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

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Summary and conclusions

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Summary and conclusions

The prevalence of type 2 diabetes mellitus and disease related complications are expected to increase dramatically in the upcoming decennia. The significance of diabetes on cardiovascular morbidity and mortality makes it imperative to install adequate therapy to prevent or reduce cardiovascular events (i.e. myocardial infarction, myocardial revascularization and cardiac death). European and American consensus opinions considered diabetes as a coronary risk equivalent, that is, comparable to a patient without diabetes mellitus but who has experienced a myocardial infarction. Furthermore, overt or latent diabetes mellitus affects almost two-third of patients with stable or unstable angina pectoris. Both forms of an abnormal glucose metabolism are associated with an increased risk of coronary artery disease. Therefore, early recognition of diabetic patients with coronary artery disease is essential to install preventive therapeutic options in time. However, patients with diabetes mellitus type 2 have a decreased awareness and an altered presentation of angina symptoms, resulting in a delay in presentation and worse prognosis. Furthermore, invasive coronary interventions for the treatment of both stable and unstable anginal complaints are less effective in diabetics compared with non-diabetics; both with regard to in- and out of hospital cardiac complications.

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

Part I: diagnosticis and prognostic aspects of myocardial perfusion scintigraphy in diabetic patients with stable angina pectoris

The first part of this thesis concerns the diagnostic and prognostic value of myocardial perfusion scintigraphy (MPS) in diabetic patients with mild and stable anginal complaints. Numerous studies on myocardial perfusion scintigraphy have been performed in diabetic patients. However, there is limited information available on the prognostic and diagnostic value of this test in type 2 diabetics with mild and stable anginal complaints. We therefore analyzed the results of MPS in these diabetic patients screened for inclusion in the MERIDIAN trial (chapter 8). In Chapter 2 the prevalence of myocardial ischemia as assessed with MPS is described and the clinical variables predictive of myocardial ischemia are presented. Approximately half (47%) of the diabetic patients with mild and stable angina pectoris showed reversible perfusion defects on perfusion scintigraphy, indicative for myocardial ischemia. Independent predictors for these reversible perfusion defects were male gender, multiple anti-anginal medication...
and previous myocardial infarction without a previous coronary revascularization were. In contrast, the use of statin therapy was negatively associated with these reversible perfusion defects on MPS. In Chapter 3 the severity of these abnormalities was related to the occurrence of future cardiac events. Type 2 diabetics with severe reversible perfusion defects on MPS had a 3-6 times higher risk of cardiac death and non-fatal MI (annual event rate 5.8%) compared to patients with a normal (annual rate 0.8%) or with only moderate myocardial ischemia (annual event rate 1.5%).

Part II: additive diagnostic aspects of the use value of biomarkers in diabetic patients with stable angina pectoris

In Part II we set out to determine whether bio-markers related to endothelial dysfunction, left ventricular wall stress and hemostasis were related to myocardial ischemia as assessed with MPS. We therefore analyzed the available blood samples of all patients screened for inclusion in the MERIDIAN trial. Patients with diabetes mellitus type 2 had mildly increased levels of myeloperoxidase, which is an enzymatic marker of endothelial dysfunction, as compared to non-diabetic patients with similar mild anginal complaints (Chapter 4). Based on this association, we speculated that myeloperoxidase plays a role in the accelerated progression of atherosclerosis seen in diabetics. Therefore we determined the levels of myeloperoxidase in relation to the presence of perfusion abnormalities on MPS. However, as described in Chapter 5, myeloperoxidase is of no value in the prediction of myocardial perfusion abnormalities in type 2 diabetic patients with stable anginal complaints. An interesting finding was the positive correlation of high levels of myeloperoxidase with a short duration of diabetes and insulin independency. These findings suggest that myeloperoxidase is related to the earlier phases of impaired glucose metabolism, in which hyperinsulinemia and insulin resistance are present. This is in line with the notion that hyperinsulinemia, and not hyperglycemia, is a contributing factor producing damage to the endothelium and acceleration of atherosclerosis.

The neurohormone NT-pro-BNP is released in response to increased left ventricular wall stress and is a well known prognostic biomarker in patients with heart failure. However, it has been suggested that this neurohormone is also associated with stress induced myocardial ischemia. In Chapter 6, this possible association was investigated in patients with diabetes mellitus type 2. The findings showed that increased levels of NT-pro-BNP above 180pg/ml are independent, albeit moderate, predictors of myocardial ischemia in patients with type 2 diabetes mellitus and mild, stable anginal complaints.
Finally, based on the hypothesis that a prothrombotic state in diabetics contributes to the pathogenesis of coronary artery disease, the association between markers of hemostasis and myocardial perfusion abnormalities were investigated (Chapter 7). Diabetics do exhibit a procoagulant state as demonstrated by an increased thrombin generation. The aforementioned hypothesis was only supported by a small increase in the von Willebrand factor (vWF) in those diabetic patients with evidence of myocardial ischemia on MPS. The other investigated markers (d-dimer, prothrombin fragment 1+2 and TAFI) were not significantly different between diabetics with and without myocardial ischemia.

**Part III: therapeutic observations in type 2 diabetic patients with stable and unstable coronary syndromes**

In this final part of the thesis, different aspects of the treatment of diabetic patients with both stable and unstable anginal complaints are described. In Chapter 8 we described the results of the MERIDIAN trial. The aim of this trial was to study the possible benefit of early invasive treatment of myocardial ischemia in type 2 diabetic patients with only mild anginal symptoms and with documented myocardial ischemia. Unfortunately, the study was prematurely terminated because of a low inclusion rate. Although no significant differences could be observed between the two treatment strategies, but the study was underpowered for the objective of the study. The observed annual event rates for the occurrence of all-cause mortality, non-fatal myocardial infarction or hospitalization for unstable angina pectoris, were 6.3% for patients randomized to optimal medical treatment vs. 5.4% for patients randomized to early invasive treatment. This annual event rate of major cardiac events was much lower than anticipated (5.8%). Keeping in mind the low annual event rate, it is conceivable that diabetic patients with stable angina pectoris do not benefit from an early invasive approach. We recommend a combination of lifestyle adjustments, optimal pharmacological therapy and close surveillance of symptoms as a first line of treatment in type 2 diabetic patients.

Invasive coronary interventions are the treatment of choice in patients presenting with ST-segment elevation myocardial infarctions. However, little is known about the long-term prognosis of diabetic patients presenting with ST-elevation myocardial infarctions who have been treated with primary coronary interventions. In Chapter 9 the one year mortality in 174 diabetic and 1130 non-diabetic patients who have undergone a primary coronary intervention is described. Secondly, the impact of previously installed anti-diabetic medication on outcome in these patients was studied. The diabetic patients were more often female, older and current smokers. Furthermore, diabetics had a
higher prevalence of cardiogenic shock; more often experienced PCI failure and had higher rates of coronary calcifications and multivessel disease. Diabetic patients showed a higher 1-year mortality rate of 17.8% compared with non-diabetic patients (7.2%). Treatment with statin therapy is indicated in all patients with stable angina pectoris. In Chapter 10, we compared the effect of high-dose statin therapy compared with the usual-dose statin therapy in diabetics with a previous myocardial infarction in a sub-analysis of the IDEAL study. No significant reductions of both the primary and the different secondary endpoints were found in these diabetic patients.

General conclusions and clinical implications

In line with this opinion, in the MERIDIAN trial was designed in the late nineties based on the assumption that type 2 diabetics with mild complaints would experience more cardiac complications (i.e. cardiac death, non-fatal myocardial infarctions and hospitalizations for unstable angina pectoris) than their non-diabetic counterparts. Although half of type 2 diabetic patients with mild anginal symptoms had proof of myocardial ischemia on MPS, the annual event rate was much lower than expected at approximately 5.8% a year. Myocardial ischemia in these MPS is a well studied and adequate tool for documentation of myocardial ischemia. Furthermore, this thesis shows that MPS provides prognostic information in these diabetic patients with only stable and mild anginal complaints. Patients without or with moderate reversible perfusion defects have a low annual event rate of cardiac death and myocardial infarction. However, those with more severe reversible perfusion defects have a 3-6 times increased risk of cardiac complications. This thesis further shows that additive diagnostic value of studied bio-markers as studied can not be used as a substitute in the diagnostic work-up of diabetic patients with stable angina pectoris. These biomarkers are of limited value as stand-alone tests. It remains unclear whether an early-invasive treatment reduces the number of cardiac complications and improves prognosis in these diabetic patients. Unfortunately, the randomized MERIDIAN trial did not provide a satisfactory answer to this question because of the low number of enrolled patients. However, the recently published COURAGE trial shows that an early-invasive strategy does not reduce cardiac complications nor does it improve prognosis in patients with stable coronary artery disease. The BARI-2D, will provide a specific answer whether this does or does not apply to patients with diabetes mellitus.
Whatsoever at present, the best treatment strategy for the prevention of cardiovascular complications in diabetics is a combination of lifestyle adjustments, optimal pharmacological therapy and close surveillance of symptoms. An invasive treatment must be considered if medical treatment fails to control anginal complaints. can no longer be controlled with medical treatment alone. As yet, it is advised to treat diabetics and non-diabetics similarly for their anginal complaints.