Chapter 9
General discussion and future perspectives
DISCUSSION

Central in this thesis was the aim to contribute in reducing the burden caused by acute myocardial infarction. I first studied the factors related to the occurrence of myocardial infarction in the general population. An epidemiologic insight in the prevalence of cardiovascular disease and the shortcomings in primary prevention is provided. Furthermore, I studied factors that predict left ventricular dysfunction and outcome after myocardial infarction. Finally, I focused on potential novel strategies to improve outcome.

PART I

The burden of cardiovascular disease and its (untreated) risk factors in the northern part of the Netherlands is very high as shown in Chapter 2. Almost 3 out of 4 participants had one or more cardiovascular risk factors and 9% of participants under 65 years of age vs. 28% of participants aged 65 years and over had one or more cardiovascular diseases. These prevalences represent the burden of cardiovascular disease in the Netherlands and are generally in line with reports of the World Health Organization on the Netherlands\(^1\). Apart from atrial fibrillation, the prevalence of myocardial infarction and heart failure is somewhat lower than reported for the American population as reported by the American Heart Association heart disease and stroke statistics\(^2\). The substantial proportion of persons with untreated cardiovascular risk factors is not new\(^3\) and even when patients receive drug treatment such as statins for hypercholesterolemia, only half of them achieve the treatment goals\(^4\). Adherence to guidelines is important to manage modifiable risk factors. Increasing knowledge on modifiable risk factors of cardiovascular disease in the past decades has not led to a decrease in risky behaviour. To the contrary, the current Western diet and the decline in physical work do not promote healthy lifestyle. We have not learned enough yet or health campaigns were not in the position to influence people to change lifestyle. There are some signs that more imperative health programmes could be effective. To illustrate, the Netherlands lacks an integral multi-sectorial national strategy and programme for the discouragement of smoking. In 2005, the Netherlands signed the WHO Framework Convention on Tobacco Control (FCTC) pursuing a smokefree society, but a lot of obligations set by the FCTC are still not met. In the United States, a governmental health programme, the Office on Smoking and Health, actively discourages smoking. Smoking rates are much lower in the United States than as found in our study in the northern part of the Netherlands\(^5\). This suggests that the United States with their state-based public health programs were way more effective in preventing smoking and tobacco use and reducing current smoking rates.
than the Netherlands. Initiatives by the Dutch government should be undertaken to
tackle these smoking rates, not only for the individual’s health, but also in light of the
increased economic burden of health care expenditures\textsuperscript{5,6}. Perhaps a more aggressive
strategy is needed, with even higher taxes and where each (general) physicians warns
smokers about the disastrous health effects of smoking and actively promotes stop
smoking programs. In the United Kingdom sugar tax has been introduced recently\textsuperscript{7}. As
sugar consumption is linked to obesity and cardiovascular risk factors\textsuperscript{8}, the tax on soft
drinks is supposed to reduce obesity, which, at the population risk level, is seen as ‘the
new smoking’. Opponents bring up that the sugar tax is an example of a nanny state
going too far and the notion that the beverage one drinks is not of the government’s
concern. The public debate is still ongoing and the long-term effects of sugar tax on
health are as of yet unknown.

Primary prevention and early detection of patients at risk has also partially failed in
younger persons and women with unrecognized myocardial infarction as shown in
Chapter 3. This was studied in 152,180 participants of the LifeLines Cohort study of
whom an electrocardiography was collected. Unrecognized myocardial infarction was
defined as electrocardiographic signs corresponding with myocardial infarction and
no history of myocardial infarction reported by the participant. Although this is not a
perfect technique, worrisome is that we estimated that one out of three myocardial
infarctions were unrecognized and observed that it was independently associated with
increased mortality risk. With the chosen method to determine myocardial infarction
this might lead to underreporting rather than being unrecognized\textsuperscript{9}. However, also in
other studies high numbers of unrecognized myocardial infarction are reported\textsuperscript{10-12}.
In our study, similar risk factors were associated with unrecognized and recognized
myocardial infarction suggesting shared etiology. The high number of unrecognized
MI, especially in young people, is bothersome. When patients present with unexplained
chest pain, the simple exclusion of myocardial infarction by electrocardiography and
(hs) Troponin T should be handled and promoted, as consequences can be severe. With
a systematic risk assessment in intermediate to high-risk patients groups including
youngsters and women the proportion of unrecognized myocardial infarction might
be reduced. Recently, in a systematic review the benefit of systematic screening-like
programmes for the primary prevention of cardiovascular disease over opportunistic
risk assessment was evaluated\textsuperscript{13}. Screening in primary care settings seemed to have no
effect on (cardiovascular) mortality, coronary heart disease, and stroke, but only limited
data was available. Several systematic risk assessment programmes are initiated such
as the Risk Or Benefit IN Screening for CArdiovascular disease (ROBINSCA) study\textsuperscript{13}. In
this study, participants are divided into three groups and undergo either classical risk
screening with the Systematic COrony Risk Evaluation (SCORE) model (lipids and
blood pressure), screening with coronary artery calcification measurement assessed
by computed tomography (CT) or usual care. We have to await the results of initiatives focused on early detection of cardiovascular disease and consider the cost-effectiveness and effects on outcome, before implementation in clinical practice.

PART II

In the second and third part of this thesis, we focused on predictors of and targets for preservation of cardiac function to optimize secondary prevention after myocardial infarction. Currently used risk scores, such as TIMI and GRACE do not make extensive use of cardiac specific biomarkers. The findings in Chapter 4 reemphasize the value of classical peak creatine kinase-MB (CK-MB) in the prediction of infarct size and LVEF after STEMI treated with primary PCI in a substudy of the Glycometabolic Intervention as Adjunct to Primary Coronary Intervention in the ST-Segment Elevation Myocardial Infarction (GIPS-III) trial. LVEF is guidance to start intensified treatment with aldosterone antagonists after STEMI and is associated with in-hospital morbidity and long-term outcome. Many biomarkers and angiographic factors during STEMI hospitalization have been associated with infarct size and LVEF, but in our study peak CK-MB appeared to be the strongest predictor. On top of the strong predictive value for infarct size and LVEF, provided peak CK-MB cutpoints were associated with mortality. The additional value of other factors was limited as shown by the multivariable models. Though, as showed in the supplement, differentiation between moderate and large infarct size the area under the curve is much higher for the model (0.95) compared to CK-MB alone (0.82), suggesting other parameters start to matter when infarct size is large. The infarct size model consisted of merely biomarkers and angiographic characteristics, namely peak CK-MB, peak Troponin T, myocardial blush grade, Thrombolysis In Myocardial Infarction flow pre-PCI and infarct related artery. The GIPS-III study focused on STEMI treated with primary PCI and excludes patients with diabetes, so it remains unknown if these patient characteristics could further improve the models. Future multimarker studies should not only focus on novel and perhaps more expensive biomarkers during admission, but also cheap and easily measurable CK-MB levels during STEMI hospitalization for adequate risk assessment.

Besides the important prognostic parameter LVEF, novel modes to evaluate left ventricular function are currently emerging. Echocardiographic strain is a relatively new cardiac imaging modality to assess left ventricular function through deformation and GLSS was previously associated with infarct size, left ventricular remodeling and adverse outcome. In Chapter 5 determinants of global longitudinal systolic strain (GLSS) were studied and indeed higher peak CK-MB was associated with impaired GLSS. In our study we showed that cardiac biomarkers, infarct related artery, and angiographic parameters
of myocardial damage were significant determinants of GLSS in STEMI patients included in the GIPS-III trial. Furthermore, GLSS correlated well with LVEF and infarct size. These findings delineate that (extent of) myocardial injury directly affects GLSS and that it is a sensitive measure to detect left ventricular dysfunction after STEMI. Increase in heart rate during echocardiography had a negative effect on GLSS and should be indexed for when applied in clinical practice. Change in GLSS over time was mainly determined by infarct-related artery. When studying the association between strain parameters and outcome in STEMI, a more case-specific strategy would help. As the left anterior descending artery (LAD) provides for the main blood supply of the left ventricle, studying GLSS in the left ventricle makes sense in case LAD was the infarct-related artery. But for other cases, such as right coronary artery infarctions, focus on GLSS in the right ventricle might also be interesting. Moreover, the atrial and ventricular interplay and their combined effect on GLSS deserves to be studied in further depth. In conclusion, GLSS could provide incremental information on the recovery of left ventricular function after STEMI and its value in clinical practice should be studied further in the future.

PART III

To further improve outcome and prevent cardiac dysfunction after myocardial infarction we evaluated several therapies targeted at metabolism, under which metformin, and inflammation. During a period of ischemia, aerobic cell metabolism dependent processes are depleted which leads to activation of necrotic and apoptotic mechanisms. In the reperfusion phase, the generated reactive oxygen species and other pro-inflammatory infiltrates are thought to contribute to the ischemia reperfusion injury. Metformin is thought to be cardioprotective in the setting of myocardial infarction, partly by acting positively on the cell metabolism. In Chapter 6 we reported the effects of 4 months metformin treatment on long-term outcome of STEMI patients included in the GIPS-III trial. The total incidence of MACE during 2-year follow-up was relatively low (4.5%), and did not differ between patients treated with metformin compared to placebo. The study might be underpowered to make a definite conclusion of long-term effects of metformin, although (together with the previous findings of the GIPS-III) it seems unlikely that metformin treatment in STEMI patients without diabetes will be able to further benefit outcome. Several arguments can be brought up about the timing and duration of metformin administration and the fact that the study was not primarily powered to detect changes in MACE. One of my major concerns is that metformin given directly after or during reperfusion could have led to different results. In positive animal experimental studies, metformin was mainly given during or prior to reperfusion. Some of the cardioprotective effects attributed to metformin are improvement of mitochondrial function,
decreased cellular vulnerability under ischemic circumstances, improvement of sodium pump activity associated with decreased intracellular calcium levels, antifibrotic effects and positive effects on glucose utilization in the heart. Considering these mechanisms of action one could conclude that metformin is most effective when given immediately after or even before reperfusion. Furthermore, due to medication already administered before hospital admission in a select group of patients the reperfusion may have well been achieved way before the PCI procedure. Also, the delay in activity caused by the time to maximum concentration of 2.5 hours may have impeded the prevention of myocardial (reperfusion) injury. With a substantial part of patients developing new-onset diabetes, this trial however does highlight the high prevalence of untreated risk factors in patients with myocardial infarction. In the search for new therapies and drug treatments we might forget how important it is to maintain the quality of standard care and to keep promoting obvious ways of secondary prevention such as lifestyle changes. In a study including patients with acute coronary syndrome both quitting smoking, diet and exercise changes were associated with a risk reduction of 41% and 54% respectively on the incidence of future cardiovascular events. Accomplishing these durable interventions with intensified lifestyle changing programs may be an important step in further optimizing secondary prevention after myocardial infarction.

Up until now, no specific therapy targeted at inflammation is practiced in the treatment of myocardial infarction. Inflammation is thought to play an important role in the development of cardiac remodeling after myocardial infarction. Higher concentrations of inflammatory markers are found in myocardial infarction and heart failure and associated with increased risk of cardiac remodeling. To prioritize future interventional trials targeting inflammation we reviewed experimental and clinical studies on cytokine inhibition and studied the effect of interleukin-6 receptor blockade on the preservation of left ventricular function in an experimental ischemia reperfusion model. Chapter 7 gives an overview of different cytokine inhibiting therapies evaluated in the setting of myocardial infarction and heart failure. Many promising results in preclinical studies have been reported, but this did not translate into positive findings in larger clinical trials. The troublesome translation is not exceptional and has been seen previously in other research fields, for instance regenerative therapies with stem cells. Apart from the complexity of cytokine activation and effects of its inhibition, study design was thought to play an important role in the diversity and inconsistency of results. In case of experimental myocardial infarction, two main models, permanent coronary artery ligation and ischemia reperfusion, have been used in the reported studies. However, animal models that align better to the pathologic process of coronary artery disease in human have already been developed, such as models of vulnerable plaque rupture, either spontaneous or induced. Methodically, many other factors such as different strains and different treatment regimens can explain inconsistency of results. Since the publication of the
Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines, one might expect to see improvement in experimental research in the future. Though, in a systematic review in acute lung injury studies evaluating stem cell therapy the completeness of reporting has gone up only slightly in journals endorsing these guidelines\textsuperscript{35}. Animal study registries might overcome this problem by promoting transparency, improving reproducibility of animal studies and preventing publication bias\textsuperscript{36}. Many hurdles are left to take when translating experimental research into clinical practice, but recent initiatives could enlighten this path.

We found of particular interest the interleukin-6 receptor (IL-6R) pathway. Elevated IL-6 levels are seen in myocardial infarction and associated with impaired left ventricular function\textsuperscript{37,38}. Furthermore, Mendelian randomization studies showed that IL-6R signaling played a causal role in the development of coronary artery disease\textsuperscript{39,40}. A non-functional single nucleotide polymorphism of the IL-6R gene showed a similar pattern on inflammatory markers C-reactive protein and fibrinogen as patients treated with tocilizumab, an IL-6R inhibitor used in rheumatoid arthritis\textsuperscript{40}. This polymorphism was also associated with decreased incidence of coronary artery disease, suggesting IL-6R could be a new therapeutic target. Chapter 8 focuses on the inhibition of one of the promising cytokines reported in chapter 7, namely interleukin-6 pathway. In an ischemia reperfusion model, mice received interleukin-6 receptor blockade by MR16-1 just before reperfusion followed by a weekly treatment for a duration of 4 weeks. LVEF was significantly lower in the treatment group compared to the placebo group, but no differences were observed in the remaining functional and histological parameters. Intervening in the interleukin-6 pathway has been shown to be a precarious process and previous studies are incongruent. Contradictory to our findings, a chronic ischemia model with permanent coronary artery ligation showed improvement of fractional shortening, a parameter comparable to LVEF\textsuperscript{41}. Chronic ischemia is believed to trigger a less pronounced inflammatory response than ischemia reperfusion\textsuperscript{42}. The initial inflammatory response in ischemia reperfusion might be beneficial rather than detrimental. Another potential explanation of the study results is that MR16-1 does not selectively block IL-6 transsignaling associated with pro-inflammatory soluble IL-6R, but also blocks classic signaling of IL-6 associated with anti-inflammatory effects via membrane bound IL-6R. A recent trial including patients with non-STEMI concluded that the inflammatory response can be attenuated by IL-6R blockade with Tocilizumab\textsuperscript{43}. Cardiac dysfunction was limited in this study population, as left ventricular function and dimensions were normal at baseline and treatment assignment did not affect LVEF or left ventricular dimensions at 6 months. The effect of attenuating the inflammatory response on cardiac function in patients with larger infarcts is uncertain and this needs to be addressed in future trials studying the effect of IL-6R blockade in the setting of myocardial infarction.
FUTURE PERSPECTIVES

As described in Part I, primary prevention of myocardial infarction and other cardiovascular diseases is currently suboptimal, and new research is essential. Early detection of patients at risk by the population based screening study ROBINSCA, will increase our knowledge on the effects of cardiovascular risk assessment. In this study, 39,000 participants aged between 55 and 74 years old will be stratified to three groups, comparing no further screening with classical risk management and CT calcium scoring. Incidence of cardiovascular disease and mortality will be collected during 5-year follow-up. Another promising research initiative is the UK Biobank imaging study in which 100,000 participants undergo (cardiac) magnetic resonance imaging. For example, this study could give an unique opportunity to gain further insight in cardiac (dys)function prior to development of cardiovascular disease.

In Part II we reemphasized the value of classical peak CK-MB and stated that this marker should be involved in future risk assessment of left ventricular dysfunction and outcome after acute myocardial infarction. At present, use of new biomarkers including micro-RNAs are upcoming and promising. Micro-RNAs were recently discovered as regulators of gene expression. To illustrate, in one study including patients with acute coronary syndrome, micro-RNA-221-3p approached the diagnostic discriminative value of Troponin for myocardial infarction. Prospective studies are currently ongoing on its prognostic, diagnostic and therapeutic value. In the second chapter of Part II, we found that the course of global longitudinal systolic strain in patients myocardial infarction was mainly determined by infarct-related artery. Global longitudinal strain is an upcoming measure of left ventricular dysfunction used in a wide field of cardiology, from cardiotoxicity in cancer patients to assessment of left ventricular function after myocardial infarction. According to one review, global longitudinal strain was superior to echocardiographic LVEF in predicting adverse cardiovascular events in >5,000 patients with myocardial infarction, valvular heart disease and heart failure. Three-dimensional strain in cardiac magnetic resonance imaging is expected to be even more sensitive in detecting cardiac dysfunction after myocardial infarction and we await new studies.

In Part III we reported the 2-year follow-up results of metformin treatment in non-diabetic STEMI patients. No significant effect, neither on LVEF, nor on long-term outcome, was found. One large trial is currently ongoing testing daily metformin treatment in the prevention of cardiovascular events in >11,000 non-diabetic hyperglycemic patients. Apart from metformin, theoretically intervening in the cell metabolism, we also studied IL-6R inhibition, a therapy targeted at inflammation, and the results were rather disappointing. The ASSAIL-MI Trial is currently ongoing and studying treatment with a single dose of tocilizumab in STEMI patients aimed at reducing myocardial injury.
CONCLUSION

In this thesis, we saw that primary prevention, by means of cardiovascular risk factor management, is being underutilized. In the LifeLines Cohort study we found a high burden of cardiovascular disease and a high percentage of untreated cardiovascular risk factors. We also demonstrated that primary prevention had partially failed as illustrated by the high proportion of young and female participants with unrecognized myocardial infarction. Second, we studied predictors of cardiac dysfunction after STEMI. Cardiac biomarkers including peak CK-MB and other markers of myocardial injury were most important in predicting left ventricular function, as measured by LVEF and global longitudinal systolic strain, and outcome. Third, we found no further evidence for cardioprotective effects of metformin and IL-6R inhibition in a clinical and experimental setting of myocardial ischemic injury.
REFERENCES


