Drug use in population screening. Pharmacoepidemiological and pharmaco economical aspects
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CHAPTER 4

The effect of statins on urinary albumin excretion and glomerular filtration rate: results from both a randomized clinical trial and an observational cohort study

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CHAPTER FOUR

ABSTRACT

Introduction
Statins improve cardiovascular outcome, but less is known on renal outcome. We therefore studied the relation between statins use and urinary albumin excretion (UAE) and GFR in two settings: an RCT and an observational cohort study, in which patients were included to study the impact of an elevated UAE on renal and cardiovascular prognosis.

Methods
We used data from the PREVEND-IT and the PREVEND cohort study. The PREVEND-IT subjects (788 with a UAE 15-300 mg/day) received pravastatin 40 mg/day vs placebo and/or fosinopril 20 mg/day vs placebo in a 2x2 factorial-RCT design. Of the cohort subjects (3440) 469 used statins during the 4-year follow-up period. Multivariate regression adjusted for confounding factors and propensity score was used to estimate the relation between statin use and UAE and GFR.

Results
In the RCT, pravastatin did not change UAE or GFR, neither in the fosinopril yes/no sub-groups. In the observational cohort statin use was associated with a rise in UAE (+12.1%), compared with non-users (+3.6%, p<0.001). This rise was most pronounced in those on statins prior to screening-1 (+24.8% [95% CI: 11.9-39.2]), those using statins >3 years (+18.5% [7.3-30.8]) and those with >1 or >2 defined daily doses (+15.7 and +17.3%, resp). These differences remained significant after adjustment for relevant variables and propensity score. The rise in UAE could not be attributed to a higher dose or a specific statin. GFR fell in 4 years in both statin users and non-users (4.6±13.5 and 2.4±11.2, resp.). The fall in GFR between groups was not different after adjustment (p=0.11).

Conclusions
We conclude from the RCT data that statins do not lower UAE in subjects selected because of an elevated UAE instead of hyperlipidemia. In the observational cohort study the use of statins similarly was not associated with a fall in UAE, UAE instead increased. Statin treatment was not associated with a significant change in GFR in these subjects with only modestly impaired GFR.
INTRODUCTION

Statins (HMG-CoA reductase inhibitor) are widely used for lowering of LDL and total cholesterol. It has been well documented that these drugs improve cardiovascular outcomes [1-5]. Less is known on the effect of statins on renal outcome, e.g. on urinary albumin excretion (UAE) and glomerular filtration rate (GFR). Experimental studies showed statins to have a renoprotective effect [6,7]. Human data mostly report a statin induced lowering of UAE in patients with advanced renal disease [8] and in type 2 diabetic patients with microalbuminuria [9-11], but no change [12] or even an increase in albuminuria has also been described [13-16].

With respect to the preservation of renal function, recent analyses of some large cardiovascular trials suggested renal function to benefit from statin therapy [17-21]. These are secondary or post hoc analyses of kidney function in studies in large secondary prevention trials mostly performed in high risk individuals with high cholesterol levels. The impact of statins in subjects with an elevated UAE without clearly elevated cholesterol levels has not been studied yet. To that purpose we analyzed the effects of statins on UAE and GFR in a clinical trial that was performed in subjects with a urinary albumin loss of 15-300 mg/day (the PREVEND-IT study). As data derived from a randomized controlled trial (RCT) cannot be extrapolated to daily clinical practice [22], we in addition studied the relation between statin use and UAE and GFR in an observational cohort study (the PREVEND study).

METHODS

Study design and population
This study is part of the PREVEND (Prevention of Renal and Vascular End-stage Disease) study, an ongoing, prospective study which is designed to investigate the impact of urinary albumin excretion on renal and cardiovascular disease in the general population. The formation of the study cohort has previously been described in detail [23]. Briefly, in 1997 a cohort of subjects aged 28-75 years enriched for an elevated urinary albumin excretion was drawn from the population of the city of Groningen. Overall 8592 subjects gave written informed consent and were included in 1997 in the observational cohort for extensive baseline screening. Of these 8592 subjects, 864 were selected for the PREVEND Intervention Trial (PREVEND IT), a clinical trial aimed to study the effect of
fosinopril and pravasatin on cardiovascular outcome (see below). The local medical ethics committee approved the PREVEND and the PREVEND-IT studies.

The observational cohort study
These 8592 subjects were followed for cardiovascular and renal morbidity and mortality since baseline screening. They were invited for a 2nd screening after a mean follow-up of 4.2 years (range 2.8-6.1). By then 246 subjects had died, 130 were lost to follow up and 1322 declined participation, leaving 6894 subjects who completed the second screening. Of these 6894 subjects we excluded those who participated in the PREVEND IT study (n=758), those of whom no complete information on drug use was available from the pharmacy prescription database (IADB) (n=2632) (see below), and the 64 subjects with incomplete data for the requested clinical parameters. Subjects with missing data were not different from the included subjects with respect to baseline characteristics. Thus 3440 subjects are available for analysis: 2963 who during the study period never had used statins and 477 statin users. The changes in UAE and in GFR from baseline versus second screening were studied in relation to the use of statins. The number of subjects included in this follow up allowed us to detect a difference in change in UAE of at least 0.20 mg/d and a change in GFR of at least 0.79 ml/min between statin users and non-statin users over the 4.2 year observational period with 80% power and alfa 0.05.

The PREVEND Intervention Trial (clinical trial)
The protocol of this study and the results on cardiovascular outcome have been described in detail elsewhere [23]. In short, 864 of the 8592 subjects participating in the PREVEND follow up cohort were included in this clinical trial. They were included when they had a UAE of 15-300 mg/day, a blood pressure less than 160/100 mmHg without use of antihypertensives, and plasma cholesterol <8.0 mmol/L, or <5.0 mmol/L in case of a previous myocardial infarction and without the use of lipid lowering agents. These 864 subjects were treated in a double blind, randomised, placebo-controlled trial with a 2x2 factorial design with fosinopril 20 mg/day or matching placebo and with pravastatin 40 mg or matching placebo during four years. In the present analysis the 788 subjects were included, of whom follow up on treatment was complete (n=644) or follow up of at least 3 months on treatment (the time that UAE and GFR were first measured on treatment) was available (n=144). The other 63 subjects had withdrawn from treatment before the effects of statin or placebo on UAE and GFR could be measured and 13 subjects had incomplete data for the requested clinical parameters. The changes in UAE
and GFR from baseline (that is for the start of the trial drugs) versus 4 year of follow up are used. The number of subjects without use of fosinopril (n=392) included in this study allowed us to detect a difference in change in UAE of at least 0.54 mg/d and a change in GFR of at least 2.16 ml/min between paravastatin and placebo over the 4 year observation period, with 80% power and alfa 0.05.

In those subjects that stopped the statin or matching placebo before the end of the trial study period, the last available value of UAE and GFR on treatment is used (last-value-carried-forward analysis).

**Measurements in both study protocols**

The methodology used in both the PREVEND observational cohort and for the PREVEND-IT randomised controlled trial has been described previously [23-24]. The screening examination included an interview on demographics, medical history and smoking habits. During physical examination, weight, height and blood pressure were measured. Body mass index (BMI) was calculated as weight (kg) divided by square of height (m²). Systolic and diastolic blood pressure were measured on two separate occasions in supine position at the right arm every minute for ten minutes with an automatic Dinamap XL Model 9300 series monitor (Johnson-Johnson Medical Inc, Tampa, Florida). Blood pressure was calculated as the mean of the last two measurements at both visits. Fasting blood was drawn for determination of total cholesterol, glucose and serum creatinine. Furthermore urine was collected during two days for measurement of urinary albumin excretion (UAE).

Plasma total cholesterol, plasma glucose and serum creatinine were determined by Kodak Ectachem dry chemistry (Eastman Kodak, Rochester, NY, USA), an automatic enzymatic method. During follow-up serum creatinine was measured by photometric determination with Jaffe method without deproteinisation (Merck KGaA, Darmstadt, Germany). Serum creatinine values at second screening were adjusted using an internally validated correction factor to correct for the change in determination technique. Urinary albumin concentration was determined by nephelometry with a threshold of 1.8 to 2.3 mg/l and intra- and interassay coefficients of variation of less than 2.2% and 2.6% respectively (Dade Behring Diagnostic, Marburg, Germany). Urinary albumin excretion is given as the mean of the two 24-hour urine excretions. GFR was estimated using the Modification of Diet in Renal Disease (MDRD) formula: 186 x (serum creatinine)⁻¹.¹⁵⁴ x (age)⁻⁰.²⁰³ x (0.742 if female).
The prescription database used in the observational study
Information on drug use was obtained from the InterAction Database (IADB), containing pharmacy-dispensing data from community pharmacies in the city of Groningen. Dutch patients usually register at a single community pharmacy and therefore this pharmacy can provide an almost complete listing of subject’s prescribed drugs. Pharmacy data contain, among others, information on the name of the drug dispensed, ATC (Anatomical Therapeutical Chemical) classification, date of prescription, number of days the drug was prescribed and the number of defined daily doses (DDDs) based on definition of WHO. The use of over the counter (OTC) drugs and in-hospital prescriptions are not included. Information on drug use was collected from at least one year prior to the date of the first screening until at least the second screening.

Exposure and outcome definitions
Subjects were defined as statin user in case they received at least one prescription of any statin the year preceding the second screening. If they already received a statin in the year prior to the first screening, they were defined as ‘continuers’. In case they started using statins after the first screening they were defined as ‘starters’. Subjects were considered as ‘non statin users’, when they had never received a prescription for any statin in the whole study period. We similarly registered the use of antihypertensive medication with a split up in agents interfering in the renin angiotensin system (RAS), such as ACE inhibitors or angiotensin II receptor blockers, and other antihypertensives. Also the use of lipid-lowering and glucose-lowering drugs was registered.

We studied also subgroups of statin users based on the prescribed daily dose (PDD), cumulative time exposure and type of statin. The PDD was calculated from the total amount of DDDs divided by the number of days of exposure. The DDDs for the most frequently prescribed statins in this study are: simvastatin 15 mg, pravastatin 20 mg, and atorvastatin 10mg. PDD was divided into PDD < 1.00, between 1.00-2.00 and more than > 2.00. Cumulative time exposure was divided into use of statin ≤ 1 year, between 1-3 years, and more than 3 years. Subjects who received only one type of statin during the study period were included into the analyses for the type of statin. Subjects who switched from one statin to another or subjects who had used a statin that was prescribed only to a small number of subjects were excluded for subgroup analysis for type of statin.

In both studies we assessed the change in UAE and GFR from first versus second screening as continuous variable. We also assessed a rise in UAE and a fall in GFR as a categorical variable. Subjects were divided into 4 classes of UAE
according to the level of UAE; normo-albuminuria (0-14.9 mg albumin/day), borderline micro-albuminuria (15-29.9 mg albumin/day), micro-albuminuria (30-299.9 mg albumin/day) or macro-albuminuria (> 300 mg albumin/day). Progression was defined as an increase of UAE of at least 50% and a change of at least one class during follow up. A fall in GFR in the categorical analysis was defined as a decline in GFR of at least 10%.

**Propensity score**

To control for potential differences in the characteristics of subjects between index group (statin users) and reference group (non-statin users), we used propensity scores. Propensity score is the probability that an individual would have been treated with statin based on individual’s observed pretreatment (in first screening) variables. The propensity score for an individual can be used to balance the covariates in observational studies, and thus reduce bias. The estimated propensity score for statin treatment was obtained from the fit of a logistic regression model for which we considered the following variables: age, gender, history of myocardial infarction, smoking status, body mass index, systolic blood pressure, diastolic blood pressure, serum cholesterol level, blood glucose level, UAE (in class category), e-GFR, use of antihypertensive, RAS agent and antidiabetic medications.

**Statistical analyses**

The baseline characteristics in both studies are reported as mean and standard deviation for continuous variables and as percentage for categorical variables. Because of its skewed distribution, logarithmic transformation of UAE was applied for further analyses and reported values are transformed back to the original scale (geometric means). Differences in population characteristics at baseline in the various groups under investigation were tested for continuous variables by Student’s t-test and for categorical variables by a Chi-square test.

In our observational study, in the primary analyses we compared the percentage change in log transformed UAE between the first and second screening for each category of statin-user with Student’s t-test.
Table-1. Baseline characteristics of the study cohort according to use of statins

<table>
<thead>
<tr>
<th></th>
<th>Observational study = 3440</th>
<th>Randomized controlled trial = 788</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No use of statins (n=2963)*</td>
<td>Use of statins (n=477)*</td>
</tr>
<tr>
<td>Male (%)</td>
<td>41.3</td>
<td>58.5</td>
</tr>
<tr>
<td>Age (years)</td>
<td>49.3 (+/- 11.8)</td>
<td>57.9 (+/- 9.8)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.0 (+/- 4.1)</td>
<td>27.7 (+/- 4.1)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>127.6 (+/- 20.2)</td>
<td>138.5 (+/- 22.1)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>73.5 (+/- 9.8)</td>
<td>77.4 (+/- 9.2)</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>4.8 (+/- 1.1)</td>
<td>5.5 (+/- 2.2)</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>5.5 (+/- 1.2)</td>
<td>6.2 (+/- 1.6)</td>
</tr>
<tr>
<td>Urinary albumin excretion (mg/24hr)</td>
<td>9.9 (4.3-23.1)</td>
<td>16.7 (4.9-56.8)</td>
</tr>
<tr>
<td>e-Glomerular filtration rate (ml/min/1.73m2)</td>
<td>79.6 (+/- 13.8)</td>
<td>75.3 (+/- 14.8)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>41.4</td>
<td>45.7</td>
</tr>
<tr>
<td>History of myocardial infarction (%)</td>
<td>1.5</td>
<td>19</td>
</tr>
<tr>
<td>Use of statins (%)</td>
<td>0</td>
<td>43.4</td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean and standard deviation and categorical variables are presented as percentage; Urinary albumin excretion is presented as geometric mean and 95% CI. * p value <.05 for all variables (except smoking) between use of statins and no use of statins (using Student’s t-test for comparing means and Chi-square test for comparing prevalences). ** p value >.05 for all variables between pravastatin vs. placebo (using Student’s t-test for comparing means and Chi-square test for comparing prevalences).
One way ANOVA was applied to test for changes in UAE between groups. Multivariate linear regression models were built to adjust for baseline age, sex, blood pressure, cholesterol, glucose, urinary albumin excretion, GFR, body mass index, history of myocardial infarction, use of agents interfering in the RAS, the change in blood pressure between the first and second screening, and for individual propensity score. In addition, in the three subgroup analyses (category of PDD, cumulative time and type of statin) we also adjusted for the two other variables. The same analyses were performed to study the association of statins and changes in GFR.

In the second analyses, we compared the association between statins and the progression of UAE, and categorical changes (more than 10%) in GFR, and calculated univariate and multivariate relative risks (RR’s) with adjustment for potential confounders and for individual propensity score [27].

In our clinical trial, we compared the change in log transformed UAE and the percentage change in GFR between pravastatin and placebo using Student’s t-test. In addition, we performed an analysis separately in subjects who had received fosinopril and in those who did not. All calculations were performed with SPSS version 12.0.1 software (SPSS, Chicago, IL, USA). A p-value <0.05 was considered statistically significant.

RESULTS

**Baseline characteristics of the observational study and the clinical trial data**

Of the 3440 subjects followed in the observational study, 477 (13.9%) used statins and 2963 had never used statins in the study period. The characteristics of these subjects at baseline (1st screening) are reported in Table-1. Compared with the subjects that had never used statins, those who used statins were older and more frequently male, had a higher body mass index, blood pressure, plasma glucose, plasma cholesterol and urinary albumin excretion, and had a lower GFR. Furthermore, the statin users tended to have more co-morbidity, as suggested by a higher prevalence of previous myocardial infarction and more frequent use of antihypertensives in general, but also RAS inhibitors in particular and antidiabetics.

The baseline characteristics of the 788 subjects from the randomised clinical trial, that fulfilled the inclusion criteria for the present analysis, are also given in Table-1, according to the use of placebo or pravastatin. A comparison of baseline characteristics did not reveal any statistically
### Table-2 Use of pravastatin in relation to urinary albumin excretion in the randomized controlled trial

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>UAE-1 (mean and 95% CI)</th>
<th>UAE-2 (mean and 95% CI)</th>
<th>p value*</th>
<th>% change (mean and 95% CI)</th>
<th>p value**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>388</td>
<td>27.2 (12.5-59.4)</td>
<td>24.0 (8.9-64.5)</td>
<td>0.002</td>
<td>-11.9 (-18.6/-4.8)</td>
<td>Ref.</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>400</td>
<td>25.8 (11.3-58.6)</td>
<td>24.0 (9.1-63.5)</td>
<td>0.07</td>
<td>-6.9 (-13.8/0.5)</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>No use of fosinopril</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>194</td>
<td>26.2 (11.4-60.2)</td>
<td>26.7 (9.9-72.4)</td>
<td>0.71</td>
<td>+1.9 (-7.8/12.7)</td>
<td>Ref.</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>198</td>
<td>23.6 (11.6-51.1)</td>
<td>24.0 (9.9-58.2)</td>
<td>0.78</td>
<td>-1.5 (-11.4/9.5)</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>Use of fosinopril</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>194</td>
<td>28.3 (13.8-58.3)</td>
<td>21.5 (8.2-56.9)</td>
<td>&lt;0.001</td>
<td>-23.9 (-32.3/-14.6)</td>
<td>Ref.</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>202</td>
<td>28.4 (11.1-66.5)</td>
<td>23.9 (8.3-68.8)</td>
<td>0.03</td>
<td>-11.9 (-21.1/-1.7)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>GFR-1 (mean +/- SD)</th>
<th>GFR-2 (mean +/- SD)</th>
<th>p value*</th>
<th>% change (mean +/- SD)</th>
<th>p value**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>388</td>
<td>75.5 (+/-12.0)</td>
<td>74.5 (+/-12.2)</td>
<td>0.01</td>
<td>-0.9 (+/- 10.9)</td>
<td>Ref.</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>400</td>
<td>75.7 (+/-12.1)</td>
<td>76.3 (+/-22.4)</td>
<td>0.54</td>
<td>+1.0 (+/- 23.7)</td>
<td>0.17</td>
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<tr>
<td><strong>No use of fosinopril</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>194</td>
<td>75.9 (+/-11.6)</td>
<td>75.2 (+/-11.3)</td>
<td>0.21</td>
<td>-0.4 (+/- 10.8)</td>
<td>Ref.</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>198</td>
<td>76.2 (+/-11.3)</td>
<td>78.4 (+/-28.6)</td>
<td>0.25</td>
<td>+0.8 (+/- 10.2)</td>
<td>0.28</td>
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<tr>
<td><strong>Use of fosinopril</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>194</td>
<td>75.1 (+/-12.3)</td>
<td>73.9 (+/-13.1)</td>
<td>0.03</td>
<td>-1.4 (+/-11.0)</td>
<td>Ref.</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>202</td>
<td>75.2 (+/-12.8)</td>
<td>74.2 (+/-13.7)</td>
<td>0.08</td>
<td>-1.0 (+/-10.7)</td>
<td>0.70</td>
</tr>
</tbody>
</table>

UAE-1 (UAE at baseline), UAE-2 (UAE after 4 years) and % change in UAE are presented as geometric means and 95% CI; GFR-1 = GFR at baseline, GFR-2 = GFR after 4 years; p-value* indicates whether mean UAE or GFR is different between baseline and after 4 years follow-up (using paired sample t-test); p-value** indicates whether mean percentage change in UAE or GFR in pravastatin group is different compared to placebo (using two-samples t-test)
significant difference between the placebo and active drug treatment groups. However, as compared to the statin users in the observational study, the statin users in the clinical trial were younger, had a lower systolic blood pressure, less frequent a previous myocardial infarction, and used less other drugs. In contrast, the trial subjects in the placebo group were older and had a higher UAE compared with the non-statin users in the observational study.

**Propensity score**

The logistic regression model with statin use as dependent variable had an area under the ROC curve of 0.82, thus the model fits well. The mean propensity score of statin users was 0.31 (SD +/- 0.23) compared with 0.11 (SD +/- 0.12) for subjects not receiving statins.

**The association between statin use and urinary albumin excretion**

The effect of pravastatin on UAE in the randomised clinical trial is given in Table-2 (top panel). The impact of pravastatin on UAE can in fact only be correctly studied in the non-fosinopril users, as the ACE inhibitor lowered UAE significantly. In the subjects that did not use the ACE inhibitor, pravastatin did not result in a change in UAE (p=0.78), and the change in UAE on pravastatin was not different from the change in the placebo group (p=0.65). The progression in UAE was also not significant different between pravastatin and placebo group (RR 1.15 95% CI 0.76-1.74), neither in those who did not receive fosinopril (1.09; 0.64-1.88), nor in those who received fosinopril (RR 1.26; 0.66-2.41).

The association between statins and changes in UAE in the observational cohort study is shown in Table-3. UAE increased by +12.1% (p=0.002) in statin users compared to +3.6% (p=0.001) in those who never used statins. The rise in UAE in the statin users was significantly greater (p=0.008) than in the non-users, also after adjustment for other differences between the two groups and individual propensity score (p<0.001). When studying the various subgroups of statin users, the rise in UAE seems to be greatest in those who used statins continuously (+24.8%), those using the highest PDD of the statin (+17.3%), those with the longest duration of use (+18.5%), and those using pravastatin (+22.3%). These differences remained statistically significant after adjustment for other variables and propensity scores for continuous use (p<0.001), and longest duration of use (p=0.002), but not anymore for the highest PDD and pravastatin.
**Table 3. Use of statins in relation to urinary albumin excretion in the observational cohort study**

<table>
<thead>
<tr>
<th>Type of user</th>
<th>N</th>
<th>UAE-1 (mean and 95% CI)</th>
<th>UAE-2 (mean and 95% CI)</th>
<th>p value*</th>
<th>% increased (mean and 95% CI)</th>
<th>p value†</th>
<th>p value‡</th>
<th>p value¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>No use of statins</td>
<td>2963</td>
<td>9.9 (4.3-23.1)</td>
<td>10.3 (4.2-25.4)</td>
<td>0.001</td>
<td>3.6 (1.6-5.8)</td>
<td>Ref.</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td>Use of statins (all) #</td>
<td>477</td>
<td>16.7 (4.9-56.8)</td>
<td>18.7 (4.8-72.3)</td>
<td>0.002</td>
<td>12.1 (4.4-20.4)</td>
<td>0.01</td>
<td>&lt;0.001</td>
<td>0.003</td>
</tr>
</tbody>
</table>

**Type of user**

- Starter
- Continuer

**PDD**

- PDD ≤ 1.00
- PDD 1.00-2.00
- PDD > 2.00

**Cumulative time**

- ≤ 1 year
- 1-3 year
- > 3 year

**Type of statins**

- Simvastatin
- Atorvastatin
- Pravastatin

UAE-1 (UAE at first screening), UAE-2 (UAE at second screening), % change in UAE are presented as geometric mean and 95% CI; # : all subjects who used statins (defined as subjects who had used any statins a year prior to second screening, see methods section); PDD : prescribed daily dose; p-value* indicates whether UAE differs between first and second screening (using paired sample t-test); p-value† (crude) indicates whether delta UAE differs between groups (using one way ANOVA); p-value‡ associated with dummy variable for group, adjusted for baseline age, sex, blood pressure, cholesterol, glucose, UAE, body mass index, history of myocard infarct, start use RAS inhibitors, change on blood pressure, type of statins (for PDD) and PDD (for type of statins) (using multivariate linear regression analysis); p-value¶ adjusted for all those variables and individual propensity score.
The statin users had a higher risk of being progressor in class of UAE compared to non-statin users (16% vs 9%; $p<0.001$) with an covariates and propensity score adjusted relative risk of 1.49 (CI 1.07-2.08). In the various subgroups, the risk for being a progressor was significant in continuers (22% vs 9%; RRadj$ = 1.71$; CI 1.11-2.62) and in those with the cumulative time 1-3 years (18% vs 9%; RRadj$ = 1.70$; CI 1.07-2.82).

**The association between statin use and GFR**

In the randomised clinical trial, in the overall analysis, thus not separated for using an ACE inhibitor or not, the use of placebo was associated with a fall in GFR ($p=0.014$), while GFR did not change in the group that used the statin ($p=0.539$). The difference in continuous changes in GFR on pravastatin compared with placebo was not significantly different in the overall analysis ($p=0.165$), neither in the sub-groups who used an ACE inhibitor, nor in those who did not (Table-2, bottom panel). Analysed in a categorical way, the fall in GFR was also not significantly different between pravastatin and placebo (RR 0.82 95% CI 0.56-1.19), neither in those who did not receive fosinopril (0.63; 0.36-1.10), nor in those who received fosinopril (RR 1.02; 0.61-1.70).

Table-4 shows the association between statins and continuous changes in GFR in the observational cohort study. GFR fell 4.6% ($\pm13.5$) in those who used statins ($p<0.001$) as compared to 2.4% ($\pm11.2$) ($p<0.001$) in those who never used a statin. The difference in changes in GFR between these two groups was not statistically different after adjustment for covariables and individual propensity score ($p=0.35$). The fall in GFR, when analysed as 10% change was also not significantly different between the statin users (30,2%) and non- statin users (23,6%) (RR 1.17 95% CI 0.91-1.51). When looking at the various subgroup analyses, neither the continuous nor the categorical fall in GFR was significantly different in those who continued, those with the highest PDD, the longest duration of use, or in any of the individual statins compared to the group who never used statins during the study. The only significant difference observed was a fall in GFR in the group that started use of statins after the first screening.
Table 4. Use of statins in relation to GFR in the observational cohort study

<table>
<thead>
<tr>
<th>N</th>
<th>GFR-1 (mean +/- SD)</th>
<th>GFR-2 (mean +/- SD)</th>
<th>p-value*</th>
<th>% changed (mean +/- SD)</th>
<th>p-value†</th>
<th>p-value‡</th>
<th>p-value¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>No use of statins</td>
<td>2921</td>
<td>79.5 (+/- 13.8)</td>
<td>77.3 (+/- 13.9)</td>
<td>&lt;0.001</td>
<td>- 2.4 (+/- 11.2)</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td>Use of statins (all) #</td>
<td>469</td>
<td>75.3 (+/- 14.6)</td>
<td>71.5 (+/- 15.2)</td>
<td>&lt;0.001</td>
<td>- 4.6 (+/- 13.5)</td>
<td>&lt;0.001</td>
<td>0.11</td>
</tr>
</tbody>
</table>

**Type of user**
- **Starter**
  - 266 | 75.8 (+/- 14.4) | 71.5 (+/- 15.2) | <0.001 | - 5.3 (+/- 13.5) | <0.001 | <0.01 | 0.04 |
- **Continuer**
  - 203 | 74.6 (+/- 14.9) | 71.4 (+/- 15.3) | <0.001 | - 3.7 (+/- 13.5) | 0.31 | 0.37 |

**PDD**
- **PDD ≤ 1.00**
  - 175 | 74.4 (+/- 14.0) | 71.3 (+/- 14.0) | <0.001 | - 3.3 (+/- 12.5) | <0.001 | 0.31 | 0.23 |
- **PDD 1.00-2.00**
  - 214 | 75.2 (+/- 14.8) | 70.4 (+/- 15.9) | <0.001 | - 6.2 (+/- 15.0) | 0.73 | 0.92 |
- **PDD > 2.00**
  - 80 | 77.6 (+/- 15.6) | 74.8 (+/- 15.7) | 0.006 | - 3.1 (+/- 11.0) | 0.07 | 0.05 |

**Cumulative time**
- **≤ 1 year**
  - 67 | 76.8 (+/- 14.3) | 71.4 (+/- 14.7) | <0.001 | - 6.5 (+/- 13.4) | 0.001 | 0.06 | 0.09 |
- **1-3 year**
  - 154 | 75.5 (+/- 15.2) | 72.4 (+/- 15.6) | <0.001 | - 3.7 (+/- 14.0) | 0.79 | 0.97 |
- **> 3 year**
  - 248 | 74.8 (+/- 14.4) | 71.0 (+/- 15.1) | <0.001 | - 4.6 (+/- 13.2) | 0.21 | 0.62 |

**Type of statins**
- **Simvastatin**
  - 195 | 75.1 (+/- 15.4) | 71.3 (+/- 14.6) | <0.001 | - 4.2 (+/- 11.9) | 0.001 | 0.91 | 0.83 |
- **Atorvastatin**
  - 118 | 76.7 (+/- 15.2) | 72.1 (+/- 17.4) | <0.001 | - 5.9 (+/- 17.0) | 0.21 | 0.24 |
- **Pravastatin**
  - 63 | 75.2 (+/- 14.5) | 71.5 (+/- 14.5) | 0.002 | - 4.8 (+/- 11.4) | 0.56 | 0.66 |

GFR-1 = GFR at first screening, GFR-2 = GFR at second screening; # : all subjects who used statins (defined as subjects who had used any statins a year prior to second screening, see methods section) PDD : prescribed daily dose; p-value* indicates whether GFR differs between first and second screening (using paired sample t-test); p-value† (crude) indicates whether delta GFR differs between groups (using one way ANOVA); p-value‡ associated with dummy variable for group, adjusted for baseline age, sex, blood pressure, cholesterol, glucose, GFR, body mass index, history of myocard infarct, start use RAAS, change on blood pressure, type of statins (for PDD) and PDD (for type of statins) (using multivariate linear regression analysis). p-value¶ adjusted for all those variables and individual propensity score.
DISCUSSION

Our clinical trial data show no effect of a 4-year treatment with pravastatin on UAE nor on GFR. In the observational study a rise in UAE was observed in the subjects that used statins, especially when used continuously, for a longer time and in a higher dose. This rise in UAE was not associated with a statistically significant change in GFR, neither in case of longer duration of use or in case of a higher dose.

How do these data on UAE relate to literature? In both our studies we found no lowering of UAE in subjects using statins, as was suggested from some previous reports [9,10]. Tonolo et al [10] reported a 25% reduction of UAE from baseline after simvastatin in 19 normotensive microalbuminuric hypercholesterolemic type 2 diabetic patients. Similar results were observed in the study conducted by Nakamura et al [9], in which allocation to cerivastatin was associated with a reduction of UAE in 60 normotensive type 2 diabetics with microalbuminuria and dyslipidemia. Both studies had low sample size and were conducted in hyperlipidemic patients at higher risk for renal impairment. In a recent study in 344 type 2 diabetics, in contrast no effect of either rosuvastatin or atorvastatin on UAE was observed [12]. In our clinical trial we found no reduction in UAE, even not when considering that the dose of pravastatin we used was 40 mg, which is relatively high when expressed in DDD: in fact two DDD. Moreover, in our clinical trial the drug was given for a relatively long period of 4 years. In the observational study we even found a rise in UAE among statin users, in particular in association to longer duration of use. These data are in agreement with experimental data that statins may interfere in tubular albumin uptake as a result of the inhibition of HMG-CoA reductase in the proximal tubular cells [6,7]. The discrepancies in both the literature and in our two studies may be explained by either differences in patient characteristics and in the dose and type of statin used. Our clinical trial patients, though older, were in general in better health as expressed by a lower blood pressure, less frequent a previous myocardial infarction, and less frequent use of antihypertensive, lipid- and glucose lowering drugs than in the observational cohort.

How do the data on GFR relate to literature? Our two studies show that statins hardly influence GFR. In the clinical trial no change in GFR was noticed on the statin, whereas in the observational study a modest fall in GFR was observed in the subjects that used statins. This fall in GFR was however not statistically significant after adjustment for differences in baseline characteristics.

These findings contrast to previous suggestions from meta-analyses and post-hoc evaluations. In a meta-analysis of placebo-controlled studies published
before 2001 a beneficial effect of lipid lowering drugs was found on GFR. In this meta-analysis 362 patients with chronic kidney disease were included, divided over 13 studies (of which in 11 studies statins were used). The authors found a lower rate of GFR decline for lipid lowering drugs compared to placebo (difference being 1.9 (0.3 to 3.4) mL/min/year) [18]. In contrast with our patient population, all subjects in this meta-analysis had renal disease, mostly diabetic nephropathy or glomerulonephritis. Athyros et al showed in a subgroup analysis of the GREACE study that treatment with atorvastatin resulted in an increase in GFR, whereas in subjects not using atorvastatin GFR fell. The beneficial effect on GFR was more prominent in the lower two quartiles of baseline GFR and with higher atorvastatin doses [29]. In a subgroup analysis of the CARE study a post hoc analysis similarly found no effect of statins on GFR overall, but in the subjects with the most severe impairment in GFR pravastatin was associated with a less severe fall in GFR during follow up [19]. A subgroup analysis of data from 3 randomized controlled trials in 18,569 subjects with a previous acute coronary syndrome or who were at high cardiovascular risk showed that pravastatin reduced the rate of renal function loss by 8% versus placebo. Again, this effect was greater in subjects with more severe renal impairment [21]. In the URANUS study GFR was not influenced by either rosuvastatin or atorvastatin [12]. Literature so far seems therefore consistent, suggesting that statins may preserve or even improve renal function, especially in subjects with renal disease or more advanced renal function impairment. Since the number of such subjects is low in the PREVEND observational study and the PREVEND-IT randomized controlled intervention study, it might be that consequently in our studies a protective effect of statins on GFR decline could not be shown.

What are the strengths and weaknesses of our data? First, we included data from both a clinical trial and a large observational study. An advantage of using observational drug utilization data is that they reflect routine practice for large and representative populations, in contrast to the much smaller and selected populations in clinical trials [22]. Large observational data allows to extend data in a specific patient categories, that normally are selected for clinical trials. This is true in our clinical trial in which we included subjects with an elevated UAE, with otherwise no indication for statin therapy. This sharply contrast to the general patient population in daily practice that on indication receives statin treatment as in our observational cohort. Indeed, the subjects in the observational cohort study that used statins were more diseased subjects. In our cohort study, the propensity score was used to correct for bias caused by non-randomized assignment between statin users and non-users. Secondly, the observational study allows to study the
impact of duration of use, dose of the drug, and individual drug from the same drug class due to the detailed information regarding drug use during the whole 4 years study period. Third, in both studies we included a sufficient number of statin using subjects to be able to detect a difference in effect of the statin on albumin excretion of less than 1.0 mg/24 hr and on GFR of less than 4.0 ml/min, that is less than 1.0 ml/min/year.

One of the limitations of the study is the fact, that we, at least in the observational study only have data on UAE and GFR 4 years apart. A second limitation is that we are not informed on the actual intake of the drug. In the observational study, our data are based on the delivery of the drug from the pharmacist to the patient. It has however been shown, that such data give reliable information on drug use by the patient [20], especially in case of drugs that have to be used constantly, as is the case for statins. Drugs are delivered for a period of three months, and the patient needs to receive his/her next prescription again after that period. In the clinical trial we checked for compliance every three months, and included in this analysis only data obtained while the patient was still on medication. Third, propensity scores technique can not adjust for residual unmeasured covariates which probably influenced both prescription of statins and clinical outcomes, and thus residual bias is still possible. Finally, our data are limited to subjects with only modest renal damage, that is subjects with an elevated UAE and no more than stage 3 diminished GFR. We feel these data are however of interest for the general nephrologists, as also early renal damage is associated with an impaired renal and vascular prognosis.

What finally, is the clinical consequence of our data? Post marketing surveillance studies frequently bring new effects of a drug under attention, be it positive or negative. In that way we should pay attention to our finding of a rise in UAE in our observational. Though that finding was not confirmed in our randomised controlled clinical trial in fact designed to lower UAE, the data require close attention. This rise in UAE, fortunately was not associated with a fall in GFR.

In conclusion, our data show that in contrast to literature statins do not lower UAE in subjects with only modest renal damage (stage 1-3 CKD), neither in the RCT, nor in the observational cohort study. In the observational cohort study, in contrast, we found a modest rise in UAE related to high daily dose and longer duration of use. Because statins are widely used in the general population our results may be of public health importance and need confirmation in other studies.
REFERENCES


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