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# Chapter 8

## No effect of statin therapy on silent myocardial ischemia in patients with type 2 diabetes without manifest cardiovascular disease

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## **ABSTRACT**

### **Objective**

Coronary artery disease is the most important cause of mortality in patients with type 2 diabetes mellitus (DM2). 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.

### **Research Design and Methods**

A randomized, placebo-controlled, double-blind trial was performed in 250 patients with DM2 without manifest cardiovascular disease. Patients were given either 0.4 mg cerivastatin or placebo daily. In August 2001, when cerivastatin was withdrawn from the market, cerivastatin 0.4 mg was replaced by 20 mg simvastatin without deblinding the study. The primary endpoint was the change in ischemic episodes, duration and burden as measured by 48 hours ambulatory electrocardiography (AECG) over 2 years.

### **Results**

At baseline 47 out of 233 (20%) evaluable AEC G'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 relationship between these cardiovascular events and the presence of SMI at baseline.

### **Conclusions**

SMI occurred in 20 % of DM2 patients without manifest cardiovascular disease. There was no effect from two years of statin therapy on SMI. In contrast, we observed a significantly lower cardiovascular event rate on statin therapy. AECG may not be a proper tool for risk stratification in patients with DM2.

## INTRODUCTION

Coronary artery disease is the most important cause of mortality in patients with type 2 diabetes mellitus (DM2)<sup>1</sup>. Individuals with diabetes not only have a higher risk for coronary events, but their outcome after such an event is worse<sup>2</sup> and more extensive atherosclerotic lesions are found at the first manifestation of coronary artery disease<sup>3</sup>. Periods of silent myocardial ischemia (SMI) might precede a first coronary event in DM2, especially if cardiac autonomic neuropathy is present<sup>4</sup>. Early detection of SMI is thus a potential tool for cardiovascular risk stratification in patients with DM2.

SMI can be detected with an exercise ECG, 24 or 48 hours ambulatory electrocardiography (AECG), or (stress) myocardial scintigraphy. Exercise testing requires a certain level of fitness of the patient. Myocardial scintigraphy is expensive, and both scintigraphy and exercise ECG are time consuming. In contrast, AECG can be applied in virtually every patient, is inexpensive, non-invasive and reflects daily life circumstances.

Treatment with HMG-Co-A reductase inhibitors (statins)<sup>5,6</sup> resulted in reduced SMI in non-diabetic patients with coronary artery disease. Data on the effect of statin therapy on SMI in DM2 are lacking. We conducted a randomized, placebo-controlled trial to determine the prevalence of SMI and to evaluate the effect from 2 years of statin therapy on SMI detected by AECG in patients with DM2 without cardiovascular disease.

## RESEARCH DESIGN AND METHODS

### Subjects and design

The study design and baseline characteristics of the original patient population have been described in detail elsewhere<sup>7</sup>. Briefly, 250 patients with DM2 for at least one year, aged 30-80 years, without cardiovascular disease (defined as angina pectoris, coronary artery disease, ECG criteria for a past myocardial infarction, ischemic stroke, peripheral artery bypass surgery, percutaneous transluminal angioplasty or amputation because of atherosclerotic disease) were included in this randomized, double-blind, clinical trial. Patients were given 0.4 mg cerivastatin (Bayer B.V., Mijdrecht, The Netherlands) or placebo daily for 2 years. After the withdrawal of cerivastatin from the market, 0.4 mg cerivastatin was replaced by 20 mg simvastatin (Merck Sharp & Dome, Haarlem, the Netherlands) without debinding the study. At that moment, all the patients had been randomized with a mean follow-up of 15 months (range 6-23 months). Eligible patients gave their written informed consent. The study was performed at the Leyenburg Hospital, The Hague. The study was approved by the hospital's Medical Ethics Committee.

## Study Objectives

The primary endpoint of the study was the change in ischemic episodes, ischemic duration and ischemic burden between 24 months and baseline. 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.

## Follow-up

Patients returned to the study site after a 12 hours fast at 3, 6, 12, 18 and 24 months for blinded plasma lipid and safety measurements. ECG and AECG measurements were performed at baseline and 24 months. A 2-year follow-up for clinical events was performed for all 250 patients. If there were signs of life threatening arrhythmia on the AECG, the patient was referred to a cardiologist.

## ECG measurements

On a resting ECG the QT interval of lead V2 was measured from the beginning of the QRS complex to the end of the downslope of the T wave. The QT interval was corrected (QTc) for heart rate using Bazett's formula:  $QTc = QT / \sqrt{RR}$ . The Minnesota ECG criteria were used to detect a past Q-wave myocardial infarction<sup>8</sup>.

## AECG measurements

AECG's were recorded on a 3 channel Marquette 8500 tape recorder with electrodes positioned to obtain pseudo V5, V6 and aVF leads. The recordings were made over a continuous period of 48 hours, during which the patient completed a diary of physical activity and symptoms. The tapes were subsequently analyzed on a Marquette MARS 8000 Holter Analyzer by SEAL (Foundation for ECG Analysis Leiden, incorporated in the Leiden University Medical Center). The registrations were evaluated by blinded computer-assisted analysis by two certified technicians. The AECG results remained blinded for patients and their physicians.

Transient myocardial ischemia was defined as the presence of episodes showing > 0,1 mV (1 mm) horizontal or downsloping ST-segment depression, 80 ms after the J-point, lasting for > 60 seconds and separated by at least 60 seconds from the next ischemic episode. The total number of ischemic episodes, the total duration of ischemia, and total ischemic burden were assessed. For ischemic episodes and ischemic duration, any overlapping episodes in the different channels were not summed. Ischemic burden was defined as ischemic duration in minutes multiplied by ST-segment depression in millimetres, for each channel separately and then summed.

Not included in the AECG study were patients with non-ischemic ST-segment abnormalities, due to intraventricular conduction delay, bundle branch block, or atrial flutter or fibrillation.

AECG recordings of insufficient quality were rejected; only those in which at least 40 hours of ST-segment analysis could be performed in either lead V5 or V6 were included; if this criterion could not be met, at least 24 hours (50%) of data in both channels V5 and V6 were analyzed and compared with the matching hours of the corresponding recording (either baseline or at 24 months).

### **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**

We assumed a 30 % prevalence of SMI in our DM2 patients<sup>9-14</sup>. From clinical studies in patients with coronary artery disease<sup>5,6</sup>, we assumed an increase in prevalence to 35 % in the placebo group and a decrease in prevalence to 15 % in the statin group after two years. The number of patients needed to detect this difference with a power of 80 % ( $\alpha = 0.05$ ) was 73 patients in each group.

The primary treatment comparison was between placebo and statin therapy in patients completing the study (on-treatment analysis). Differences between the groups were analyzed by Student's independent samples t-test, (Pearson's) Chi-squared test or Mann-Whitney test where appropriate. Changes from baseline within each treatment group were analyzed by Student's paired t-test, Mc Nemar Chi-squared test or Wilcoxon signed-rank test where appropriate. Comparisons of the effects between the treatment groups were performed using Mann-Whitney test.

Ischemic episodes, total ischemic duration and ischemic burden were categorized as 0 (no ischemia), 1, 2 or 3 according to tertiles at baseline in the patients with ischemia. With these ischemic scores, determinants of baseline ischemia were evaluated using ordinal regression techniques. The association between ischemia at baseline and cardiovascular events during follow-up was evaluated by Chi-squared test.

Analyses were performed using SPSS 11.0 for Windows software. All analyses were 2-sided, with a level of significance of  $\alpha = 0.05$ .

## **RESULTS**

Of the 250 patients randomized, 233 had evaluable AECG at baseline. Of these 233 patients, 45 in the placebo group and 21 in the statin group dropped out during the study. There were 17 AECG recordings at baseline and 12 at follow-up that were not valid because of: intraventricular conduction delay (9), atrial fibrillation or flutter (5), background noise (2), technical problems with tape or recorder (8), or patient refusal or invalidation (5). This left 155 patients

with full valid AECG data both at baseline and at 24 months. Two patients were referred to a cardiologist because of arrhythmia at their 2-year AECG. One patient had frequent nocturnal sinus arrests; after cessation of labetolol treatment, a control AECG showed normalization. One patient had a 12-beat ventricular tachycardia; subsequent cardiological analysis revealed normal echocardiography results and no further action was taken.

The characteristics of the study population are given in Table 1. No statistical differences between the groups were observed. There were no differences in baseline characteristics between the 155 patients with valid AECG recordings and the other 78 patients.

## Lipids

Mean LDL cholesterol in the 155 patients was  $3.41 \pm 0.72$  mmol/l at baseline and  $2.64 \pm 0.96$  mmol/l at 2 years (- 22 %,  $p < 0.001$ ) in the statin group and  $3.53 \pm 0.72$  mmol/l at baseline and  $3.76 \pm 0.83$  mmol/l at 2 years (+ 8%,  $p=0.007$ ) in the placebo group ( $p < 0.001$  for difference between groups). Mean HDL cholesterol was  $1.24 \pm 0.41$  mmol/l at baseline and  $1.21 \pm 0.38$  mmol/l at 2 years (-1%,  $p=0.161$ ) in the statin group and  $1.21 \pm 0.38$  mmol/l at baseline and  $1.21 \pm 0.39$  mmol/l at 2 years (+1%,  $p=0.866$ ) in the placebo group ( $p=0.372$  for difference between groups). Mean triglycerides were  $1.80 \pm 0.95$  mmol/l at baseline and  $1.65 \pm 1.49$  mmol/l at 2 years (-11 %,  $p=0.218$ ) in the statin group and  $1.85 \pm 0.80$  mmol/l at baseline and

**Table 1.** Baseline Characteristics of 250 Randomized Patients

|  | Placebo (n=125) | Statin (n=125)  |
|--|-----------------|-----------------|
| Male sex                                   | 57 (46)         | 61 (49)         |
| Age (years)                                | $58.2 \pm 11.4$ | $58.8 \pm 11.3$ |
| Ethnicity:                                 |                 |                 |
| <i>Caucasian</i>                           | 86 (69)         | 83 (66)         |
| <i>Asian-Indian</i>                        | 20 (16)         | 28 (22)         |
| <i>other</i>                               | 19 (15)         | 14 (11)         |
| BMI (kg/m <sup>2</sup> )                   | $31.0 \pm 6.0$  | $31.0 \pm 6.3$  |
| Waist-to-hip ratio                         | $0.99 \pm 0.09$ | $0.98 \pm 0.08$ |
| Current smoker                             | 33 (26)         | 28 (22)         |
| Hypertension                               | 66 (53)         | 60 (48)         |
| Diabetes duration (years)*                 | $7 \pm 8$       | $6 \pm 7$       |
| Insulin use                                | 69 (55)         | 62 (50)         |
| HbA1c (%)                                  | $7.60 \pm 1.48$ | $7.53 \pm 1.10$ |
| Vasoactive medication :                    | 70 (56)         | 58 (46)         |
| <i>Beta blocking agents</i>                | 16 (13)         | 14 (11)         |
| <i>Calcium channel blockers</i>            | 16 (13)         | 15 (12)         |
| <i>renin-angiotensin system-inhibitors</i> | 46 (37)         | 47 (38)         |
| <i>Diuretics</i>                           | 29 (23)         | 34 (27)         |
| Microalbuminuria†                          | 19 (15)         | 24 (19)         |
| Silent myocardial ischemia                 | 26 (22)         | 21 (18)         |
| QTc (seconds)                              | $0.39 \pm 0.03$ | $0.40 \pm 0.03$ |

Data are means  $\pm$  SD or numbers of patients (%) unless otherwise indicated.

\*Median  $\pm$  SD. † Men, > 2.5 g/mol creatinine; women, > 3.5 g/mol creatinine.

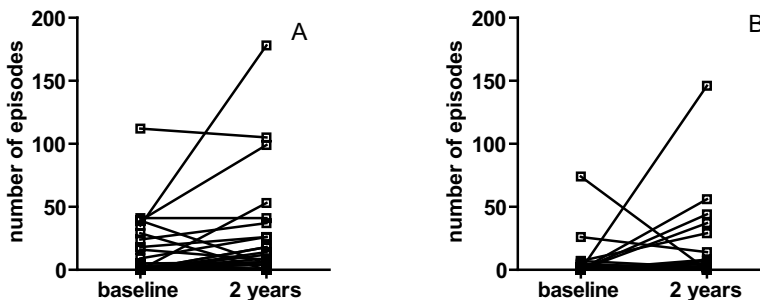
1.70 ± 1.26 mmol/l at 2 years (-4%,  $p=0.284$ ) in the placebo group ( $p=0.436$  for difference between groups). Average LDL cholesterol levels in the statin group were higher after the switch to simvastatin (2.37 before versus 2.63 mmol/l after the switch,  $p < 0.001$ ).

### AECG's

At baseline, 47 of 233 (20%) evaluable AECG's showed evidence of ischemia, equally distributed among the treatment groups. In the patient group completing the study with full AECG data ( $n=155$ ), there was a nonsignificant difference between the placebo and statin group with a higher prevalence of ischemia in the placebo group at baseline ( $p=0.069$ , Pearson chi square with continuity correction). Patients in the group with complete AECG data had the same amount of baseline ischemic episodes as the noncompleting group. After two years, there was a nonsignificant trend toward more ischemic episodes, duration, and burden in the placebo group as well as in the statin group (Figure 1 and Table2). When the whole group was taken together ( $n=155$ ), increases after 2 years in ischemic episodes and duration were significant ( $p = 0.019$  and  $0.018$ , respectively), with total prevalence of ischemia rising from 20.0 to 24.5 %. There were no significant differences between the changes in ischemic episodes ( $p=0.498$ ), duration ( $p=0.697$ ) or burden ( $p=0.798$ ) in the two treatment groups. Correcting for baseline ischemia did not change these results.

Determinants for **baseline** ischemic episodes were QTc ( $p=0.011$ ) and diastolic and systolic blood pressure ( $p=0.048$  and  $0.017$ , respectively). When included into an ordinal regression model, QTc and systolic blood pressure remained significant determinants and explained 6% of the variance (Nagelkerke pseudo  $r^2$ ) in baseline ischemia.

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



**Figure 1.** Changes in ischemic episodes in placebo group (A) ( $n=26$ ) and statin group (B) ( $n=21$ ) in patients with any ischemia at baseline or 2 years



**Table 2.** Parameters for ischemia in 155 patients with complete AECG data

|                       | score* | placebo(n=70) |         |       | statin(n=85) |         |       | p†    |
|-----------------------|--------|---------------|---------|-------|--------------|---------|-------|-------|
|                       |        | baseline      | 2 years | p**   | baseline     | 2 years | p**   |       |
| <b>episodes(nr)</b>   |        |               |         | 0.056 |              |         | 0.191 | 0.498 |
| 0                     | 0      | 51            | 48      |       | 73           | 69      |       |       |
| 1-2                   | 1      | 5             | 2       |       | 6            | 5       |       |       |
| 3-15                  | 2      | 5             | 10      |       | 4            | 6       |       |       |
| ≥16                   | 3      | 9             | 10      |       | 2            | 5       |       |       |
| <b>duration(min)</b>  |        |               |         | 0.151 |              |         | 0.050 | 0.697 |
| 0                     | 0      | 51            | 48      |       | 73           | 69      |       |       |
| 1-6.74                | 1      | 5             | 4       |       | 5            | 3       |       |       |
| 6.75-72.74            | 2      | 6             | 8       |       | 5            | 8       |       |       |
| ≥72.75                | 3      | 8             | 10      |       | 2            | 5       |       |       |
| <b>burden(min*mm)</b> |        |               |         | 0.485 |              |         | 0.054 | 0.798 |
| 0                     | 0      | 51            | 48      |       | 73           | 69      |       |       |
| ≥0-6.33               | 1      | 5             | 3       |       | 5            | 2       |       |       |
| 6.34-124.37           | 2      | 6             | 11      |       | 5            | 9       |       |       |
| ≥124.38               | 3      | 8             | 8       |       | 2            | 5       |       |       |

data are numbers of patients

\* score: 0= no ischemia, 1-3= category according to tertiles of baseline ischemic parameters as described in text. \*\* Wilcoxon signed-rank test for change between baseline and 2 years. † Difference in change between placebo and statin groups.

### Clinical events

As reported before <sup>7</sup>, in the total population of 250 patients, cardiovascular events occurred in 12 patients in the placebo group and in two patients in the statin group ( $p=0.006$ ). Ischemic episodes, duration, or burden at baseline were not related to the occurrence of cardiovascular events during the 2-year follow-up, neither in the placebo group nor in the statin group.

### CONCLUSIONS

This is the first study on the effect of long-term statin therapy on SMI in DM2 patients. We did not find any effect of statin therapy on the occurrence of SMI, in spite of a significant reduction in cardiovascular events.

The reported prevalence of SMI in asymptomatic DM2 varies between 9 to 52% <sup>4,9-20</sup> and is strongly dependent on method of detection and on the population studied. In our DM2 population without prior cardiovascular disease with a broad range in age and diabetes duration we found a 20% incidence of SMI. In most cross-sectional studies the incidence of SMI is increased in DM2 compared with non-diabetic subjects <sup>11,13</sup>. It has been suggested that this is caused by diabetic autonomic neuropathy. However, recent clinical and epidemiological data suggest that this increase mainly reflects accelerated atherosclerosis <sup>21</sup>. This concept is confirmed by the modest relationship in our data with QTc, a parameter for diabetic cardiac

autonomic neuropathy<sup>22</sup>. Our findings are in concordance with the modest but consistent relationship that was found between other parameters of cardiac autonomic neuropathy, including Ewing tests<sup>23</sup>, and SMI in a meta-analysis<sup>24</sup>. The relationship between QTc and SMI in patients with DM2 has not been studied before.

Other investigators found a relationship between SMI in DM2 and cholesterol<sup>12,14</sup>, smoking<sup>18</sup>, age<sup>12,17</sup>, blood pressure<sup>12,25</sup> and microalbuminuria<sup>4,12,17,18,25</sup>. Our data do not confirm these data as we only found an association with blood pressure.

Results of studies on the predictive value of SMI in DM2 for cardiovascular events<sup>4,10,16,17,26</sup> show contradictive results and might be biased because treatment regimens were often influenced by the results of SMI testing<sup>16,17,26</sup>. The studies are also difficult to compare because of inclusion of patients with type 1 diabetes<sup>16,26</sup> and because of various methodology to detect SMI: some studies use a combination of exercise ECG and myocardial scintigraphy<sup>16,17,26</sup>, whereas others assess SMI with exercise ECG only<sup>4,10</sup>. To our knowledge, only one study on the predictive value of SMI in DM2 included AECG in their evaluation<sup>16</sup>, showing that SMI as detected with a combination of exercise ECG, myocardial scintigraphy and AECG was a poor predictor of major cardiac events. In the present study, we did not find a relationship between the presence of 48 hour AECG detected SMI at baseline and the 2-year risk of cardiovascular events. However, our study was not designed nor powered for this purpose, so we cannot conclude from our data that SMI is not predictive for cardiovascular events in patients with DM2.

In non-diabetic patients with coronary artery disease, two earlier studies have reported a beneficial effect of statin therapy on ischemic episodes<sup>5,6</sup> and ischemic duration and burden<sup>6</sup> as detected with AECG. We did not find any effect of statin therapy on SMI in our DM2 population; from the present data, one can only speculate whether these contradictory findings are due to the fact that we studied patients with diabetes or to the fact that we studied asymptomatic patients. However, we did find a beneficial effect on cardiovascular event rates. This result implies that the beneficial effects of statin therapy may not directly be mediated through reduction of silent ischemic episodes, which is in line with the perception that most cardiovascular events do not evolve from progressive narrowing of the vessel lumen, but rather from thrombus formation on a ruptured nonobstructing instable plaque<sup>27</sup>. Searching for SMI might therefore not be a rational way of risk stratification in asymptomatic patients with DM2.

Our study has possible limitations. First, cerivastatin was withdrawn from the market, resulting in a change from cerivastatin to simvastatin. After correcting the change in ischemic parameters for duration of cerivastatin treatment, however, the results remained unchanged. Second, at baseline, patients with complete AECG data in the statin group tended to have less ischemia than in the placebo group. This might have lead to less power to detect a treatment effect. However, the clear trend toward more ischemia after 2 years, equal in both groups and reflecting the natural history of atherosclerosis in DM2, makes a type II error unlikely.

In conclusion, we found a 20% prevalence of SMI in asymptomatic patients with DM2. We did not find any effect from two years of statin therapy on SMI, despite a significant reduction in cardiovascular events. SMI as detected with 48 hour AECG may not be a proper tool for risk stratification in patients with DM2.

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