The effect of statin therapy on vessel wall properties in type 2 diabetes without manifest cardiovascular disease

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Chapter 1

Introduction

INTRODUCTION

Cardiovascular disease (CVD) is the principal cause of mortality in patients with type 2 diabetes mellitus (DM2). CVD was the cause of death in approximately 60 % of the diabetic subjects in the 12 year follow-up in MRFIT[1]. In the 22 year follow-up of NHANES 1, heart disease was the cause of death in 69.5 % of the diabetic subjects[2]. The relative risk of death for diabetic versus non-diabetic subjects is reported to vary between 1.5 and 4 and is highest in women[2,3]. Patients with diabetes but without a prior myocardial infarction have a similar 7- and 18-year incidence of myocardial infarction compared to those with prior myocardial infarction but without diabetes[3-5]. These studies have lead to the expression of diabetes as a "coronary heart disease equivalent". Apart from the higher incidence rates of cardiovascular events, diabetic patients also have a worse outcome after a first myocardial infarction[6].

Before CVD becomes manifest as angina pectoris, myocardial infarction, claudicatio intermittens or stroke, years of progressive atherosclerotic plaque formation may have preceded. Endothelial dysfunction precedes the development of atherosclerotic plaques. The actual cardiovascular event is not always the result of a narrowing arterial lumen caused by progressive plaque formation, but can be the result of an instable plaque rupture where damage to the endothelium triggers a cascade of thrombotic and inflammatory factors. Both endothelial dysfunction, atherosclerotic plaque formation and the process of plaque rupture is enhanced in patients with DM2 and more extensive atherosclerotic lesions are found at a first cardiac event[7]. The underlying mechanisms for the accelerated atherosclerotic process in DM2 are complex and related to hyperglycemia, insulin resistance and coexisting hypertension, dyslipidemia, and obesity. One of the effects of hyperglycemia is increased oxidative stress, hereby impairing endothelial function and beta cell function, so-called "glucose toxicity". Moreover, advanced glycation endproducts are formed with detrimental effects on endothelial function. Visceral obesity results in increased levels of free fatty acids and inhibition of insulin action.This insulin resistance in relation to obesity comprises a complex change towards a more pro-inflammatory and hypercoagulable state. Insulin resistance, high levels of free fatty acids and thereby increased very low density lipoprotein(VLDL) production and impaired VLDL clearance lead to the typical diabetic dyslipidemia: low levels of high density lipoprotein (HDL) cholesterol, high triglycerides and small, dense and therefore atherogenic low density lipoprotein (LDL) particles. LDL cholesterol is an important risk factor for coronary artery disease in DM2[1,8].

With this new insight in the risk factors for the accelerated process of atherosclerosis in DM2, numerous trials have been designed to investigate the effect of risk factor modification on the incidence of CVD in DM2.

In the UKPDS, treatment of hyperglycemia had a modest effect on cardiovascular morbidity and mortality[9,10]. Blood pressure lowering regimens, however, have lead to a 34 % risk

reduction in cardiovascular endpoints in the same UKPDS study[11,12]. Numerous other studies underscore the importance of tight blood pressure control in DM2[13].

In 1994, the first landmark trial with simvastatin, a HydroxyMethylGlutaryl coenzyme A reductase inhibitor (statin), was published[14]. In this study, a 34 % relative risk reduction in major coronary events in patients with a history of myocardial infarction was shown. In the 4S study only 202 patients with diabetes on a total of 4444 were enrolled. In spite of these low numbers, the risk reductions for the diabetic subgroup were even more pronounced compared with non-diabetics with a 55 % versus 32 % relative risk reduction for major coronary events[15]. In the CARE study, an other secondary prevention trial comparing 5 years of pravastatin 40 mg versus placebo, 586 of the 4159 patients had DM2. In this diabetic subgroup, the relative risk reduction in coronary events was 25 % versus 23 % in the non-diabetic group[16]. In the LIPID study [17] the risk reductions in the diabetic subgroup were non-significant.

In two primary prevention studies, the WOSCOPS and the AFCAPS/TexCAPS, the number of diabetic patients was too small to draw conclusions[18,19]; moreover, in AFCAPS/TexCAPS, use of insulin was an exclusion criterion. ALLHAT-LLA and ASCOT-LLA were the lipid lowering arms of primary prevention trials in hypertension. In ALLHAT-LLA no beneficial effect was seen of pravastatin 40 mg in the total and the diabetic subgroup[20], in ASCOT-LLA atorvastatin 10 mg lead to a 36 % risk reduction of major coronary events, leading to a premature termination of this trial arm. There was no significant risk reduction in the subgroup with DM 2[21].

The Heart Protection Study included diabetes as a prespecified subgroup[22]. In this study subjects with coronary artery disease, DM2 or other risk factors were randomized to simvastatin 40 mg or placebo. In the diabetic subgroup the relative risk reduction for first major vascular event was 33 % in primary prevention. The CARDS, published in 2004, has been the only study to investigate the effect of statin therapy in primary prevention in patients with DM2[23]. Included patients had to have at least one additional risk factor (smoking, hypertensiom, albuminuria or retinopathy) for CVD. The trial was prematurely terminated because of a relative risk reduction for major cardiovascular events of 37 %.

The results of these trials have been translated into new guidelines in which strict glycaemic and blood pressure control, and the use of statins is advocated[24]. The LDL target for statin therapy is related to the absolute risk of the diabetic patient. These LDL goals are based on the assumption that the beneficial effect of statin therapy is solely caused by reduction in LDL cholesterol, "lower is better"[25]. The background for these assumptions arises from the PROVE-IT and REVERSAL studies where pravastatin 40 mg was compared to atorvastatin 80 mg in secondary prevention. In both studies, PROVE-IT being a clinical endpoint study and REVERSAL using intravascular ultrasound to measure atheroma volume, atorvastatin 80 mg was superior to the less intensive regimen with pravastatin.

Others question this emphasis on maximal LDL cholesterol reduction as statins also have an effect on markers of inflammation, coagulation, fibrinolysis, immunomodulation and endothelial function independent of lowering of LDL cholesterol[26,27]. These modes of ac-

tions might lead to plaque stabilisation in coronary artery disease, improved left ventricular ejection fraction in nonischemic dilated cardiomyopathy and reduction of stroke incidence shortly after initiation of statin therapy. To date it remains unsolved however, whether these other, nonlipid ("pleiotropic") effects on the vascular wall play an important role in the risk reductions as seen in the clinical trials[28,29].

AIMS AND OUTLINE OF THE THESIS

The present thesis describes a study, designed at a timepoint when no primary prevention trial had yet been performed to investigate the effects of statin therapy on patients with DM2 without manifest CVD. We have performed a randomized, double-blind placebo-controlled trial in 250 DM2 patients without manifest CVD. The aim of the study was to study non-invasively the effect of two year statin therapy on the vessel wall. Chapter 2 describes the technique and the current status of the non-invasive vascular tools used in this thesis, as well as more recent developed techniques.

Our *first* aim was to determine the effect of statin therapy on the progress of atherosclerosis, as measured non-invasively by ultrasonographic measurements of the intima-media thickness (IMT) of the carotid and femoral arteries (Chapter 3)

Our *second* aim was to study the effect of statin therapy on endothelial function as measured non-invasively with flow mediated dilation (FMD) (Chapter 4).

Our *third* aim was to analyse the effect of statin therapy on C-reactive protein (CRP), a marker of the inflammatory process in atherosclerotic plaques (Chapter 5). We further elaborated the role of inflammatory markers in relation to the metabolic syndrome. For this purpose we analyzed the data from the DALI study (Chapter 6). The DALI study was performed to evaluate the efficacy of atorvastatin 10 and 80 mg versus placebo in patients with DM2 and mild dyslipidemia without CVD. Endpoints in the original study were lipid parameters and endothelial function as assessed by FMD[30]. In the present substudy the baseline laboratory parameters for inflammation and hemostasis and the baseline sonographic parameters IMT and FMD were used to assess the impact of the metabolic syndrome and low grade chronic inflammation as assessed by CRP on vascular phenotype in DM2.

As we performed the main study in an area with a large community of Asian Indians from Surinam, we were not surprised that 19% of the included subjects were Asian Indians. As epidemiological data reveal a high and partly unexplained risk of DM2 and CVD in this population[31], we wanted to evaluate conventional risk factors and the above mentioned vascular parameters separately for this population. Therefore, our *fourth* aim was to produce a vascular phenotype of the Asian Indian population (Chapter 7).

Periods of silent myocardial ischemia can precede a cardiac event in DM2, with a possible etiological role for cardiac autonomic neuropathy. Our *fifth* aim was therefore to determine

the prevalence of silent myocardial ischemia in these patients and to evaluate the effect of statin therapy on silent myocardial ischemia (Chapter 8).

In Chapter 9 the results of these studies are discussed and summarized.

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