Diabetes mellitus type 2 and angina pectoris: novel insights in diagnosis, prognosis and treatment

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Introduction and outline of the thesis

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General introduction

Diabetes mellitus type 2

Diabetes mellitus is a growing epidemic in both industrialized and developing countries, with an expected increase in worldwide prevalence of 35% to approximately 300 million people (5.4% of the entire world’s population) by the year 2030. This is almost exclusively due to an increase in diabetes mellitus type 2, representing more than 90% of all cases. Modernization with decreasing physical activity, increasing consumption of high-caloric diets, and increasing prevalence of obesity play a pivotal role in this growing worldwide problem. However, the expected increase in prevalence of diabetes mellitus is most likely an underestimation of the problem, as half of the patients are thought to be undiagnosed. It is assumed that the typical patient with new-onset type 2 diabetes suffered from latent diabetes for at least 4-7 years before the diagnosis is established.

The pathogenesis of diabetes mellitus type 2 is complex and involves the interaction of both genetic and environmental factors. A number of environmental factors has been shown to play a pivotal role in the development of the disease, particularly physical inactivity and a sedentary lifestyle in combination with excessive caloric intake, leading to obesity. Furthermore, demographic factors such as ethnicity, gender and age, as well as pregnancy-related determinants play a role in the development of diabetes mellitus type 2. The precise interaction between these genetic and environmental factors resulting in overt type 2 diabetes mellitus is unknown. However, there is an emerging consensus that the common forms of diabetes mellitus type 2 are due to a combination of insulin resistance and abnormal insulin secretion. The clinical presentation is heterogeneous, with a wide range in age of onset, degree of obesity and severity of associated hyperglycaemia.

Type 2 diabetic patients consistently demonstrate three key abnormalities: resistance to the action of insulin in peripheral tissues, particularly muscle and fat but also liver; impaired or defective insulin secretion, particularly in response to a glucose stimulus; and increased glucose production by the liver. The pancreatic beta cell is unable to adapt to the reductions in insulin sensitivity that occur over lifetime. Pregnancy, sedentary lifestyle and overeating leading to weight gain are contributing factors determining the secretory burden of the beta cell. Superimposed on a genetic predisposition leading to beta cell failure.
Vascular complications in patients with diabetes mellitus type 2

Diabetes mellitus is associated with both invalidating micro- and macrovascular complications. Microvascular complications include: diabetic retinopathy, which is the leading cause of blindness in patients between 20 and 74 years of age; diabetic renal disease, which is the major cause of end stage renal disease; diabetic peripheral neuropathy, responsible for 50-75% of non-traumatic limb amputations; and autonomic dysfunction with sexual, motor, and bladder dysfunction and cardiac manifestations including hypotension, syncope, resting tachycardia. Furthermore, patients with diabetes mellitus are at a particularly high risk for macrovascular complications such as cardiovascular, cerebrovascular and peripheral artery disease.

The increased risk of cardiovascular disease in diabetes mellitus can be linked in part to the fact that a clustering of different cardiovascular risk factors, as obesity, dyslipidemia and hypertension is more often found in these patients. Approximately 80% of type 2 diabetic patients are overweight, with almost half of these patients meeting the criteria of severe obesity (>30kg/m²). Obesity is directly associated with the development of insulin resistance, glucose intolerance and diabetes. Furthermore, abnormalities in the lipid profile are common in diabetics, developing concomitantly with the failure of insulin activity. This leads to a release of free fatty acids from adipose tissue, increased delivery of these acids to the liver and increased hepatic synthesis of lipoproteins, resulting in a pro-atherogenic lipid profile consisting of small dense LDL-particles, low HDL concentrations and high levels of triglycerides. Moreover, up to 50% of diabetic patients have hypertension and associated nephropathy and proteinuria is common. Finally, cerebral and cardiovascular disease and other diabetic complications such as renal insufficiency add to the worse prognosis.

Besides the co-existence of cardiovascular risk factors and co-morbidity, patients with type 2 diabetes mellitus have an early development of abnormal endothelial dysfunction, platelet hyperactivity and impaired fibrinolysis with a tendency for thrombosis and inflammation. This leads to early development of aggressive atherosclerosis and adverse arterial remodelling. The alterations in vasoconstriction, inflammation, and thrombosis collectively further create a dysfunctional endothelium and contribute to the microvascular and macrovascular complications seen in diabetics. This results in a 2-4 times increase in cardiovascular morbidity compared with non-diabetic patients, and a 70% cardiac mortality rate. Moreover, diabetics have a higher rate of multi-vessel disease, a worse outcome after myocardial infarction, with higher rates of mortality, re-infarction, and heart failure. Finally, after revascularization, clinical outcome is worse with longer hospitalizations, more repeated revascularizations and...
increased cardiovascular morbidity and mortality\textsuperscript{22, 23}. Based on these findings and previous epidemiological studies, European and American consensus opinions consider diabetes as a coronary risk equivalent, that is as conferring the same risk of myocardial infarction as established coronary heart disease\textsuperscript{24, 25}. Moreover, diabetes mellitus is a common finding in patients presenting with both stable or unstable coronary syndromes. Bartnik et al. reported that at presentation at the department of Cardiology, 30\% of patients presenting with stable or unstable angina pectoris had known diabetes mellitus, and of those without diabetes, 14\% had newly detected diabetes and 32\% had newly detected impaired glucose tolerance. Of the total population of patients, only a minority of 32\% of patients had a normal glucose regulation\textsuperscript{26}. Impaired glucose tolerance and to a lesser extent impaired fasting glucose are both associated with an increased risk of coronary artery disease. The absolute risk of cardiovascular morbidity and mortality is approximately doubled in patients with impaired glucose tolerance relative to patients without abnormalities in glucose metabolism\textsuperscript{27, 28}. Improvements in medical treatment of cardiovascular disease and in the reduction of cardiac risk factors have resulted in a decline of cardiac mortality in the general population. However, this decline in cardiac mortality is much smaller in diabetic patients, indicating that these patients have not benefited to the same extent as non-diabetic patients\textsuperscript{18}. In fact, with the increasing prevalence of diabetes and the smaller decline in cardiac mortality, it is likely that diabetes becomes an increasingly important factor in cardiac mortality and morbidity\textsuperscript{18}. Based on these findings, diabetes mellitus and its associated vascular complications, produce a substantial impact on public health care resources\textsuperscript{29}. Therefore, risk assessment and early diagnosis of coronary artery disease is warranted to install adequate therapy in order to reduce the cardiovascular complications in these patients.

**Diagnosis and prognosis of coronary artery disease in patients with diabetes mellitus**

Early adequate diagnosis of coronary artery disease is a prerequisite for well-timed risk stratification and installment of treatment. Unfortunately patients with diabetes mellitus type 2 have an altered presentation of myocardial ischemic pain due to autonomic dysfunction. Approximately 20-30\% of diabetic patients with myocardial ischemia have no symptoms at all\textsuperscript{30}. The presence of silent ischemia is associated with a worse prognosis in these diabetics\textsuperscript{31}. In spite of this, current American College of Cardiology/American Heart Association guidelines on exercise testing do not
specifically address the diagnostic and prognostic utility of exercise ECG testing among diabetic patients, and in particular, asymptomatic diabetic patients. Fortunately, a recent joint European Society of Cardiology (ESC)/ European Association for the Study on Diabetes (EASD) task force has been formed and they recommend a screening for coronary artery disease and myocardial ischemia in diabetic patients, not only with but also without anginal complaints, to install an appropriate treatment. A detailed description however, regarding the frequency of testing and the choice of test is not provided in these ESC/EASD guidelines.

Several non-invasive tests are available for the detection of coronary artery disease. First of all the exercise ECG testing remains a well-established, inexpensive test available to assist clinicians in the diagnosis and prognosis of coronary artery disease in general and also in diabetic patients. However, it has limited diagnostic power: the sensitivity and specificity of this test are relatively low although parameters including cardio-respiratory fitness and heart rate recovery after exercise appear to offer important information, particularly in diabetic patients with autonomic dysfunction. There is no convincing evidence to recommend routine screening of asymptomatic diabetic patients with an exercise ECG test.

Non-invasive imaging techniques are also available for detection and diagnosis of coronary artery disease. The functional tests enable the assessment of myocardial perfusion to document myocardial ischemia and allow integrated assessment of function and perfusion at rest and after exercise. These functional techniques include single photon emission computed tomography (SPECT) or positron emission tomography (PET), first-pass perfusion imaging with magnetic resonance imaging (MRI), and myocardial contrast echocardiography. Non-invasive imaging techniques available to assess the presence and extent of atherosclerosis by direct visualization of the coronary arteries include multislice computed tomography (MSCT), electron beam computed tomography (EBCT), or MRI. Calcification of the coronary artery can be assessed by a calcium score using MSCT or EBCT. The latter techniques do not provide integrated information on function and perfusion at rest and after exercise. The diagnostic accuracy of these functional and anatomical imaging tests in patients with diabetes is rather similar to patient without diabetes.

An invasive diagnostic test, and the “gold standard” for detection of coronary artery disease remains coronary angiography (CAG) by which the degree of luminal narrowing can be quantified precisely. This is however, an invasive and expensive procedure with a small but definite risk for complications. Moreover coronary angiography is hampered by the lack of information on hemodynamic severity of a luminal narrowing.
Prognostic data are widely available for the nuclear techniques (SPECT) and stress echocardiography, and recently information on the prognostic value of MSCT and coronary artery calcium scoring has become available \(^{35-37}\). In general, patients with normal test results have an excellent prognosis. However, some studies suggest that annual cardiac event rates are higher in diabetics with a normal test compared to non-diabetics \(^{38-41}\). Furthermore, there is discussion on possible differences in the “warranty” period of a normal perfusion scan or stress echo between diabetics and non-diabetics. It is suggested that in diabetics the maximum period is 2 years, and therefore, these patients may be in need of repeat testing after 2 years \(^{39,42}\). The functional imaging modalities are widely available and have been subject of multiple studies. Studies on myocardial perfusion scintigraphy with SPECT are widely available supporting its clinical usefulness in diabetic populations for diagnostic and prognostic purposes. On the other hand, modalities for anatomical imaging are now becoming available and these new tests might provide information on the development of atherosclerosis at an earlier stage. Integration of these two imaging modalities may provide optimal information for the management of the diabetic patients with suspected or known coronary artery disease.

**Diagnostic biomarkers in patients with diabetes mellitus and coronary artery disease**

Other novel diagnostic or prognostic tools, such as inflammatory markers have been studied prospectively in patients with stable angina pectoris and some studies focused on their predictive value in patients with diabetes mellitus. The most thoroughly investigated marker is high sensitive C-reactive protein (hs-CRP) which is an independent predictor of cardiovascular risk among healthy people, in patients with acute chest pain as well as in diabetics with stable and unstable anginal complaints \(^{43-46}\). Furthermore, patients with stable angina pectoris with persistently high levels of hs-CRP (above 3mg/L) are at an increased risk of adverse cardiovascular events \(^{47}\). Levels of von Willebrand factor, cell adhesion molecules, fibrinogen and PAI-1 are also associated with diabetes mellitus and are thought to be independent predictors of cardiovascular events \(^{48,49}\).

**Treatment of coronary artery disease in patients with diabetes mellitus**

When the diagnosis coronary artery disease is overt, all patients should receive appropriate medical treatment. Moreover, life style changes and patient education (i.e. weight loss and cessation of smoking) are important contributors in optimal
conservative management. Coronary revascularization is in general indicated when anginal symptoms can not be adequately controlled by medical treatment.

**Medical treatment**

Management of dyslipidemia

Diabetic patients typically have dyslipidemia characterized by elevated triglycerides, small dense LDL particles and reduced levels of HDL. Because abdominal adiposity is strongly associated with dyslipidemia, lifestyle modification is the first measure in the treatment of dyslipidemia. Subgroup analyses of virtually all landmark intervention studies on statin therapy have shown that lipid management with statins is effective in reducing cardiovascular risk in type 2 diabetics. The Heart Protection study demonstrated a 27% relative risk reduction for every 1mmol/l decrease in LDL-cholesterol in the diabetic subgroup. Lowering LDL cholesterol reduced risk of cardiovascular complications, irrespective of the baseline levels of LDL, HDL and triglyceride levels. Recent guidelines from the American Diabetes Association (ADA) suggest statin therapy in all type 2 diabetics without cardiovascular disease but with total cholesterol above 3.5mmol/L, aiming at a 30-40% reduction in LDL cholesterol. Whether to start statin therapy in diabetics with LDL-levels below 2.6mmol/L remains unclear. For diabetics with known cardiovascular disease, recommended treatment goals are for total cholesterol <4.5mmol/L and LDL cholesterol <2.5mmol/L, while it is recommended to reduce the LDL-cholesterol even further to 1.8mmol/L in high risk populations. Although the effects of fibrates on triglyceride levels are well known, this therapy is only recommended in patients with hypertriglyceridemia who are already on maximum dose of statin therapy. However, one must bear in mind that complications such as rhabdomyolysis may occur more often. Finally, fibrates also slightly increase the concentration of HDL, as does nicotinic acid, the latter does however have several side-effects. At the moment studies are conducted to investigate the positive effect of cholesterol ester transfer protein inhibitors on HDL concentrations. Diabetics may especially benefit from these new drugs, for they are known to have low levels of HDL. However, although the first results are promising, a large clinical trial observed an increased risk of mortality and morbidity due to off-target toxic effects, in patients receiving Torcetrapib. Other studies with Anacetrapib and Dalcetrapib, CETP inhibitors with a different molecular structure, are still in progress.
Management of hypertension

Hypertension is three times more common in type 2 diabetic patients, and it enhances cardiovascular risk in diabetic patients. Every 10 mmHg increase in systolic pressure is associated with an increase in risk for myocardial infarction or death of 11-15%. The UKPDS study revealed that intensive blood pressure-lowering is associated with a reduction of cardiovascular complications and renal failure. The recommended blood pressure target in diabetics is below 130/80 mmHg and even lower in diabetics with nephropathy. A combination of drugs is, in general, most likely required to achieve a satisfactory blood pressure lowering. In general, all types of blood pressure-lowering drugs reduce cardiovascular events, and therefore, it is of less importance which drug or combination of drugs is chosen. However, it appears that blockade of the renin-angiotensin-aldosterone system is of particular value in diabetic patients as these specific drugs prevent or retard occurrence of micro-albuminuria and reduce incidence of diabetes mellitus, independent of blood pressure lowering effects. Based on these findings it is recommended that an ACE-inhibitor should therefore be prescribed to all diabetic patients with coronary artery disease, independent of its effect on blood pressure.

Anti-platelet and anti-thrombotic treatment

Type 2 diabetics have an increased risk of prothrombotic complications. Platelet adhesion and aggregation are abnormal in diabetics. Platelets of diabetics are larger, have an increased number of glycoprotein IIb/IIIa receptors and are prone to aggregate more frequently when stimulated. In addition platelets of diabetics are more sensitive to tromboxane A2 and adenosinediphosphate (ADP). Furthermore, elevated levels of coagulation factors such as von Willebrand factor, factor VII, factor VIII, fibrinogen and PAI-1 are present in diabetic patients. Aspirin inhibits tromboxane A2 and subsequently platelet aggregation. Furthermore, it inhibits smooth muscle cell proliferation and has an endothelial stabilizing effect with modest anticoagulant activity. Although evidence of the assumed positive effects of aspirin in the primary prevention of coronary artery disease in type 2 diabetics is lacking, American guidelines suggest starting aspirin therapy in all type 2 diabetic patients with an increased cardiovascular risk (i.e. with multiple cardiac risk factors, or above 40 years of age). Furthermore aspirin should be started in diabetics with a history of peripheral, cerebral or cardiovascular disease, and/or anginal complaints. If aspirin is contra-indicated, Clopidogrel, an ADP-antagonist can be started. Furthermore the combination of these two anti-platelet drugs is favourable in patients with acute coronary syndromes and this combination should therefore be considered in diabetic
patients with unstable angina pectoris\textsuperscript{58}. Finally, intravenously administered GPIIb/IIIa receptor inhibitors are powerful antiplatelet agents and these agents are efficient in reducing procedure-related complications as well as long-term cardiovascular complications in diabetics undergoing percutaneous interventions\textsuperscript{56, 59, 60}.

**Invasive treatment**

Revascularization

Coronary revascularization, both percutaneous coronary interventions (PCI) and coronary artery bypass-grafting (CABG), plays an important role in the treatment of anginal symptoms in diabetics. Approximately 25\% of all coronary revascularizations in the United States of America are performed in diabetic patients. Irrespective of the type of revascularization diabetic patients have worse outcome compared to patients without diabetes\textsuperscript{61}. Diabetics undergoing CABG have a decreased short- and long-term survival after the procedure and exhibit more complications such as wound infections, mediastinitis and delayed healing in general, particularly among those treated with insulin. Diabetics undergoing PCI have a lower survival rate and an increased risk of in-hospital CABG, stent thrombosis and higher rates of repeat revascularization, primarily due to target-vessel restenosis\textsuperscript{62-65}.

The anatomical patterns of CAD in diabetic patients may influence their prognosis and response to revascularization: they more frequently have left main or diffuse multi-vessel disease, including more completely obstructed segments\textsuperscript{66-69}. Furthermore, the atherosclerotic plaque of diabetics is lipid-rich and more prone to rupture, especially in unstable angina. Finally, diabetics exhibit more fissured plaques and intracoronary thrombi. It is suggested that diabetic patients have an impaired ability to develop coronary collateral vessels, and coronary arteries of diabetics less often undergo a favourable form of remodelling (i.e. an early compensatory enlargement at atherosclerotic sites to maintain luminal area and flow). In addition to the anatomical patterns that influence outcome and progression, metabolic and biological factors related to inflammation, endothelial dysfunction, pro-thrombotic state and restenosis contribute to a worse prognosis after PCI\textsuperscript{70}.

The choice between PCI and CABG in patients with diabetes mellitus remains controversial. The majority of studies addressing this problem were performed before the current era of stents and adjunctive therapy, and only included small subgroups of diabetic patients. Based on one of these studies, the BARI trial, it was assumed that CABG was the treatment of choice for diabetics. However this assumption was not confirmed by data from the BARI registry\textsuperscript{71, 72}. Sub-studies of randomized studies
conducted in the stent era found no difference in survival between diabetics treated with CABG or with PCI, but there was an increased rate of repeated revascularization in those patients undergoing PCI. With the development of novel devices (i.e. drug-eluting stents) and medication, outcome after PCI has improved in all patients. It seems prudent to consider CABG with LIMA grafting in diabetic patients who have severe multi-vessel disease and to consider angioplasty in selected patients who have more discrete and less severe disease. Two randomized trials are ongoing, addressing the question whether CABG or PCI is the choice of revascularization in diabetic patients with multivessel disease.

It remains unclear whether an early-invasive treatment reduces the number of cardiac complications and improves prognosis in diabetic patients with stable anginal complaints. This has been analyzed in the MERIDIAN trial and the BARI-2D trial. The results of the former are described in this thesis; the results of the BARI-2D trial are expected to be published in the near future. The current guidelines on percutaneous coronary intervention state that the majority of non-diabetic patients with stable coronary artery disease can be treated medically for their complaints. These guidelines were reinforced by the findings of the recently published COURAGE trial. As yet, it is advised to treat diabetics and non-diabetics similarly for their anginal complaints.
Outline of this thesis

According to the current American and European guidelines for percutaneous coronary intervention, the majority of patients with only mild anginal symptoms (Canadian Cardiovascular Society (CCS) class I-II/IV) can be treated medically for their complaints. However, whether these recommendations apply to patients with diabetes mellitus remains unclear. We therefore conducted a prospective randomized multicenter trial, the Multicenter trial of Elective Revascularization In patients with DIabetes mellitus and mild ANginal symptoms (MERIDIAN) trial to determine whether patients with diabetes mellitus type 2, mild anginal symptoms and documented myocardial ischemia would benefit from an optimized early invasive treatment (with drug-eluting stents and GPIIb/IIIa receptor inhibitors, when indicated) compared to an optimized continued pharmacological treatment.

This thesis focuses on different diagnostic and prognostic aspects of type 2 diabetic patients with mild, stable angina pectoris, and on the treatment of both stable and unstable coronary syndromes in this patient category.

Part I:

diagnostic and prognostic aspects of myocardial perfusion scintigraphy in diabetic patients with stable angina pectoris

Part I focuses on the diagnostic and prognostic value of myocardial perfusion scintigraphy (MPS) in diabetic patients with stable and mild complaints of angina pectoris, who were eligible for inclusion in the MERIDIAN trial. Chapter 2 shows the prevalence and predictors of reversible myocardial perfusion defects in diabetic patients with stable, mild anginal complaints, whereas Chapter 3 describes the prognostic value of these perfusion defects on the prediction of cardiac events.

Part II:

diagnostic aspect of the use of biomarkers in diabetic patients with stable angina pectoris

Part II describes the relation of different bio-markers for endothelial dysfunction (myeloperoxidase), left ventricular wall stress (NT-pro-BNP) and hemostasis (vWF,
d-dimer, prothrombin fragment 1+2 and thrombin activatable fibrinolysis inhibitor) to the presence of myocardial ischemia on MPS in the diabetic patients eligible for inclusion in the MERIDIAN trial. Chapter 4 emphasizes on the association between myeloperoxidase and diabetes mellitus and Chapter 5 investigates the predictive value of this marker for the presence of myocardial ischemia in diabetic patients with mild anginal symptoms. In Chapter 6 the predictive value of NT-pro-BNP for myocardial ischemia is described. In Chapter 7 the use of homeostasis-markers in the detection of myocardial ischemia in type 2 diabetic patients with mild anginal symptoms is analyzed.

Part III:

therapeutic observations in diabetic patients with stable and unstable coronary syndromes

Part III of this thesis describes different aspects of the treatment of stable and unstable coronary syndromes in patients with diabetes mellitus. Chapter 8 focuses on the results of the MERIDIAN trial, investigating the value of invasive treatment in diabetic patients with mild stable angina pectoris. Chapter 9 describes the one-year mortality rates of diabetic patients presenting with acute ST-elevation myocardial infarction, treated with primary PCI. Furthermore, the impact of preadmission treatment with oral anti-diabetic medication or insulin was analyzed. Chapter 10 depicts the effects of a subgroup analysis of the diabetic patients in the IDEAL study, Incremental Decrease in Endpoints through Aggressive Lipid Lowering trial, which was designed to investigate the efficacy and safety of aggressive lipid lowering therapy compared to usual-dose statin therapy in patients with previous myocardial infarction.
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