The cardiovascular metabolic syndrome
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Summary
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Cardiovascular disease (CVD) is one of the most important causes of morbidity and mortality facing humanity. Such a paradigm shift of disease pattern in the last century has only worsened due to the alarming global prevalence of obesity and type 2 diabetes. In recent years there is increased focus on inflammation as one of the key players in the pathophysiology of these disorders. In addition to these overt risk factors, new research is showing the importance of a constellation of early metabolic abnormalities that include weight gain, insulin resistance, pre-hypertension and a specific pattern of dyslipidemia i.e. the “Metabolic Syndrome”. The complex patho-physiological inter-relationships of these metabolic abnormalities and their immense impact on CVD makes it imperative to treat and prevent “The Cardiovascular Metabolic Syndrome” as an entity. Chapter 1 describes and introduces the syndrome. It also discusses various definitions of the metabolic syndrome and therapeutic and preventive interventions that can be implemented. An effort has been made in this thesis to study the role of the above mentioned risk factors, as they affect various aspects of CVD.

Part I pertains to the impact of obesity. Chapter 2 evaluates the role of obesity and the risk of death after acute myocardial infarction (MI). In the general population, obesity is associated with an increased risk of all-cause mortality. However, the importance of obesity in patients with established coronary heart disease (CHD) is less well defined. As part of the Determinants of Myocardial Infarction Onset Study, we performed a prospective cohort study of 1898 patients hospitalized with a confirmed acute MI, with a median follow-up of 3.8 years. We found that body mass index (BMI) appeared to have a positive, graded relationship with post-MI mortality. Weight reduction can play an effective role in the prevention of mortality in such a high risk population.

A controversial topic of impact of obesity on clinical restenosis after coronary stent placement is assessed in Chapter 3. Obesity has been associated with improved clinical outcomes after percutaneous coronary intervention - “obesity paradox”. We studied 6,186 patients pooled from six major coronary stent clinical trials. Clinical restenosis was defined as target lesion revascularization (TLR) at one year. We showed that after
coronary stenting, the odds of undergoing TLR were higher in patients with obesity class II/III compared with normal-weight patients.

**Part II** consists of studies regarding type 2 Diabetes. In **Chapter 4**, effect of diabetes mellitus and its treatment on ventricular arrhythmias complicating acute MI is evaluated. The Onset Study was conducted in 64 U.S. medical centers and 3882 patients were interviewed after having an acute MI. We showed that compared to patients without diabetes, the risk of ventricular arrhythmias complicating acute MI was lower in patients with diabetes treated with second generation sulfonylureas or insulin, but not in those treated with first generation sulfonylureas or diet alone. This suggests that differences in the mechanism of action of different sulfonylureas may result in clinically relevant differences in arrhythmic risk. Given the various novel medications being used to combat diabetes, it remains important to assess their possible effect on ventricular arrhythmias in patients with diabetes.

There are conflicting reports regarding circadian variation in the onset of acute MI among patients with diabetes mellitus. We therefore, studied in **Chapter 5** the circadian pattern of the incidence of acute MI in patients enrolled in the Onset Study stratified by the presence, type and duration of diabetes. We used a harmonic regression model to evaluate the circadian variation of MI symptom onset in patients with and without diabetes. Patients without diabetes exhibited a prominent morning peak in the incidence of acute MI symptom onset. In contrast, patients with type 1 diabetes and type 2 diabetes e” 5 years had a marked attenuation of the morning peak. Patients with type 2 diabetes diagnosed within the previous 5 years had a pattern of onset of acute MI similar to patients without diabetes. Inconsistency in the observation of such an effect in patients with diabetes in the past may well have been due to difference in the duration of diabetes and thus to the variable extent of underlying autonomic dysfunction.

**Part III** focuses on the role of inflammation, since in recent years it has emerged as an important pathophysiologic link in various chronic disease from atherosclerosis to insulin resistance and diabetes. Inflammation plays a key role in chronic obstructive
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Pulmonary disease (COPD) and asthma. In **Chapter 6** we wanted to determine the relation of COPD and asthma with the development of type 2 diabetes. We tried to answer this question in The Nurses' Health Study, which is a prospective cohort study. From 1988 to 1996, 103,614 female nurses were asked biennially about a physician diagnosis of emphysema, chronic bronchitis, asthma and diabetes. During 8 years of follow-up, we documented a total of 2,959 new cases of type 2 diabetes. The risk of type 2 diabetes was significantly higher for patients with COPD than those without. The asthma results remained non-significant even when we evaluated diabetes risk by duration of asthma exposure. Our findings suggest for the first time, that COPD may be a risk factor for developing type 2 diabetes. Differences in the inflammation and cytokine profile between COPD and asthma might explain why COPD, but not asthma, is associated with increased risk of type 2 diabetes.

Percutaneous coronary interventions (PCI) including coronary stent placement is a frequent therapeutic option in patients with CHD. However, clinical restenosis remains a significant problem. Also, inflammation seems to play a role in the restenotic process. Although increased fibrinogen levels have been shown to be associated with increased risk of CHD, the effect of preprocedural fibrinogen levels on in-stent restenosis is largely unknown. Moreover, the -455 G/A polymorphism of the fibrinogen b-gene is associated with baseline plasma level or acute phase increase of fibrinogen. We tried to answer this question by studying it in The GENetic DEterminants of Restenosis (GENDER) project. A multicenter follow-up study that enrolled 3,146 consecutive patients after successful PCI. A coronary stent was placed in 2,309 patients. As described in **Chapter 7**, The presence of -455G/A polymorphism in the fibrinogen b-gene and preprocedural fibrinogen level is not associated with an increased risk of target vessel revascularization (TVR) or combined endpoint in a patient population with coronary stent placement. Therefore, we showed that these parameters are not important in the stratification of patients at risk for restenosis pre-stenting.

In the same population we studied the role of preprocedural serum levels of Erythrocyte Sedimentation Rates (ESR) and risk of clinical restenosis in patients with coronary stent placement. As described in **Chapter 8**, we show that the pre-procedural
levels of ESR are not associated with clinical restenosis. Our studies warrant future studies measuring inflammatory markers at various time points, including before and after the procedure.

**Part IV** concerns pathophysiology of lipids. Variations in the lipoprotein lipase (LPL)-gene have been implicated in a number of pathophysiological conditions associated with CHD. In chapter 9 we examined the impact of polymorphisms in the LPL-gene on restenosis as defined by TVR in GENDER study. These patients were genotyped for four different LPL-gene polymorphisms. Using multivariable analysis, carriers of the 447Ter allele of the LPL-enzyme showed a lower risk of TVR compared to 447Ser homozygotes. The LPL C/G polymorphism (Ser447Ter) resulting, in a truncation of the two C-terminal amino acids of the mature LPL-protein, appears to be an important protective factor for TVR in man. LPL's role in this process was further established in a mouse model, where LPL-expression was very strongly upregulated in the target arterial wall, suggesting a contribution of this lipolytic enzyme to restenosis. Possibly, LPL Ser447Ter genotyping may lead to better risk stratification and tailored therapy in the prevention of restenosis after PCI.

**Part V** deals with the role of metabolic syndrome in various settings. In chapter 10, we sought to assess whether the higher levels of cardiorespiratory fitness attenuates the levels of inflammation in people with metabolic syndrome. In our study population of 449 asymptomatic men (47±7 yrs), 23% of the participants had the metabolic syndrome. The white blood cell (WBC) count increased with increasing number of risk factors for metabolic syndrome; however there was an inverse relationship with increasing tertiles of fitness. We demonstrated that as compared to individuals with no metabolic risk factors, the WBC count remained significantly higher in men with metabolic syndrome in first tertile and second tertile of cardiorespiratory fitness, respectively. However, in the highest tertile of fitness no increase in level of WBC count was observed with increasing metabolic syndrome risk factors. Our findings suggest that in people with metabolic syndrome an increased level of physical fitness might exert its beneficial effect via attenuating inflammation.
Only limited data are available on the effect of metabolic syndrome on restenosis in patients undergoing PCI. To assess the role of metabolic syndrome in the development of restenosis, we performed an analysis in a population of patients from the GENDER study. This subpopulation of GENDER consisted of 901 patients, 448 of whom (49.7%) had metabolic syndrome. This study as described in Chapter 11, demonstrates that metabolic syndrome is not associated with TVR or the combined end point after PCI. Furthermore, accumulating characteristics of metabolic syndrome were neither associated with increased risk of TVR nor with the combined end point. Therefore, PCI has equal beneficial results in patients with or without metabolic syndrome. This is important information in light of the pandemic proportion of metabolic syndrome facing the medical community.

There is increased risk of CVD due to presence of metabolic syndrome, however there is paucity of data for effect of metabolic syndrome, specifically on cerebrovascular disease (CeVD) and peripheral vascular disease (PVD) in addition to coronary heart disease (CHD). Additionally there are very few studies looking at prevalence of metabolic syndrome in a Dutch population. In chapter 12, we studied 1698 patients with familial hypercholesterolemia from 27 Dutch lipid clinics. In a population of patients with familial hypercholesterolemia, metabolic syndrome was not only associated with increased total CVD and CHD but also with PVD. However there was no association between metabolic syndrome and risk of CeVD. Exploring the impact of metabolic syndrome in different dyslipidemias remains an important area of future research.