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

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Chapter 9

Summary and Conclusions

SUMMARY

Cardiovascular disease is the principal cause of mortality in patients with type 2 diabetes mellitus (DM2). Cardiovascular events are preceded by years of endothelial dysfunction, atherosclerotic plaque formation and finally the thrombotic occlusion after rupture of an unstable plaque. Hyperglycemia, insulin resistance and coexisting dyslipidemia, hypertension and obesity are responsible for the enhanced atherosclerotic process in DM2.

The typical dyslipidemia in DM2 consists of low levels of HDL cholesterol, high levels of triglycerides and small, dense, atherogenic LDL particles, where total LDL cholesterol levels are not higher than in the general population. LDL cholesterol has proven to be an important risk factor for coronary artery disease in DM2.

Since 1994, several trials have proven the beneficial effect of HMG-CoA reductase inhibitors (statins) on cardiovascular morbidity and mortality in the setting of secondary prevention and in primary prevention in high-risk patients. These early trials, however, did not include diabetes as a prespecified subgroup. In spite of the lack of randomized trials in DM2, guidelines advocated the use of statins in primary prevention based on the assumption that DM2 is a "coronary heart disease equivalent". In 2004, with the publication of the CARDS study, the beneficial effect of statin therapy in primary prevention, was proven.

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 cardiovascular disease. We have performed a randomized, double-blind placebo-controlled trial in 250 DM2 patients without manifest cardiovascular disease. The aim of the trial was to study non-invasively the effect of two year statin therapy on the vessel wall.

In *Chapter 2* the techniques and current status in DM2 of these non-invasive vascular tools are desciribed. Non-invasive imaging techniques as parameters for atherosclerosis, may help in risk stratification and in implementation of tailored therapy for the individual patient. However, many of these vascular tools have not been validated in diabetic individuals.

Since the introduction in the early 1990's, intima-media thickness (IMT) of the vessel wall, especially of the carotid artery, is used more and more as a surrogate marker for atherosclerotic disease. IMT can be assessed non-invasively using B-mode ultrasound. Ultrasonographic IMT measurements of the *far* wall relate to histological IMT measurements. Carotid IMT is higher in DM2 versus controls, and IMT progression might be higher. In prospective studies, carotid IMT has proven to be a consistent and independent predictor for coronary events and stroke in the general population, but in DM2 only in combination with several other novel risk factors. Intervention studies in non-diabetic individuals with statins have shown that IMT progression can be stopped or even reversed. Intervention studies with lipid lowering regimens in diabetic subjects are sparse.

Flow Mediated Dilation (FMD) of the brachial artery, as first described by Celermajer, is a non-invasive technique for measuring endothelial function. FMD is measured with B-Mode ultrasound or a wall-track system. FMD is impaired in DM2, in some studies already in the prediabetic state. FMD has proven to be predictive for the presence of coronary artery disease and for future cardiovascular events in high-risk populations. There are however no studies on the predictive power of FMD in DM2. Intervention studies with statins in diabetic individuals have shown conflicting results regarding the effect on FMD.

Ambulatory ECG (AECG) can detect silent myocardial ischemia. The prevalence of silent myocardial ischemia in asymptomatic DM2 is reported from 9.1 to 52% and is strongly dependent on method of detection and on the population studied. The frequency of significant coronary artery stenoses in diabetic patients with silent myocardial ischemia varies between 22 and 94 %. Silent myocardial ischemia predicts future coronary events in asymptomatic diabetic subjects, as well as in diabetic patients with documented coronary artery disease. Treatment with beta-blockers or statins resulted in reduced silent myocardial ischemia in patients with coronary artery disease, but studies in DM2 were not performed.

Chapter 3 describes the primary endpoint of the study, the effect of two year statin therapy on IMT in patients with DM2 without manifest cardiovascular diesease. 250 patients were randomized to either 0.4 mg cerivastatin, or placebo daily. In August 2001, when cerivastatin was withdrawn from the market, 0.4 mg cerivastatin was replaced by 20 mg simvastatin, without deblinding the study. The primary endpoint was the change of mean common carotid IMT, as measured by B-mode ultrasound, over 2 years.

Common carotid IMT at baseline was 0.780 mm in the placebo group and 0.763 mm in the statin group and did not change significantly after two years. LDL cholesterol was reduced by 25 % in the statin group and increased by 8% in the placebo group ($p<0.001$). There was no significant difference in IMT change in any carotid segment between the groups. Cardiovascular events occurred in 12 patients in the placebo group and in 2 patients in the statin group ($p=0.006$). We discuss that prognostic tools other than IMT should be explored in this patient group.

Chapter 4 describes the effect of two year statin therapy on FMD in patients with DM2 without manifest cardiovascular disease. The primary endpoint was the change in FMD, measured by B-mode ultrasound, after 2 years.

Determinants of baseline FMD were diabetes duration, common carotid IMT and brachial artery diameter. FMD at baseline was 1.51 % in the placebo group and 1.66 % in the statin group and did not change significantly after two years.

In conclusion, there was no effect of 2 years' statin therapy on FMD in DM2. Statin induced improvement of cardiovascular risk in patients with DM2 may be mediated through other mechanisms than increased NO availability.

Chapter 5 describes the effect of two year statin therapy on C-reactive protein (CRP), a marker of the inflammatory process in atherosclerotic plaques. We evaluated the effect of statin therapy on CRP in 250 patients with DM2 without manifest cardiovascular disease. The primary endpoint was the change in high sensitivity CRP after 2 years. CRP in the statin group was 1.58 mg/L at baseline and 1.69 mg/L at 2 years (p= 0.413), in the placebo group it increased from 2.03 mg/L at baseline to 2.54 mg/L at 2 years (p = 0.058) (p= 0.269 for comparison between the groups). In a high-risk subgroup with the metabolic syndrome (MS) and LDL levels > 2.6 mmol/L (40 % of the cohort) CRP levels increased significantly in the placebo group (from 2.97 mg/L at baseline to 3.99 mg/L at 2 years, p=0.036) in comparison to the statin group (from 2.13 mg/L at baseline to 2.10 mg/L at 2 years, p=0.885) (p=0.042 for comparison between the groups).

In conclusion, there was no effect of two year statin therapy on CRP in patients with DM2 without manifest cardiovascular disease, except in a subgroup with the metabolic syndrome (MS) and LDL > 2.6 mmol/L. We discuss that studies supporting risk stratified therapy in primary prevention in DM2 are needed.

In *Chapter 6* the relationship between CRP and MS is further elaborated by analysing the baseline data of the DALI study. 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 cardiovascular disease. Endpoints in the original study were lipid parameters and endothelial function as assessed by FMD. 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 MS and low grade chronic inflammation as assessed by CRP on vascular phenotype in 62 DM2 patients.

Serum sVCAM, sTM, and tPA levels significantly increased with increasing MS load. IMT also significantly increased from 0.602 ± 0.034 (one MS criterion) to 0.843 ± 0.145 (four MS criteria, p = 0.007). LogCRP significantly correlated with fibrinogen, PAI-1, and IMT. In a multiple regression, model MS and low-grade chronic inflammation have an independent impact on vascular phenotype including IMT in DM2.

A total of 19 % of our original study population of 250 patients were Asian Indians from Surinam. Although Asian Indian patients with DM2 are at high-risk for cardiovascular disease, not all patients develop cardiovascular disease. The vascular phenotype of Asian Indians with DM2 without cardiovascular disease has not been elucidated and may point to protective features. In *Chapter 7* we analyzed the baseline data of our main study to provide an initial description of vascular parameters in Asian Indians compared with Europid Caucasian controls (all with DM2), matched for age and gender. Endpoints of the study were endothelial function as measured by FMD, low-grade systemic inflammation as assessed by CRP and carotid IMT. Asian Indians had longer duration of diabetes, worse glycemic control and more

microangiopathy. Both groups demonstrated marked endothelial dysfunction. CRP levels were similar: 1.7 (4.9) mg/L in Asian Indians and 2.8 (3.6) mg/L in Europid Caucasians. Carotid IMT values were significantly lower in Asian Indians than Europid Caucasians (0.655 mm (0.12) versus 0.711 mm (0.15), p = 0.03). Multiple regression analysis showed that variability in CRP was mainly determined by waist circumference, not by ethnicity. In contrast, ethnicity was a significantly explanatory variable for carotid IMT.
Vascular phenotype of Asian Indians with DM2 without CVD was characterized by endothelial dysfunction and relatively low levels of CRP, comparable to Europid Caucasian controls with DM2. In contrast, lower carotid IMT values were observed in Asian Indians despite longer duration of diabetes and worse metabolic control. We propose that mechanisms slowing its progression may have atheroprotective potential in Asian Indians with DM2.

In *Chapter 8* we aimed to determine the prevalence of silent myocardial ischemia (SMI) and the effect of statin therapy on SMI in DM2 patients without manifest cardiovascular disease.

The primary endpoint was the change in ischemic episodes, duration and burden as measured by 48 hours ambulatory electrocardiography (AECG) over 2 years. At baseline, 47 out of 233 (20%) evaluable AECG's showed evidence of ischemia. After 2 years, there was a trend towards more ischemia in both treatment groups, without significant differences between the changes in ischemic parameters (episodes:p=0.498; duration:p=0.697; burden:p=0.798) in the two treatment groups. Cardiovascular events occurred in 12 patients in the placebo group and in 2 patients in the statin group (p=0.006). There was no relation between these cardiovascular events and the presence of SMI at baseline. In conclusion, SMI occurred in 20 % of DM2 patients without manifest cardiovascular disease. There was no effect of two years' statin therapy on SMI. In contrast, we observed a significantly lower cardiovascular event rate on statin therapy. We discuss here that AECG may not be a proper tool for risk stratification in patients with DM2.

CONCLUSIONS

The present thesis describes the effect of statin therapy on the process of atherosclerosis in patients with DM2 without cardiovascular disease. We used several parameters to assess this process. We found no effect of two year statin therapy on carotid IMT as a reflection of the progress of atherosclerosis. We found no effect on endothelial function as assessed by FMD. The effect of statin therapy on CRP, as a marker for low grade inflammation, was only significant in a high-risk subgroup with the metabolic syndrome and a high LDL cholesterol. There was no effect of two-year statin therapy on the prevalence of silent myocardial ischemia. In spite of these findings, we observed a lower cardiovascular event rate in patients on

statin therapy, which is in line with other clinical trials. Several possible explanations for these findings should be discussed.

First, the vascular tools used were all validated in non-diabetic populations, but the prognostic value of most of them was not validated in patients with DM2. Vessel wall biology in DM 2 is distinct from that of a non-diabetic population and the question arises whether changes in the vessel wall induced by DM2 are reversible by statin therapy. The intimal and medial layers of the vessel wall in DM2 are most likely irreversibly changed by processes such as extracellular matrix glycosylation and media calcification. These changes may resist global regression based on interference with local intravascular cholesterol metabolism. It can be hypothesized that, although statins do not improve NO availability nor the irreversibly changed glycosylated extracellular matrix, it may well have an effect on outcome in DM2 patients by its beneficial influence on plaque vulnerability. This is in line with the perception that most cardiovascular events do not evolve from progressive narrowing of the vessel lumen (as assessed by IMT and silent myocardial ischemia), but from thrombus formation on a ruptured non-obstructing instable plaque. 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.

Second, cerivastatin was withdrawn from the market, at a time when inclusion was completed, resulting in a change from cerivastatin to simvastatin. The reduction in LDL cholesterol with simvastatin 20 mg was slightly lower than that achieved with cerivastatin 0.4 mg. After correcting the change in all described endpoints for duration of cerivastatin treatment however, the results remained unchanged, so we do not believe that this switch has had a major influence on our results.

Third, contrary to the postulated progression of mean IMT per 2 years, in the present study the placebo group did not show any progression in IMT. It could be argued that our patient population has been low-risk. However, we included diabetic patients with a broad range in age and diabetes duration, while their baseline CCA IMT was well comparable to those of patients in other studies. Moreover, the observed rate of first major vascular events in our placebo group is comparable with the diabetic subgroup without prior cardiovascular disease on placebo in the Heart Protection Study. Thus, it seems unlikely that our results have been influenced by any "healthy volunteer" effect.

Implications for clinical practice

The non-invasive vascular tools described in this thesis were not able to detect beneficial effects of statin therapy in DM2 patients. To date, IMT and CRP are frequently used as risk markers for atherosclerosis in the general population. Their prognostic clinical usefullness in patients with DM2 still remains to be established. Recent cholesterol guidelines do not include these risk markers in risk scores. ATP III (Adult Treatment Panel III) uses risk stratification by means of classical risk factors for their recommended LDL goals. The American Diabetes

Association recommends prescribing statins to all patients with DM2 in a primary prevention setting with LDL cholesterol levels > 3.5 mmol/L to achieve a 30 to 40 % reduction in LDL cholesterol. The Joint European Guidelines advocates an LDL goal of < 2.5 mmol/L for all patients with DM2.

Other non-invasive vascular tools, more aimed at detection of plaque characteristics, may have better prognostic value. The use of non-invasive vascular tools in daily practice for risk stratification and tailored therapy warrants further investigation.