Impact of statins in microalbuminuric subjects with the metabolic syndrome: a substudy of the PREVEND Intervention Trial

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Aims Microalbuminuria frequently clusters with the metabolic syndrome and may identify subjects at increased coronary risk. Statin treatment may reduce the incidence of major adverse cardiac events in subjects with the metabolic syndrome, but evidence is limited. We evaluated the impact of pravastatin treatment on the incidence of major adverse cardiac events in microalbuminuric subjects with the metabolic syndrome.

Methods and results This substudy of the PREVEND Intervention Trial (a randomized, placebo-controlled trial with a 2x2 factorial design) included 864 microalbuminuric subjects, who were randomized to fosinopril 20 mg or matching placebo and pravastatin 40 mg or matching placebo (mean follow-up 46 months). The metabolic syndrome was defined according to the NCEP ATPIII-report. Subjects with or without the metabolic syndrome were characterized by a higher age, male sex, and increased albuminuria. The incidence of major adverse cardiac events in subjects with the metabolic syndrome [9.1%; 95% confidence interval (CI) 6.0–13.0%] was increased vs. those without [3.6%; 95% CI 2.3–5.5%; \( P = 0.007 \)]. Pravastatin treatment lowered the incidence of major adverse cardiac events in subjects with the metabolic syndrome after adjustment for age and sex (hazard ratio \( = 0.39; \) 95% CI 0.17–0.89; \( P = 0.025 \)).

Conclusion This study supports the use of statins in microalbuminuric subjects with the metabolic syndrome to reduce the incidence of major adverse cardiac events.

KEYWORDS
PREVEND; Microalbuminuria; Metabolic syndrome; Clinical trial; Statin

Introduction
Microalbuminuria may reflect generalized vascular dysfunction1 and identify subjects at increased coronary risk.2,3 Microalbuminuria frequently clusters with the metabolic syndrome, which is characterized by a constellation of risk factors, among which are insulin resistance, dyslipidaemia, hypertension, obesity, and endothelial dysfunction.4–7 Presence of the metabolic syndrome is associated with increased risk for coronary heart disease (CHD).8–12 As a considerable part of the western population is affected by the metabolic syndrome,13,14 prevention guidelines have advocated risk reduction in these subjects for the prevention of cardiovascular disease.15,16 Large statin trials have shown coronary risk reduction in a primary prevention setting.17–20 The effects of statin therapy in high-risk subjects with the metabolic syndrome have been promising, but equivocal.8,20–23 Recently, the PREVEND Intervention Trial (PREVEND IT) has evaluated the effects of interventional treatment on cardiovascular disease incidence in microalbuminuric subjects.24 Pravastatin treatment did not lower the incidence of coronary events in the total study cohort, but the treatment effect has not yet been described in a subgroup of microalbuminuric subjects with the metabolic syndrome. We therefore have performed a supplemental analysis of the PREVEND IT for the effects of pravastatin on major adverse cardiac events in microalbuminuric subjects stratified according to presence or absence of the metabolic syndrome.

Methods
Patients
This study is a supplemental analysis of PREVEND IT, which is a sub-study of the PREVEND program. The objective of the PREVEND program is to assess the value of microalbuminuria as an indicator of increased cardiovascular and renal risk in the general
Details of the PREVEND IT objectives, design, and methods have been reported previously. Planned additional analyses in the PREVEND program include the Framingham risk score, hs-CRP, intima media thickness, and metabolic syndrome. In summary, the PREVEND IT was an investigator driven, single-centre, double-blind, randomized, 2 × 2 factorial design, placebo-controlled trial. The intention-to-follow-up time of 4 years was the same for each subject. The median follow-up duration was 47.4 months (interquartile range 46.7–47.9 months). Eight-hundred and sixty-four subjects were randomized to fosinopril 20 mg or matching placebo and to pravastatin 40 mg or matching placebo. The key entry criteria were persistent microalbuminuria (once a urinary albumin concentration >10 mg/L in an early morning spot urine sample) and at least once 15–300 mg/24 h in 2 × 24 h urine samples, blood pressure (BP) <160/100 mmHg without the use of antihypertensive medication and total cholesterol <8.0 mmol/L without the use of lipid lowering drugs.

The metabolic syndrome was defined as the presence of at least three out of five risk determinants according to the NCEP ATP-III report [increased waist circumference (men >102 cm, women >88 cm), fasting triglycerides (TG) >1.69 mmol/L, low HDL-cholesterol (HDL-C) (men <1.03 mmol/L, women <1.29 mmol/L), systolic RR >130 and/or diastolic RR >85 mmHg, and fasting plasma glucose level >6.1 mmol/L]. The primary endpoint was defined as the occurrence of major adverse cardiac events consisting of total mortality and cardiovascular morbidity at 4 years. Total mortality was defined as all-cause mortality. Cardiovascular morbidity was defined as hospitalization for documented non-fatal myocardial infarction (MI) or myocardial ischaemia. Non-fatal MI was defined as a non-fatal event accompanied by at least two out of four of the following which should include either new Q waves (iii) and/or enzyme elevation (iv): (i) Presence or history of typical or atypical chest pain of at least 15 min duration, (ii) ECG detection of ST segment changes of at least 0.1 mV and/or T wave inversion in at least 2 out of 12 leads, (iii) ECG detection of new significant Q waves in at least two out of 12 leads, and (iv) Elevation of measurements of total CPK and/or its isoenzyme CPK-MB in at least two samples drawn within 48 h of development of chest pain. CPK levels should be >2× the upper limit of normal local laboratory range and/or CPK-MB/CPK ratio >10%. Myocardial ischaemia was defined as ischaemic events accompanied by the appearance of an ST segment change of >0.1 mV and/or T wave inversion in at least 2 out of 12 leads or objective evidence by means other than ECG or a need for revascularization (PCI/CABG) severe enough to justify immediate hospital admission. As all ischaemic events were accompanied by a revascularization procedure, these events are reported as revascularisations. This study of the PREVEND IT reports the incidence of major adverse cardiac events by pravastatin treatment and does not focus on the fosinopril component of the trial. In the text, the group without pravastatin treatment is labelled as ‘control group’. The study was approved by the Institutional Review Board and conducted in accordance with the guidelines of the declaration of Helsinki. Informed consent was obtained from all subjects before randomization.

Analytical methods

The urinary albumin excretion was measured as the mean of two 24-h urine collections. Urinary albumin concentrations were determined by nephelometry with a threshold of 2.3 mg L⁻¹ and intra- and inter-assay coefficients of variation of <2.2 and 2.6%, respectively (Dade Behring Diagnostic, Marburg, Germany). Systolic and diastolic BP measurements were calculated as the mean of the last two out of 10 consecutive measurements with an automatic Dinamap XL model 9300 series device (Johnson & Johnson Medical INC, Tampa, FL, USA). Blood glucose, serum total, and LDL-cholesterol (LDL-C) were determined by Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, NY, USA). In the text and the tables, glucose levels are reported as plasma glucose concentrations. Blood glucose levels were therefore converted to equivalent plasma glucose concentrations by factor (1.125 × whole blood glucose) − 0.4375 according to the procedure proposed by Passing and Bablok.

Statistical analysis

All analyses were performed on an intention-to-treat basis and P-values were two-sided and needed to be <0.05 to be significant. Baseline characteristics are given as mean (± standard deviation). In case of a skewed distribution the median (interquartile range) was used. Differences between groups were evaluated by Student’s t-test or Wilcoxon two sample test, when appropriate. A subject was considered compliant if >75% of the supplied study medication was taken during the period of the trial. Log rank statistics are used to test differences in the incidence of major adverse cardiac events between subjects with and without the metabolic syndrome. Because of inequality in distribution of age and sex in the study population, the significance of the difference in major adverse cardiac events between treatment groups was tested by Cox regression analysis after adjustment for age and sex. In addition, adjustment for fosinopril treatment was performed. The significance of the difference in major adverse cardiac events was additionally tested in subjects with the metabolic syndrome who were compliant users of pravastatin, non-diabetics, and free of prior CHD, respectively. Results are summarized by hazard ratios (HR) with 95% confidence intervals (CI). Times to first major adverse cardiac events are presented as Kaplan–Meier estimates or Cox-adjusted survival curves. Finally, the effect of pravastatin and the metabolic syndrome was tested, taking into account the interaction between the pravastatin treatment group and the metabolic syndrome. Plots of the distribution of the residuals against time and log–log survival curves were used to evaluate adherence of the Cox proportional hazard model assumptions. All calculations were performed with SPSS version 11.0 software (SPSS, Chicago, IL, USA).

Results

Baseline characteristics

Thirty-three per cent of the subjects (n = 286) fulfilled the criteria for the metabolic syndrome, whereas 67% (n = 578) did not have three or more of the qualifying characteristics. Table 1 reports baseline characteristics and the qualifying characteristics of the metabolic syndrome. Levels of albuminuria, total and LDL-C levels, were increased in subjects with metabolic syndrome. Subjects with the metabolic syndrome were characterized by a higher age, male sex, and a higher prevalence of diabetes. Furthermore, they were more often prescribed medication at baseline. The number of prior cardiovascular events was low and not significantly different between the two groups. Statin use by the control group was 3.5% and comparable in subjects with or without the metabolic syndrome (P = 0.587)

In subjects with the metabolic syndrome, those who were treated with pravastatin (n = 147) vs. controls (n = 139) were older. No other significant differences in baseline characteristics were found between the treatment groups (Table 2). In subjects without the metabolic syndrome, no baseline differences were present in the pravastatin (n = 286) vs. control group (n = 292) except for medication (Table 2).

The use of fosinopril was equally divided in the pravasta-tin and control groups: in those with the metabolic syndrome 51.7 and 45.3% (P = 0.281), respectively, and in
Table 1  Baseline characteristics and qualifying characteristics of the metabolic syndrome of 864 subjects in the PREVEND IT divided according to the presence of the metabolic syndrome

<table>
<thead>
<tr>
<th>Metabolic syndrome</th>
<th>Present (n = 286)</th>
<th>Absent (n = 578)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>55 (11)</td>
<td>50 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>70</td>
<td>62</td>
<td>0.020</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>96</td>
<td>97</td>
<td>0.381</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29.3 (4.5)</td>
<td>24.9 (3.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>39</td>
<td>40</td>
<td>0.186</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>6.1 (1.0)</td>
<td>5.7 (1.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>4.2 (1.0)</td>
<td>4.0 (0.9)</td>
<td>0.012</td>
</tr>
<tr>
<td>Albuminuria (mg/24 h)</td>
<td>28.5 (18.8–51.9)</td>
<td>21.0 (14.6–38.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>20.3</td>
<td>1.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior cardiovascular diseasea (%)</td>
<td>3.9</td>
<td>3.1</td>
<td>0.571</td>
</tr>
<tr>
<td>Medicationb (%)</td>
<td>8.7</td>
<td>4.0</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Qualifying characteristics of the metabolic syndrome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>140 (15)</td>
<td>126 (17)</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>81 (9)</td>
<td>74 (9)</td>
<td></td>
</tr>
<tr>
<td>Increased BP (%)</td>
<td>82</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>102 (11)</td>
<td>87 (11)</td>
<td></td>
</tr>
<tr>
<td>Abdominal obesity (%)</td>
<td>64</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>0.85 (0.19)</td>
<td>1.11 (0.34)</td>
<td></td>
</tr>
<tr>
<td>Low HDL-C (%)</td>
<td>96</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>1.99 (1.69–2.81)</td>
<td>1.08 (0.78–1.44)</td>
<td></td>
</tr>
<tr>
<td>Elevated TG (%)</td>
<td>75</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.7 (1.7)</td>
<td>4.8 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Elevated glucose levels (%)</td>
<td>33</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean (SD) or median (interquartile range) for albuminuria and TG which were skewed distributed. To convert values for cholesterol to mg/dL, divide by 0.02586. To convert values for TG to mg/dL, divide by 0.01129. Please see text for the definition of the metabolic syndrome.

aMyocardial infarction, angina pectoris, coronary angioplasty or bypass, heart failure, or cerebrovascular accident.

bAspirin and anti-platelet agents, beta-blockers, nitrate, diuretics, calcium channel blockers, or digoxin.

those without the metabolic syndrome 49.0 and 52.1% (P = 0.456), respectively.

LDL-C and systolic BP measurements during study follow-up

LDL-C and BP measurements were performed at consecutive timepoints during study follow-up: at baseline, after 3 months, and after 1, 2, 3, and 4 years (Figure 1). Owing to premature discontinuation of the study and technical failure of five baseline LDL-C measurements, some data are missing. In subjects treated with pravastatin, LDL-C after 3 months was higher in subjects with or without the metabolic syndrome (P = 0.037), although reductions in LDL-C after 3 months were similar (respectively 2.19 ± 0.71 and 1.18 ± 0.79 mmol/L; P = 0.927). No significant differences at other timepoints were found. In the control group, no significant differences were found in LDL-C in subjects with the metabolic syndrome when compared with those without (Figure 1; left panel). No significant effect of pravastatin treatment was found on HDL-C and TG levels in those with or without the metabolic syndrome. Systolic BP levels in those with or without the metabolic syndrome were similar in those treated with or without pravastatin at all timepoints (Figure 1; right panel).

The incidence of major adverse cardiac events according to the presence of the metabolic syndrome

The incidence of major adverse cardiac events at 4 years was increased in subjects with the metabolic syndrome vs. those without: 9.1% (95% CI 6.0–13.0%) vs. 3.6% (95% CI 2.3–5.5%) (P = 0.007). The Kaplan–Meier survival curves are shown in Figure 2.

The incidence of major adverse cardiac events in microalbuminuric subjects according to the metabolic syndrome and treatment

In subjects with the metabolic syndrome, the incidence of major adverse cardiac events at 4 years was 12.2% in the control group and 6.1% in the pravastatin group. The distribution of the separate components of major adverse cardiac events was similar in the control group when compared with the pravastatin group: 5 vs. 2 MIs, 7 vs. 4 revascularizations, and 7 versus 4 deaths, respectively. The incidence of these single components was not significantly different between the two groups. However, regarding the composite endpoint, pravastatin treatment showed a significant beneficial effect on the incidence of major adverse cardiac events (Figure 3). In an unadjusted model, treatment with pravastatin tended to reduce the HR for major adverse cardiac
events two-fold (HR = 0.48; 95% CI 0.21–1.07; P = 0.074). After adjustment for age and sex pravastatin treatment significantly lowered the HR for major adverse cardiac events (HR = 0.39; 95% CI 0.17–0.89; P = 0.025). Additional adjustment for fosinopril treatment did not affect the results (HR = 0.39; 95% CI 0.17–0.89; P = 0.026). The effect of pravastatin treatment on the incidence of major adverse cardiac events was significant in compliant pravastatin users (HR = 0.35; 95% CI 0.15–0.82; P = 0.015), in non-diabetics (HR = 0.28; 95% CI 0.11–0.74; P = 0.010), and in subjects without prior CHD (HR = 0.38; 95% CI 0.16–0.89; P = 0.027).

In subjects without the metabolic syndrome, the incidence of major adverse cardiac events at 4 years was 3.1% in the control group and 4.2% in the pravastatin group. Treatment with pravastatin did not significantly reduce the incidence of major adverse cardiac events (HR = 1.40; 95% CI 0.59–3.31; P = 0.45) in an unadjusted model, neither after adjustment for age and sex (HR = 1.31; 95% CI 0.55–3.12; P = 0.54) nor additionally adjusted for fosinopril treatment (HR = 1.32; 95% CI 0.56–3.15; P = 0.53).

The interaction between pravastatin treatment and the metabolic syndrome on the incidence of major adverse cardiac events, adjusted for age, sex, and fosinopril, was statistically significant (P = 0.040).

**Discussion**

This substudy of the PREVEND IT shows that in microalbuminuric subjects in whom the metabolic syndrome was present, the incidence of major adverse cardiac events at 4 years was increased when compared with subjects

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### Table 2  Baseline characteristics of 286 subjects with the metabolic syndrome (upper panel) and 578 subjects without the metabolic syndrome (lower panel) in the PREVEND IT in the pravastatin and control group

<table>
<thead>
<tr>
<th>Metabolic syndrome present</th>
<th>Pravastatin</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>147</td>
<td>139</td>
<td>0.015</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56 (11)</td>
<td>53 (11)</td>
<td></td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>75</td>
<td>66</td>
<td>0.083</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>44</td>
<td>33</td>
<td>0.060</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>139 (17)</td>
<td>140 (13)</td>
<td>0.809</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>4.2 (1.0)</td>
<td>4.2 (1.0)</td>
<td>0.989</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>0.85 (0.18)</td>
<td>0.84 (0.20)</td>
<td>0.575</td>
</tr>
<tr>
<td>Albuminuria (mg/24 h)</td>
<td>28.0 (18.4–50.9)</td>
<td>29.4 (19.2–53.5)</td>
<td>0.488</td>
</tr>
<tr>
<td>Medication (%)</td>
<td>6.1</td>
<td>11.5</td>
<td>0.107</td>
</tr>
</tbody>
</table>

| Metabolic syndrome absent  | n = 286    | n = 292 | 0.496   |
| Age (years)                | 50 (12)    | 19 (12) |         |
| Male gender (%)            | 64         | 61      | 0.403   |
| Current smoking (%)        | 59         | 60      | 0.707   |
| Systolic BP (mmHg)         | 125 (17)   | 126 (17) | 0.382 |
| LDL-C (mmol/L)             | 4.0 (0.9)  | 4.0 (0.9) | 0.602 |
| HDL-C (mmol/L)             | 1.1 (0.3)  | 1.1 (0.4) | 0.388 |
| Albuminuria (mg/24 h)      | 19.8 (14.1–38.2) | 21.3 (15.0–38.5) | 0.407 |
| Medication (%)             | 2.1        | 5.7     | 0.022   |

Values are mean (SD) or median (interquartile range) for albuminuria which was skewed distributed. To convert values for cholesterol to mg/dL, divide by 0.02586.

*aAspirin and anti-platelet agents, beta-blockers, nitrate, diuretics, calcium channel blockers, or digoxin.*
without the metabolic syndrome. Pravastatin treatment effectively lowered the incidence of major adverse cardiac events in subjects with the metabolic syndrome.

The importance of the metabolic syndrome as a risk factor for CHD has been recognized by both the NCEP ATP III and the European Third Joint Task Force prevention guidelines. Large statin trials have shown coronary risk reduction in subjects without clinically overt atherosclerosis. In these trials, distinct inclusion criteria were employed, such as an adverse lipid profile, hypertension, CHD, diabetes, or vascular disease, all identifying subjects at increased CHD risk. However, the number of trials which focused on subjects with the metabolic syndrome is limited and the results are not consistent. Some trials showed superior or equal risk reduction in patients with features of the metabolic syndrome.

The PREVEND IT was designed to study the incidence of cardiovascular events in microalbuminuric subjects treated by pravastatin or fosinopril in a 2 × 2 design. This supplemental analysis of the PREVEND IT shows that the presence of both the metabolic syndrome and the microalbuminuria identifies a group of subjects at high coronary risk who are candidates for statin treatment to reduce the incidence of major adverse cardiac events. Our results are in concordance with previous reports that showed that statin treatment was most effective in diabetes patients and in non-diabetic subjects with features of the metabolic syndrome (substudies of the WOSCOPS, 4S trial, and CARE trial).

The WOSCOPS has evaluated the effects of pravastatin treatment (40 mg) vs. placebo in 6595 hypercholesterolemic men in a primary prevention setting. Twenty-six percent of the total study population had the metabolic syndrome. The incidence of coronary death and MI was similarly reduced in subjects with the metabolic syndrome (HR = 0.73; 95% CI 0.53–1.01) when compared with those without (HR = 0.69; 95% CI 0.54–0.89).

The 4S trial reported the effects of simvastatin (20 or 40 mg) vs. placebo in CHD patients with elevated LDL-C levels. In one substudy, patients were divided by the presence of the lipid triad (high TG, low HDL-C, and high LDL-C), which was accompanied by features of the metabolic syndrome. The relative risk reduction of major adverse cardiac events was significant in 458 subjects with the lipid triad (RR = 0.48; 95% CI 0.33–0.69), but no significant risk reduction was observed in 545 patients with isolated high LDL-C (RR = 0.86; 95% CI 0.59–1.26). Another substudy of the 4S trial confirmed the benefit of statin treatment in patients with impaired glucose tolerance.

The CARE trial studied the effects of pravastatin 40 mg vs. placebo in 3553 non-diabetic CHD patients. Patients with impaired glucose tolerance (n = 342) and a concomitant disadvantageous cardiovascular risk profile suffered more recurrent MIs than 3104 patients with normal glucose tolerance during 5 years of follow-up. Although relative risk reductions by pravastatin treatment were equal in both groups, absolute risk reduction was greater in those with impaired glucose tolerance. The WOSCOPS, 4S trial, and the CARE trial therefore provide evidence on the use of statin treatment in subjects with features of the metabolic syndrome.

Only 3% of our study group had a history of cardiovascular disease. The 4 year incidence of major adverse cardiac events was 12.2% in microalbuminuric subjects with the metabolic syndrome in the PREVEND IT (control group), which was comparable to the event rate in the metabolic syndrome WOSCOPS substudy (5 year placebo event rate 10.4%), but much lower when compared with the 35.9% 5 year major adverse cardiac events incidence in patients with the lipid triad in the 4S study (on placebo) and the 34.7% 5 year event incidence (CHD death, MI, and revascularization procedure) in patients with impaired glucose tolerance in the CARE trial (on placebo). As the incidence of major adverse cardiac events was affected by statin treatment in subjects with the metabolic syndrome only, our substudy of PREVEND IT supports the use of statins in subjects with microalbuminuria, in whom the presence of the metabolic syndrome reveals a high CHD risk.

This study therefore contributes to the current knowledge on the benefit of statin therapy in subjects with the metabolic syndrome. This is in contrast with the results from the ASCOT-LLA substudy on the metabolic syndrome. The ASCOT-LLA investigated the effects of atorvastatin 10 mg (vs. placebo) on the incidence of major adverse cardiac events in 10 305 hypertensive subjects with three additional cardiovascular risk factors, but without previous CHD or hypercholesterolaemia. The event rate (non-fatal MI plus fatal CHD) was 3.1% in 3926 subjects with the metabolic syndrome (on placebo) during 3.3 years of follow-up, which is similar to the event rate in our study. In contrast to our study results, atorvastatin treatment did not result in clinical benefit in subjects with the metabolic syndrome.

The beneficial effects of statin therapy in subjects with the metabolic syndrome may be partly explained by its lipid independent effects. In our study, equal reductions of LDL-C were found in subjects with and without the metabolic syndrome. Reductions in BP were equal in diabetes patients and in non-diabetic subjects with features of the metabolic syndrome (subudies of the WOSCOPS, 4S trial, and CARE trial). The lipid independent effects of statins may reduce cardiovascular burden through plaque stabilization or through beneficial effects on the vasculature, e.g. NO mediated vasodilatation, a decrease in
inflammation and an improvement of fibrinolytic balance. All of these processes are harmed in an insulin resistant state, which is the fundamental disorder of the metabolic syndrome. The link between microalbuminuria and insulin resistance is not fully known. In our study, microalbuminuric subjects with the metabolic syndrome had higher levels of urinary albumin than those without. Our study results are in agreement with previous studies that showed that levels of urinary albumin were associated with metabolic risk factors. Microalbuminuria has also been associated to parameters of vascular dysfunction that may accompany the metabolic syndrome. In addition, microalbuminuria may reflect the atherosclerotic burden present in patients with the metabolic syndrome. Therefore, one may hypothesize that subjects with the metabolic syndrome and microalbuminuria are among the most vulnerable for development of atherosclerotic processes. This may be improved by statin treatment. However, as participants in our study were selected for microalbuminuria, our study design does not allow us to assess the clinical impact of statin therapy in normoalbuminuric subjects with the metabolic syndrome.

Limitations

The PREVEND IT was limited by an unexpected small number of events, resulting in an insufficient power to detect an effect of pravastatin treatment on the incidence of major adverse cardiac events in subjects without the metabolic syndrome. It should be addressed that no specific information was available regarding microalbuminuric subjects in the design phase of this intervention study. However, our results are in line with results of earlier clinical trials, which showed that in subjects at increased risk of CHD, LDL-C lowering resulted in a reduction of CHD risk. We therefore feel that our results are generalizable to patients with microalbuminuria who are at high risk of CHD such as due to the presence of the metabolic syndrome. In the PREVEND IT, subjects with a BP >160/100 mmHg were excluded. This may have led to an underestimation of the prevalence of the metabolic syndrome. However, we assume that the benefit of pravastatin in microalbuminuric subjects with the metabolic syndrome at higher BP levels is not significantly different from the subjects included in our study.

Conclusion

This study supports the prescription of statin treatment in microalbuminuric subjects with the metabolic syndrome to reduce the incidence of major adverse cardiac events.

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