classical parameter creatine kinase MB (CK-MB) as marker of infarct size. Therefore, it remains uncertain whether recently reported markers have any value above and beyond the CK-MB. We generated a multimarker risk model, making use of easily obtainable values during hospitalization rather than biomarker levels measured only on admission. Chapter 4 discusses the value of cardiac biomarkers available during STEMI hospitalization in relation to infarct size and LVEF as assessed by cardiac magnetic resonance imaging. In addition, we determined the optimal biomarker cutpoints to differentiate small from large infarct size were determined and predictive ability of these cutpoints with mortality was tested. LVEF is an important predictor of prognosis after STEMI, however, other measures of cardiac function are emerging that might also be relevant. For example, previous studies established the relation of global longitudinal strain with other cardiac function parameters and outcome. Global longitudinal systolic strain is a measure of LV deformation. Global longitudinal systolic strain is often affected after STEMI, and is thought to correlate well with LVEF and infarct size. Less is known about its predictors and course over time. Therefore, in chapter 5 we aimed to further understand the clinical and biochemical correlates of (change in) of global longitudinal systolic strain and its relation with LVEF, infarct size and long-term outcome.

**PART III**

In part III I studied future therapies targeting risk of LV dysfunction after myocardial infarction. Timely PCI in STEMI is the treatment of choice and superior to thrombolytic
therapy. However, even reperfusion therapy is believed to cause some form of injury\textsuperscript{30}. Ischemia reperfusion injury is thought to account for approximately half of the final infarct size\textsuperscript{31}. One of the proposed underlying mechanisms for this phenomenon is the restoration of blood flow accompanied by distal embolization of debris and microvascular obstruction\textsuperscript{30}. The latter has been associated with adverse left ventricular remodeling and impaired prognosis\textsuperscript{31}. Other mechanisms include the activation of inflammatory cells and the release of iron from red blood cells (in case of hemorrhage) in the injured myocardium and compression of the microcirculation by tissue edema caused by reperfusion. The key to tackling ischemia reperfusion injury in order to restrict myocardial injury and preserve cardiac function after myocardial infarction is still a matter of debate. Many nonpharmacological and pharmacological interventions have been evaluated, many with contradictory results, including those focused on ischemic post-conditioning and the use of β-blockers\textsuperscript{32}, without convincing results so far. One of the trials evaluating the effect of a new pharmacologic intervention, namely metformin, on left ventricular function in STEMI patients was the Glycometabolic Intervention as Adjunct to Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction III (GIPS-III) trial\textsuperscript{33}. This was a double-blind placebo controlled trial including 380 STEMI patients undergoing primary PCI and randomized to metformin or placebo treatment. The primary endpoint left ventricular ejection fraction (LVEF) at 4 months was assessed by cardiac magnetic resonance imaging. The study showed neutral results of metformin treatment on the primary endpoint LVEF at 4 months. In chapter 6 we studied the effect of metformin treatment on long-term outcome in the GIPS-III trial. Another target to reduce myocardial injury is inflammation. Apart from statins, also thought to reduce inflammation burden caused by atherosclerosis, several other less successful therapies have been evaluated so far, such as interleukin-1 inhibition and other cytokine-inhibiting agents. A translational overview of cytokine-targeting therapies in the setting of myocardial infarction and heart failure is given in chapter 7. One of the promising new targets of inflammation is the interleukin-6 receptor (IL-6R). IL-6R signaling is involved in the inflammatory response during STEMI\textsuperscript{34}. In myocardial infarction elevated IL-6(R) levels have been found\textsuperscript{35} and in acute coronary syndrome increased IL-6 was associated with reduced cardiac function\textsuperscript{36}. IL-6R inhibition and other cytokine-targeting therapies are widely used in inflammatory diseases including rheumatoid arthritis\textsuperscript{37} and its potential in the treatment of myocardial infarction and heart failure is currently under investigation. Here, findings of experimental and clinical studies as well as the translational shortcomings will be reviewed. To further test whether IL-6R represents a target we studied IL-6R inhibition in an experimental ischemia reperfusion mouse model. We hypothesized that treatment with IL-6R inhibition improves cardiac function after myocardial infarction. The results of the study are addressed in chapter 8.
REFERENCES


