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

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Chapter 3

Two year statin therapy does not alter the progression of Intima-Media Thickness in patients with type 2 diabetes mellitus without manifest cardiovascular disease

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ABSTRACT

Objective

Cardiovascular disease (CVD) is the most important cause of mortality in patients with type 2 diabetes mellitus (DM2). We aimed to determine the effect of statin therapy versus placebo on the progression of carotid Intima-Media Thickness (IMT) in DM2 patients without manifest CVD.

Research Design and Methods

A randomized, placebo-controlled, double-blind clinical trial was performed in 250 patients with DM2. Patients were given 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 In August 2001, when cerivastatin was withdrawn from the market, 0.4 mg cerivastatin was replaced by 20 mg simvastatin, without deblinding the study.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.

Results

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. There was no significant difference in IMT change in any carotid segment between the groups. LDL cholesterol was reduced by 25 % in the statin group and increased by 8% in the placebo group ($p<0.001$). Cardiovascular events occurred in 12 patients in the placebo group and in 2 patients in the statin group ($p=0.006$).

Conclusions

There was no effect of 2 years' statin therapy on carotid IMT in DM2. The natural history of IMT in our patients was milder than anticipated. In contrast, we observed a significantly lower cardiovascular event rate on statin therapy. Prognostic tools other than IMT should be explored in this patient group.

INTRODUCTION

Cardiovascular disease (CVD), including cerebrovascular disease, coronary artery disease (CAD), and peripheral vascular disease, is the most important cause of mortality in patients with type 2 diabetes[1]. The severity and progression of atherosclerosis can be assessed non-invasively by ultrasonographic measurements of the intima-media thickness (IMT) in the carotid and femoral arteries. Ultrasonographic IMT measurements of the far wall relate to histological IMT measurements[2]. Carotid IMT correlates with prevalent CVD[3], angiographically proven coronary atherosclerosis[4], and risk factors for CVD, including LDL cholesterol[5,6]. In prospective studies, carotid IMT has proven to be predictive of CVD[7-9], and as a consequence, IMT is increasingly used as an intermediate end point in clinical trials. Mean common carotid IMT in middle- aged subjects without CAD is reported to range from 0.71 to 0.91 mm in diabetic patients vs. 0.66 to 0.74 mm in control subjects[10,11]. In diabetes, IMT is less consistently correlated to classical risk factors such as LDL cholesterol. Importantly, at the time our study was designed, data on the progression and predictive value of IMT in type 2 diabetes were lacking.

During the last 10 years, large clinical trials have demonstrated that HMG-CoA (hydroxy-methylglutaryl coenzyme A) reductase inhibitors (statins) reduce the risk of cardiovascular events in the setting of secondary and primary prevention[12-15]. Subgroup analyses in diabetic patients in several of these studies showed conflicting results[14-16]. However, these trials were not specifically designed for type 2 diabetic patients in the setting of primary prevention. We therefore set out to evaluate the effect of statin therapy versus placebo on the progression of carotid and femoral IMT in type 2 diabetic patients without established CVD.

RESEARCH DESIGN AND METHODS

Patients

Patients were recruited from the departments of internal medicine at two nonacademic teaching hospitals, the Leyenburg Hospital and the Red Cross Hospital, the Hague, the Netherlands. Subjects were eligible for the study if they had been diagnosed with type 2 diabetes for at least 1 year, were aged 30–80 years, and were without a history of CVD (defined as CAD, electrocardiographic criteria for a past myocardial infarction, ischemic stroke, peripheral artery bypass surgery, percutaneous transluminal angioplasty, or amputation because of atherosclerotic disease).

At a screening visit, fasting blood samples were drawn and a resting electrocardiogram performed. Patients with fasting total cholesterol > 6.9 mmol/l or < 4.0 mmol/l, triglycerides > 6.0 mmol/l, creatinine kinase values more than three times and alanine aminotransferase (ALT) more than two times the upper limit of normal, or creatinine clearance < 30 ml/min

were excluded. Any lipid-lowering therapy had to be discontinued 8 weeks before the screening visit. The study was approved by the medical ethics committees of both hospitals and performed in accordance with the Declaration of Helsinki.

Study Objectives

The primary end point of the study was the change in mean IMT of the common carotid artery after 24 months. Secondary end points were the changes in mean and maximum IMT of the carotid bifurcation, internal carotid artery, common femoral artery, and superficial femoral artery and the changes in aggregate carotid IMT (defined as the average of the mean IMT of the three carotid segments), all after 24 months. The change in mean IMT after 12 months was also considered a secondary end point. The following predefined cardiovascular events were evaluated during the study: cardiovascular death, nonfatal myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass graft surgery, nonfatal stroke, peripheral artery bypass graft, percutaneous transluminal angioplasty, or amputation because of atherosclerotic disease.

Study design

After giving written informed consent, 250 patients participated at least 1 week after the screening visit. Patients were randomly assigned to receive 0.4 mg cerivastatin (Bayer, Mijdrecht, the Netherlands) or placebo daily for a period of 2 years. Double-blind study medication was assigned using a predetermined computer- generated randomization scheme with a block size of 10. On 8 August 2001, cerivastatin was withdrawn from the market due to reports of serious morbidity and mortality possibly related to the drug [17]. At that moment, all 250 patients had been included in the study with a mean follow-up of 15.4 months (range 6–23).

All patients were instructed to discontinue the study drug. The study was not unblinded at any time point. No patient had developed myopathy, and creatinine kinase values above five times the upper limit of normal had not been observed. After consultation with independent experts in lipid-lowering treatment studies, it was decided to continue the study. Cerivastatin (0.4 mg) was replaced by simvastatin (20 mg) daily, on the basis of a comparable LDL reduction[18,19]. Both simvastatin and matching placebo tablets (Merck Sharp & Dohme, Haarlem, the Netherlands) were given according to the original allocation. The study was continued 1 month after the discontinuation of cerivastatin. The total use of study medication was kept at 24 months, resulting in the study being prolonged for 1 month.

Follow-up

Patients returned to the study site after a 12-h fast at 3, 6, 12, 18, and 24 months, when blinded lipid and safety measurements (creatinine kinase and ALT) were performed. Carotid IMT was measured at baseline, 12 months, and 24 months. Femoral IMT was performed at baseline and 24 months. Two-year follow-up for clinical events was performed for all 250 patients.

Ultrasound measurements

Ultrasound imaging was performed with an Acuson Aspen scanner with a linear array 7.5-MHz probe. All images were recorded digitally and on a S-VHS videotape for off-line, blinded analysis by an independent core laboratory (Heartcore, Leiden, the Netherlands). During the study, all measurements were performed by the same two certified ultrasonographers.

In the supine position, the left and right carotid arteries, near and far walls, were examined longitudinally at the angle that resulted in an optimal and maximal IMT (while avoiding plaques) for each segment. The segments scanned were the distal 1.0 cm of the common carotid artery, the carotid bifurcation, and the proximal 1.0 cm of the internal carotid artery. The optimal angle was used for follow- up. The same procedure was done for the common femoral artery and superficial femoral artery.

For each segment, three R wave– triggered images were stored. Mean and maximal IMT were measured, when possible, over the entire 1 cm of the vessel segment. The three IMT measurements were averaged. To obtain mean and maximal IMT per vessel segment, far and near wall, left and right values were averaged.

During the first year of the study, a reproducibility investigation was performed for the two ultrasonographers in 16 subjects. For the common carotid artery, interobserver variability (expressed as mean difference ± SD) was 0.0082 ± 0.050 mm and intraobserver variability was 0.0067 ± 0.049 and 0.00036 ± 0.058 mm for the two observers. For the common femoral artery, interobserver variability was 0.039 ± 0.11 mm and intraobserver variability was 0.0085 ± 0.10 and 0.060 mm ± 0.078 mm for the two observers.

Laboratory investigations

All laboratory measurements were performed at the Department of Clinical Chemistry and Hematology of the Leyenburg Hospital, according to ISO 15189 standard procedures.

Statistical analysis

When this study was designed, no data were available on IMT progression in type 2 diabetes. From clinical studies in patients with CAD, we assumed a progression rate of 0.03 mm per 2 years for the common carotid artery IMT. The number of patients needed to detect a difference in mean common carotid artery IMT of 0.04 mm after 2 years (expected SD 0.10) with a power of 80% ($\alpha = 0.05$) was 100 patients in each group. To allow for a 20% drop-out rate, the total number of patients randomized would be 250.

The primary treatment comparison is between placebo and statin therapy in patients completing the study (on-treatment analysis). Changes from baseline within each treatment group were analyzed using Student's paired t test. Comparisons of the effects between the treatment groups were performed using Student's independent samples t test. Mixed-model analysis was used as a sensitivity analysis to assess the influence of missing values on the

results, under the assumption of "missing at random" [20], and to investigate systematic differ-
ences between replications, positions, and between far and near wall.

Stepwise regression techniques were used to investigate the effect on baseline IMT and on
changes in IMT of sex, age, smoking habits, ethnicity, blood pressure, anthropometric param-
eters, and duration of cerivastatin versus simvastatin use. To test the equivalence of 0.4 mg
cerivastatin and 20 mg simvastatin, LDL levels before and after the switch to simvastatin were
compared using Student's paired t test. Correlation between changes in IMT and changes in
lipid levels were evaluated by calculating Pearson's correlation coefficients. The occurrence of
clinical events was expressed as a proportion and evaluated using Chi-squared test or Fisher's
exact test as appropriate. All analyses were two sided with a level of significance of $\alpha = 0.05$.

RESULTS

Of a total of 302 patients screened, 52 did not fulfill the entry criteria. The baseline characteris-
tics of the 250 randomized patients did not differ between the groups and are reported in Table
1. None of the patients had recently been on lipid-lowering therapy.

Of the 250 patients randomized, 68 did not complete the study: 46 in the placebo group
and 22 in the statin group. In 16 patients in the placebo group and in 8 in the statin group, the
only reason for discontinuation was the withdrawal of cerivastatin from the market. Drop-out
rates were slightly lower in the Caucasian group than in the Asian-Indian and other ethnic

Table 1 Baseline Characteristics of 250 Randomized Patients

	Placebo (n=125)	Statin (n=125)
Male sex	57 (46)	61 (49)
Age (years)	58.2 ± 11.4	58.8 ±11.3
Ethnicity:		
Caucasian	86 (69)	83 (66)
Asian-Indian	20 (16)	28 (22)
other	19 (15)	14 (11)
BMI (kg/m²)	31.0 ± 6.0	31.0 ± 6.3
Waist-to-hip ratio	0.99 ± 0.09	0.98 ± 0.08
Current smoker	33 (26)	28 (22)
Hypertension	66 (53)	60 (48)
Diabetes duration (years)*	7 ± 8	6 ± 7
Insulin use	69 (55)	62 (50)
HbA1c (%)	7.60 ± 1.48	7.53 ± 1.10
Microalbuminuria†	19 (15)	24 (19)

Data are means ± SD or n (%);
*Median values ± SD
† Men, > 2.5 g/mol creatinine;women > 3.5 g/mol creatinine

groups (22 vs. 35%, respectively, 42%, p = 0.02). The other baseline characteristics of the 182 patients who completed the study did not differ from the 68 drop outs (data not shown).

Overall compliance, as assessed by pill counting, was 97% and was equal in the statin and placebo groups. Compliance was not reduced after the switch to simvastatin.

Lipids

LDL cholesterol was reduced by 25% in the statin group and increased by 8% in the placebo group (P < 0.001), and changes in HDL cholesterol and triglycerides were not significantly different between the groups (Table 2). Average LDL cholesterol levels were higher after the switch to simvastatin (2.34 before vs. 2.56 mmol/l after the switch, p < 0.001).

Table 2 Plasma lipid and lipoprotein concentrations

	Placebo (n=79)			Statin(n=103)			
	baseline	2 year	p	baseline	2 year	p	p*
TC (mmol/l)	5.60 ± 0.77	5.74 ± 0.93	0.058	5.49 ± 0.72	4.49 ± 1.01	<0.001	<0.001
LDL-c(mmol/l)	3.55 ± 0.71	3.78 ± 0.81	0.003	3.44 ± 0.71	2.58 ± 0.95	<0.001	<0.001
HDL-c(mmol/l)	1.21 ± 0.37	1.22 ± 0.38	0.963	1.23 ± 0.39	1.20 ± 0.36	0.144	0.284
TG (mmol/l)	1.88 ± 0.79	1.72 ± 1.22	0.206	1.82 ± 0.97	1.60 ± 1.38	0.043	0.371
ApoB100 (mg/l)	1.15 ± 0.23	1.11 ± 0.24	0.094	1.10 ± 0.21	0.84 ± 0.26	<0.001	<0.001

Data are means ± SD
* p value for difference in percent change between placebo and statin group
TC = total cholesterol; LDL-c = LDL cholesterol; HDL-c =HDL cholesterol; TG = triglycerides. Apo = Apolipoprotein
To convert to mg/dl: cholesterol: multiply by 38.6; triglycerides: multiply by 88.5

IMT

Baseline mean IMT's were not significantly different between the groups. Common carotid artery IMT in the placebo group was 0.780 ± 0.129 mm at baseline and 0.774 ± 0.124 mm at 2 years (p = 0.50), and in the statin group, it was 0.763 ± 0.124 mm at baseline and 0.765 ± 0.116 mm at 2 years (p = 0.78) (Table 3). There was no significant difference between the change in IMT in the placebo and statin groups (mean difference - 0.0075 mm [95% CI -0.0281 to 0.0132 mm], p = 0.48). After 2 years, the mean changes in IMT of the other segments were also not significantly different between the groups and compared with baseline. This was also observed for the changes in maximal IMT (data not shown). Finally, the changes in mean common carotid artery IMT after 1 year were equal in both groups (-0.0155 mm in the placebo group vs. -0.0166 mm in the statin group, p for difference in change = 0.90). Mixed-model analysis confirmed these results.

Determinants for baseline IMT were age (r = 0.358, p < 0.001) and systolic blood pressure (r = 0.26, p < 0.001). Baseline IMT and changes in IMT were not correlated with LDL cholesterol or any other lipid parameter. Baseline IMT and changes in IMT were also not related to sex, ethnicity, diabetes duration, insulin use, HbA1c, anthropometric parameters, or smoking

Table 3 mean IMT of 182 patients who completed the study

	Baseline		2 years		Mean change		
	IMT	SD	IMT	SD	IMT	95% CI	p*
Placebo (n=79)							
Primary endpoint							
CCA	0.780	0.129	0.774	0.124	-0.006	-0.0223 to 0.0109	0.50
Secondary endpoint							
BIF	0.815	0.148	0.805	0.143	-0.010	-0.0267 to 0.0072	0.25
ICA	0.640	0.136	0.670	0.130	0.031	-0.0104 to 0.0718	0.14
aggrCA	0.757	0.137	0.763	0.120	0.006	-0.0117 to 0.0229	0.52
CFA	0.663	0.149	0.652	0.141	-0.011	-0.0390 to 0.0165	0.42
SFA	0.551	0.111	0.549	0.099	-0.002	-0.0236 to 0.0197	0.86
Statin (n=103)							
Primary endpoint							
CCA	0.763	0.124	0.765	0.116	0.002	-0.0112 to 0.0149	0.78
Secondary endpoint							
BIF	0.823	0.140	0.806	0.122	-0.017	-0.0358 to 0.0017	0.07
ICA	0.684	0.183	0.689	0.181	0.005	-0.0211 to 0.0314	0.69
aggrCA	0.759	0.116	0.762	0.105	0.003	-0.0116 to 0.0175	0.69
CFA	0.630	0.151	0.635	0.148	0.005	-0.0152 to 0.0258	0.61
SFA	0.543	0.092	0.538	0.107	-0.005	-0.0187 to 0.0078	0.42

Values are in millimeters. Mean change: mean change from baseline to 2 years. CCA: common carotid artery; BIF: carotid bifurcation; ICA: internal carotid artery; aggrCA: aggregate carotid artery (mean of all segments); CFA: common femoral artery; SFA: superficial femoral artery

habits. The effect of the two statins used was analyzed by correcting the change in IMT for duration of cerivastatin treatment (range 6–23 months). This did not change the results.

Clinical events

Cardiovascular events occurred in 12 patients in the placebo group and 2 in the statin group (p = 0.006). Coronary events occurred in four patients in the placebo group and none in the statin group (p = 0.122). Four patients in the placebo group and three in the statin group died. The causes of death were cancer (*n* = 4), sepsis (*n* = 1), and hemorrhagic stroke (*n* = 2). Malignancies occurred in eight patients: four in the placebo group and four in the statin group. Myalgia was reported 18 times in the statin group and 26 times in the placebo group and was never accompanied by an increase in creatinine kinase. In one patient in the statin group, at his 24-month visit, ALT was raised more than three times above the upper limit of normal. This was attributed to steatosis hepatis.

CONCLUSIONS

This is the first prospective study in patients with type 2 diabetes but without overt CVD that investigated the effect of statins versus placebo on carotid and femoral IMT. Despite a mean LDL cholesterol reduction of 25%, we did not find any effect of 2 years' statin therapy on mean common carotid IMT.

In patients with familial hypercholesterolemia and in patients with established CAD, statin therapy has resulted in significantly less progression or even regression of carotid IMT[21-23]. In the only other randomized controlled lipid intervention IMT study in type 2 diabetic patients, 3 years' therapy with bezafibrate did not have any effect on carotid and femoral IMT [24]. Our findings warrant several remarks. First, the mean LDL cholesterol reduction of 25% is fully comparable to statin-induced LDL cholesterol reductions ranging between 22 and 29% in studies of non-diabetic patients, showing a significant effect after 18–24 months on carotid IMT [21,23,25,26]. Second, contrary to the postulated progression of mean common carotid artery IMT of 0.03mm per 2 years, in the present study there was a nonsignificant regression of 0.006 mm per 2 years in the placebo group. It could be argued that our patient population had been low risk. However, we included diabetic patients with a broad range in age and diabetes duration, while their baseline common carotid artery IMT was quite comparable to that of patients in other studies[10,27]. Moreover, the observed rate of first major vascular events (myocardial infarction, strokes, and revascularizations) in our placebo group, which translates to 14% per 5 years, is similar to the incidence rate of 13.5% in the diabetic placebo subgroup without prior CVD in the Heart Protection Study [16]. Thus, it seems unlikely that our results have been influenced by any healthy volunteer effect. Third, in our study, we observed no association between LDL cholesterol reduction and IMT reduction. This is at variance with the effect of statin therapy on IMT in non-diabetic patients [22] but in agreement with the effect of 3 years' bezafibrate treatment (LDL cholesterol reduction 9.6%) on carotid and femoral IMT in type 2 diabetic patients [24]. Equally, baseline IMT in the present study was not correlated to baseline LDL cholesterol or any other lipid level, similar to the results of several previous cross-sectional studies in type 2 diabetes[10,28]. Finally, given the low inter- and intra-observer variability in our IMT measurements compared with other studies[29], we strongly feel that the quality of the assessments has not biased the results.

As our study was designed with the assumption of similar IMT progression rates in diabetic and coronary patients, we conclude from the lack of IMT progression in our placebo group that IMT progression rates in diabetic patients are lower than those of patients with CAD. This is supported by recently published cohort studies in which diabetes was not predictive of IMT progression [30,31]. Moreover, the ARIC (Atherosclerosis Risk in Communities) study[32] and the IRAS (Insulin Resistance Atherosclerosis Study)[33] have recently shown progression rates for diabetic subjects of 0.011 and 0.0072 mm/year, respectively, both of which are lower than those observed in patients with CAD[34].

We observed a statistically significant effect on the incidence of predefined cardiovascular events. This is in agreement with the results of the recently published CARDS (Collaborative Atorvastatin Diabetes Study)[35] and with the results of a meta-analysis on the effects of lipid management for type 2 diabetic patients in primary prevention[36]. As we did not find any IMT regression, we postulate that statin-induced cardiovascular event reduction in diabetic patients is not related to IMT regression. From a pathophysiological point of view, the intimal and medial layers of the vessel wall in type 2 diabetes are most likely irreversibly changed by processes such as extracellular matrix glycosylation and media calcification[37,38]. These changes may resist global regression based on interference with local intravascular cholesterol metabolism. We hypothesize that although statins do not influence the irreversibly changed glycosylated extracellular matrix, it may well have an effect on outcome in type 2 diabetic patients by its beneficial influence on plaque vulnerability. To accurately measure IMT in our study, we avoided eccentric plaques; therefore, we cannot address this hypothesis with the available data.

Our study has its limitations. First, cerivastatin was withdrawn from the market, resulting in a change from cerivastatin to simvastatin. After correcting the change in IMT for duration of cerivastatin treatment, however, the results remained unchanged. Second, as a result of the withdrawal of cerivastatin, we had a higher withdrawal rate than anticipated in our sample size estimation. However, except for ethnicity, which was not a determinant of IMT or IMT progression, baseline characteristics did not differ between the drop outs and the 182 patients who fulfilled the study. Moreover, given the narrow CI of the mean difference in common carotid artery IMT change between placebo and statin (95% CI -0.0281 to 0.0132 mm), we can exclude a type II error.

In conclusion, 2 years of statin therapy in a broad range of type 2 diabetic patients without prior manifest atherosclerotic disease did not have any effect on carotid and femoral IMT. The natural history of atherosclerosis progression, as measured by IMT in type 2 diabetic patients, was milder than previously postulated.

We observed a lower cardiovascular event rate in patients on statin therapy, which is in line with other clinical trials. As this benefit has not been related to IMT regression, other mechanistic explanations, like a beneficial effect on plaque vulnerability, might be of importance. Vessel wall biology in type 2 diabetes is distinct from other high-risk patients, and this implies that prognostic tools other than IMT should be evaluated in this patient group.

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