

28. Kalantar-Zadeh K, Moore LW, Tortorici AR *et al*. North American experience with Low protein diet for non-dialysis-dependent chronic kidney disease. *BMC Nephrol* 2016; 17: 90
29. KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2012; 3: 1–150
30. Kalantar-Zadeh K, Fouque D. Nutritional management of chronic kidney disease. *N Engl J Med* 2017; 377: 1765–1776
31. Isakova T, Gutiérrez OM, Smith K *et al*. Pilot study of dietary phosphorus restriction and phosphorus binders to target fibroblast growth factor 23 in patients with chronic kidney disease. *Nephrol Dial Transplant* 2011; 26: 584–591
32. Sigris M, Tang M, Beaulieu M *et al*. Responsiveness of FGF-23 and mineral metabolism to altered dietary phosphate intake in chronic kidney disease (CKD): results of a randomized trial. *Nephrol Dial Transplant* 2013; 28: 161–169
33. Shimada T, Muto T, Urakawa I *et al*. Mutant FGF-23 responsible for autosomal dominant hypophosphatemic rickets is resistant to proteolytic cleavage and causes hypophosphatemia in vivo. *Endocrinology* 2002; 143: 3179–3182
34. Ito N, Fukumoto S, Takeuchi Y *et al*. Comparison of two assays for fibroblast growth factor (FGF)-23. *J Bone Miner Metab* 2005; 23: 435–440
35. Karp HJ, Vaihia KP, Kärkkäinen MUM *et al*. Acute effects of different phosphorus sources on calcium and bone metabolism in young women: a whole-foods approach. *Calcif Tissue Int* 2007; 80: 251–258
36. St-Jules DE, Jagannathan R, Gutekunst L *et al*. Examining the proportion of dietary phosphorus from plants, animals, and food additives excreted in urine. *J Ren Nutr* 2017; 27: 78–83
37. Moe SM, Zidehsarai MP, Chambers MA *et al*. Vegetarian compared with meat dietary protein source and phosphorus homeostasis in chronic kidney disease. *Clin J Am Soc Nephrol* 2011; 6: 257–264
38. Iqbal TH, Lewis KO, Cooper BT. Phytase activity in the human and rat small intestine. *Gut* 1994; 35: 1233–1236
39. Schlemmer U, Frølich W, Prieto RM *et al*. Phytate in foods and significance for humans: food sources, intake, processing, bioavailability, protective role and analysis. *Mol Nutr Food Res* 2009; 53(Suppl 2): S330–S375
40. Ix JH, Anderson CAM, Smits G *et al*. Effect of dietary phosphate intake on the circadian rhythm of serum phosphate concentrations in chronic kidney disease: a crossover study. *Am J Clin Nutr* 2014; 100: 1392–1397
41. Vervloet MG, van Ittersum FJ, Büttler RM *et al*. Effects of dietary phosphate and calcium intake on fibroblast growth factor-23. *Clin J Am Soc Nephrol* 2011; 6: 383–389
42. Block GA, Wheeler DC, Persky MS *et al*. Effects of phosphate binders in moderate CKD. *J Am Soc Nephrol* 2012; 23: 1407–1415

Received: 12.6.2018; Editorial decision: 29.10.2018

Nephrol Dial Transplant (2019) 34: 1699–1706

doi: 10.1093/ndt/gfy159

Advance Access publication 1 September 2018

Proteinuria and cholesterol reduction are independently associated with less renal function decline in statin-treated patients; a *post hoc* analysis of the PLANET trials

Nienke M.A. Idzerda¹, Michelle J. Pena¹, Hans-Henrik Parving², Dick de Zeeuw¹ and Hiddo J.L. Heerspink¹

¹Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands and ²Department of Medical Endocrinology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Correspondence and offprint requests to: Hiddo J.L. Heerspink; E-mail: h.j.lambers.heerspink@umcg.nl

ABSTRACT

Background. Statins have shown multiple effects on different renal risk factors such as lowering of total cholesterol (TC) and lowering of urine protein:creatinine ratio (U_{PCR}). We assessed whether these effects of statins vary between individuals, the extent of discordance of treatment effects on both TC and U_{PCR} within an individual, and the association of responses in TC and U_{PCR} with estimated glomerular filtration rate (eGFR) decline.

Methods. The PLANET I and II (Renal effects of Rosuvastatin and Atorvastatin in Patients Who Have Progressive Renal Disease) trials examined effects of atorvastatin and rosuvastatin on proteinuria and renal function in patients with proteinuria. We *post hoc* analysed 471 therapy-adherent proteinuric patients from the two trials and assessed the individual variability in U_{PCR} and TC response from 0 to 14 weeks and whether these

responses were predictive of eGFR decline during the subsequent 9 months of follow-up.

Results. U_{PCR} and TC response varied between individuals: mean U_{PCR} response was -1.3% (5th–95th percentile -59.9 to 141.8) and mean TC response was -93.9 mg/dL (-169.1 to -26.9). Out of 471 patients, 123 (26.1%) showed a response in U_{PCR} but not in TC, and 96 (20.4%) showed a response in TC but not in U_{PCR} . eGFR (mL/min/1.73 m²) did not decrease significantly from baseline in both U_{PCR} responders [0.4; 95% confidence interval (CI) -1.6 to 0.9 ; $P = 0.54$] and TC responders (0.3; 95% CI -1.8 to 1.1 ; $P = 0.64$), whereas U_{PCR} and TC non-responders showed a significant decline in eGFR from baseline (1.8; 95% CI 0.6 – 3.0 ; $P = 0.004$ and 1.7 ; 95% CI 0.5 – 2.9 ; $P = 0.007$, respectively). A lack of response in both parameters resulted in the fastest rate of eGFR decline (2.1; 95% CI 0.5 – 3.7 ; $P = 0.01$). These findings were not different for rosuvastatin or atorvastatin.

Conclusions. Statin-induced changes in cholesterol and proteinuria vary between individuals and do not run in parallel within an individual. The initial fall in cholesterol and proteinuria is independently associated with a reduction in eGFR decline. This highlights the importance of monitoring both cholesterol and proteinuria after initiating statin therapy.

Keywords: cholesterol, proteinuria, renal function, response variability, statins

INTRODUCTION

Although statins uniformly confer cardiovascular protection in diabetic and non-diabetic patients [1, 2], their effects on slowing chronic kidney disease (CKD) progression are inconsistent [3]. The Study of Heart and Renal Protection (SHARP) trial showed that treatment with simvastatin plus ezetimibe did not slow renal disease progression in a large population of CKD patients during 4.8 years of follow-up [4]. In the PLANET I and II trials, rosuvastatin did not confer beneficial renal effects, whereas treatment with atorvastatin reduced proteinuria and slowed renal function decline [5]. Of note, in the PLANET trials, it seemed that the individual cholesterol and proteinuria response to atorvastatin and rosuvastatin varied between patients. Whether individual responses in both proteinuria and cholesterol are congruent within an individual is unknown. In other words, no studies have investigated whether a response in cholesterol is accompanied by a response in proteinuria within an individual. It is not yet known how this variability in response in proteinuria and cholesterol between and within individual patients is associated with renal function decline.

We therefore performed a *post hoc* analysis of the PLANET I trial (Renal Effects of Atorvastatin and Rosuvastatin in Patients with Diabetes Who Have Progressive Renal Disease) and the PLANET II trial (Prospective Evaluation of Proteinuria and Renal Function in Non-diabetic Patients with Progressive Renal Disease). First, we assessed the variability in cholesterol and proteinuria response between individual patients. Secondly, we examined the extent of discordance in proteinuria and cholesterol within individual patients, and subsequently determined whether these responses were predictive of change in renal function.

MATERIALS AND METHODS

This *post hoc* analysis includes the combined population of the PLANET I and PLANET II trials. The PLANET I trial (NCT00296374) was a randomized, double-blind, multicentre study in patients with type 1 or 2 diabetes and proteinuria [urine protein:creatinine ratio (U_{PCR}) 500–5000 mg/g]. The PLANET II trial (NCT00296400) was a similar study of patients with proteinuria but without diabetes. A total of 545 patients were included in the intention-to-treat population of the combined trials. The design of the study has been described previously [5]. In brief, patients were randomly assigned to treatment with rosuvastatin 10 mg, rosuvastatin 40 mg or atorvastatin 80 mg, and followed for 1 year. During an 8-week lead-in period, patients were given dietary advice, underwent

optimization of existing anti-hypertensive treatment and discontinued statin therapy (if applicable). Patients had to be receiving treatment with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or both for at least 3 months before the first screening visit. After randomization, patients collected first morning void urine samples on 3 consecutive days prior to the randomization visit (Week 0), and then at 14, 26, 39 and 52 weeks for assessment of U_{PCR} .

The trials were performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Ethics committees and institutional review boards approved the research protocol. All patients gave written informed consent.

Patients

Patients aged ≥ 18 years and with low-density lipoprotein cholesterol (LDL-C) concentrations of ≥ 90.1 mg/dL with type 1 or 2 diabetes (PLANET I) or without diabetes (PLANET II) were enrolled. The main exclusion criteria were glycated haemoglobin (HbA1c) levels $> 11\%$, statin intolerance, presence of familial hypercholesterolaemia or known Type 3 hyperlipoproteinaemia, severe renal impairment [estimated glomerular filtration rate (eGFR) < 40 mL/min/1.73 m², 1 week before randomization], active liver disease and use of immunosuppressive drugs for treatment of proteinuria or renal disease or both within 3 months of the first screening visit.

For this *post hoc* study, data were analysed from 471 patients who adhered to study medication (defined as administration of $> 80\%$ of dispensed study medication as determined by pill count), and had total cholesterol (TC) and U_{PCR} measurements available at baseline and at 14 weeks post-randomization.

Measurements

Serum creatinine concentration was measured at the screening visit, randomization visit and then after 4, 8, 14, 26, 39 and 52 weeks follow-up. eGFR was calculated with the Modification of Diet in Renal Disease equation [6]. LDL-C was calculated by the Friedewald equation unless triglyceride concentration was > 400 mg/dL, in which case a β -quantification measurement was used. All laboratory analyses, including first morning void urine analysis, were performed at central laboratories (Covance; Indianapolis, IN, USA, and Geneva, Switzerland).

Statistical analysis

We assessed the change in U_{PCR} and the change in TC from baseline to Week 14. U_{PCR} change was calculated as the ratio of U_{PCR} at Week 14 divided by baseline on the log scale. Change in TC was calculated as the difference between TC levels at Week 14 and at baseline on the natural scale. We considered the treatment effects of the statins to be fully present at Week 14.

Patients were divided into subgroups according to their response in U_{PCR} and TC. A response in U_{PCR} was defined as a decrease in U_{PCR} compared with baseline and a non-response in U_{PCR} was defined as an increase in U_{PCR} , compared with baseline. A response in TC was defined by a decline of ≥ 100 mg/dL, compared with baseline, whereas a non-response in TC was defined by a decline of < 100 mg/dL, compared with baseline. A response or a non-response in both

U_{PCR} and TC were considered concordant responses, whereas a response in one parameter and a non-response in the other was classified as a discordant response. In an additional analysis we considered finer categories of U_{PCR} response (≤ -30 , > -30 to ≤ 0 , > 0 to ≤ 30 and $> 30\%$ change) and TC response (≤ -125 , > -125 to ≤ -100 , > -100 to ≤ -75 and > -75 mg/dL change). All categories were chosen *post hoc*, with the aim of providing easily understandable thresholds and approximately equal sample sizes in each subgroup. Similar categories of proteinuria responses were used in previous studies [7, 8].

Categorical variables are reported as frequencies and percentages. Means (SD) were provided for variables with a normal distribution. Means [calculated by $1 - \exp(\text{geometric mean change on log scale})^* - 100$] and 95% confidence intervals (CIs) or 5th–95th percentile are presented for U_{PCR} change. Differences between groups in continuous variables were tested with analysis of variance with Bonferroni adjustments for multiple comparisons, or with Kruskal–Wallis test with Dunn’s test for multiple comparisons for non-normally distributed data. Chi-square tests were used to test differences in categorical variables.

For this *post hoc* study, we used a landmark approach and determined the slope of eGFR change after the initial response to statin therapy was established [9]. Since it is known that eGFR varies from day to day within an individual [10], the mean eGFR of Weeks 8 and 14 was used as the baseline value to calculate the ‘on treatment’ eGFR slope to Week 52.

A random effects mixed measures model was used to assess the relationship between the magnitude of TC and U_{PCR} response and the ‘on treatment’ rate of subsequent eGFR change. In order to explore this relationship, U_{PCR} and TC response groups, stratified by responder and non-responder groups, were entered in the model as a fixed effect. The model also included visit as a fixed effect and response strata by visit as interaction term. The analysis was adjusted for age, sex, race and baseline eGFR, systolic and diastolic blood pressure, cholesterol, body mass index, HbA1c and log-transformed proteinuria. To allow generality for the covariance structure, the variance-covariance structure was assumed to be unstructured.

Two-sided P-values < 0.05 indicated statistical significance. Data were analysed with Statistical Analysis System (SAS) version 9.3 (SAS Institute, Cary, NC, USA) and R version 3.3.1 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Variability in cholesterol and proteinuria response between individuals

U_{PCR} response showed a large variability between patients in all treatment groups combined: the mean U_{PCR} response was -1.3% (5th–95th percentile -59.9 to 141.8) and the mean TC response -93.9 mg/dL (-169.1 to -26.9). In the atorvastatin group, mean U_{PCR} response was -9.9% (-58.9 to 84.4) and mean TC response was -99.0 mg/dL (-168.8 to -36.5). In the rosuvastatin 10 mg/day group, mean U_{PCR} response was -4.2% (-62.5 to 119.9) and mean TC response was -79.5 mg/dL (-156.5 to -32.1). In the rosuvastatin 40 mg/day group, mean

U_{PCR} and TC response were $+9.6\%$ (-54.8 to 167.8) and -98.1 mg/dL (-174.5 to -14.5), respectively. In the atorvastatin group, 57.3% of patients showed a reduction in U_{PCR} and 49.1% showed a > 100 mg/dL reduction in TC. In the low-dose and high-dose rosuvastatin group, a reduction in U_{PCR} was observed in 45.2 and 43.9% of patients, respectively, and 30.3 and 48.0% showed a > 100 mg/dL reduction in TC, respectively. The distribution of patients according to all pre-defined response categories is illustrated in Figure 1.

Variability in proteinuria and cholesterol response within individuals

The number of patients with various response patterns in both TC and U_{PCR} is reported in Table 1. In 26.1% of patients, there was a reduction in U_{PCR} but no response in TC ($\Delta TC > -100$ mg/dL). Conversely, 20.4% of patients showed a > -100 mg/dL reduction in TC but not a reduction in U_{PCR} . Thus, 46.5% of patients showed a discordant response in U_{PCR} and TC. A similar discordance in response was observed when atorvastatin and rosuvastatin groups were analysed separately (Table 1). As expected from the original article, the proportion with a lack of response in both U_{PCR} and TC was lowest with atorvastatin 80 mg. Results remained similar when the analysis was performed for LDL-C and urinary albumin excretion (U_{ACR}) instead of TC and U_{PCR} (Supplementary data, Tables S2 and S3). Results remained consistent when TC was expressed as percentage change (Supplementary data, Table S4). When analysed on a continuous scale, we observed no correlation between U_{PCR} and TC response in the combined treatment groups (Pearson correlation $r = 0.06$, $P = 0.23$) and when they were analysed separately ($r = 0.10$, $P = 0.22$; $r = 0.06$, $P = 0.45$; $r = 0.02$, $P = 0.80$) for rosuvastatin 10 mg, rosuvastatin 40 mg and atorvastatin 80 mg, respectively; Figure 1).

The baseline characteristics stratified for combined U_{PCR} and TC response are presented in Table 2. Both baseline U_{PCR} and TC levels were significantly different across response groups, with higher baseline values in the responder population. The response groups differed in statin treatment and body mass index. Statin-naïve patients ($N = 234$) showed on average a larger reduction in TC (-95.7 , -108.1 and 108.1 mg/dL for rosuvastatin 10 mg, rosuvastatin 40 mg and atorvastatin 80 mg, respectively) in comparison with patients who used statins before enrolment into the trial ($N = 237$; -73.8 , -89.0 and -88.7 mg/dL, respectively; Supplementary data, Table S6). The variability in cholesterol response between patients as well as the discordance of cholesterol and proteinuria response did not differ between these groups.

Association of short-term changes in U_{PCR} and TC with changes in renal function

We finally assessed whether changes in U_{PCR} and TC were associated with the slope of renal function decline. After multi-variable adjustment, U_{PCR} responders did not show a significant fall in eGFR (0.4; 95% CI -1.6 to 0.9 ; $P = 0.54$), whereas a significant decline in eGFR was observed in patients who did not show a reduction in U_{PCR} (1.8; 95% CI 0.6 – 3.0 ; $P = 0.004$; P versus non-responders 0.1; Figure 2A). Similarly, in TC

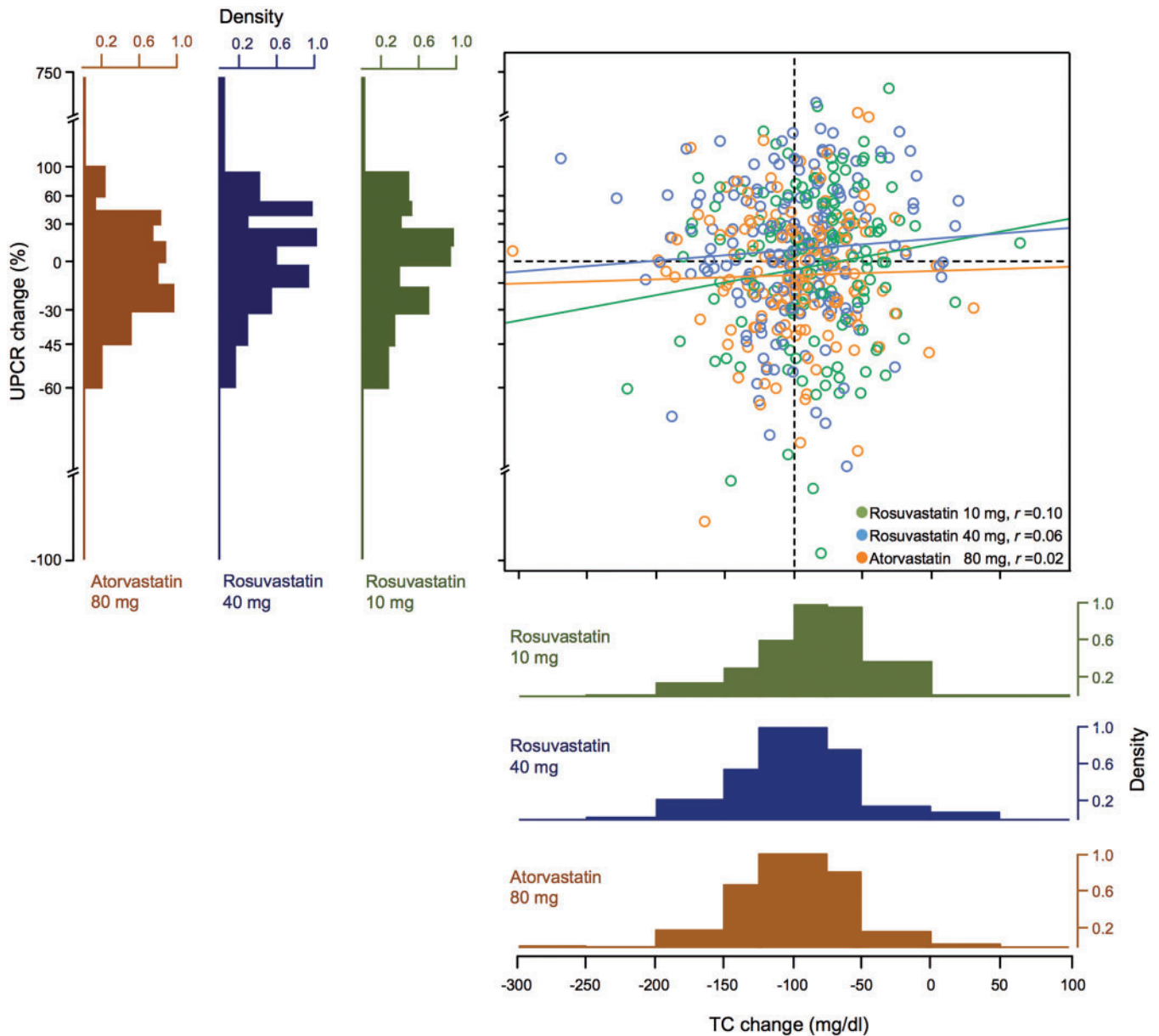


FIGURE 1: Correlation between U_{PCR} change and TC change from baseline to Week 14, represented for all treatment groups and per treatment group.

responders there was no evident change in eGFR (0.3; 95% CI -1.8 to 1.1; $P = 0.64$), whereas TC non-responders showed a significant eGFR decline (1.7; 95% CI 0.5–2.9; $P = 0.007$; P versus non-responders 0.2; **Figure 2B**). Additionally, the rate of eGFR decline in relation to the combined change in U_{PCR} and TC showed a stepwise increase in the rate of eGFR decline across the combined response groups (**Figure 2C**). The combination of a lack of response in both U_{PCR} and TC was associated with the fastest rate of eGFR decline (2.1; 95% CI 0.5–3.7; $P = 0.01$), whereas patients with a response in both parameters showed a stable renal function (0.4; 95% CI -1.5 to 2.2; $P = 0.70$; P versus non-responders 0.05). Similar associations between treatment responses and renal outcome were observed in the atorvastatin group as well as in both rosuvastatin groups.

DISCUSSION

The PLANET trials showed that the proteinuria response to rosuvastatin and atorvastatin differ despite a similar response in TC at a population level [5]. In this *post hoc* analysis we showed that U_{PCR} and TC response were not only variable between the statins, but also highly variable between patients for both statins. In addition to this between-patient variability, we also observed that a reduction in U_{PCR} was not accompanied by a TC reduction in a substantial number of patients. Intriguingly, the individual responses in U_{PCR} and TC correlated with individual renal function: a response in both U_{PCR} and TC resulted in a stable renal function, whereas non-responders in both U_{PCR} and TC showed the fastest rate of eGFR decline, independent of the type of statin. These new findings indicate that reductions

Table 1. Distribution of patients according to change in proteinuria (U_{PCR}) and change in TC from baseline to Week 14 in all treatment groups (A) and stratified for treatment with rosuvastatin 10 mg (B), rosuvastatin 40 mg (C) and atorvastatin 80 mg (D)

ΔU_{PCR} ΔTC	≤ -125 mg/dL	> -125 to ≤ -100 mg/dL	Total (%)	> -100 to ≤ -75 mg/dL	> -75 mg/dL	Total (%)
A. Total analysed population						
$\leq -30\%$	20 (4.2)	28 (5.9)	<i>10.2</i>	24 (5.1)	31 (6.6)	<i>11.7</i>
> -30 to $\leq 0\%$	30 (6.4)	28 (5.9)	<i>12.3</i>	27 (5.7)	41 (8.7)	<i>14.4</i>
Total (%)	<i>10.6</i>	<i>11.9</i>	22.5	<i>10.8</i>	<i>15.3</i>	26.1
> 0 to $\leq 30\%$	24 (5.1)	22 (4.7)	<i>9.8</i>	33 (7.0)	30 (6.4)	<i>13.4</i>
$> 30\%$	28 (5.9)	22 (4.7)	<i>10.6</i>	31 (6.6)	52 (11.0)	<i>17.6</i>
Total (%)	<i>11.0</i>	<i>9.3</i>	20.4	<i>13.6</i>	<i>17.4</i>	31.0
B. Rosuvastatin 10 mg						
$\leq -30\%$	7 (4.7)	8 (5.4)	<i>10.1</i>	8 (5.4)	13 (8.8)	<i>14.2</i>
> -30 to $\leq 0\%$	4 (2.7)	3 (2.0)	<i>4.7</i>	10 (6.8)	14 (9.5)	<i>16.2</i>
Total (%)	<i>7.4</i>	<i>7.4</i>	14.9	<i>12.2</i>	<i>18.2</i>	30.4
> 0 to $\leq 30\%$	7 (4.7)	5 (3.4)	<i>8.1</i>	9 (6.1)	17 (11.5)	<i>17.6</i>
$> 30\%$	5 (3.4)	6 (4.1)	<i>7.4</i>	10 (6.8)	22 (14.9)	<i>21.6</i>
Total (%)	<i>8.1</i>	<i>7.4</i>	15.5	<i>12.8</i>	<i>26.4</i>	39.2
C. Rosuvastatin 40 mg						
$\leq -30\%$	5 (2.9)	12 (6.9)	<i>9.8</i>	6 (3.5)	7 (4.0)	<i>7.5</i>
> -30 to $\leq 0\%$	16 (9.2)	10 (5.8)	<i>15.0</i>	8 (4.6)	12 (6.9)	<i>11.6</i>
Total (%)	<i>12.1</i>	<i>12.7</i>	24.9	<i>8.1</i>	<i>11.0</i>	19.1
> 0 to $\leq 30\%$	7 (4.0)	10 (5.8)	<i>9.8</i>	13 (7.5)	7 (4.0)	<i>11.6</i>
$> 30\%$	15 (8.7)	10 (5.8)	<i>14.5</i>	15 (8.7)	20 (11.6)	<i>20.2</i>
Total (%)	<i>12.7</i>	<i>11.6</i>	24.3	<i>16.2</i>	<i>15.6</i>	31.8
D. Atorvastatin 80 mg						
$\leq -30\%$	8 (5.3)	8 (5.3)	<i>10.6</i>	10 (6.7)	11 (7.3)	<i>14.0</i>
> -30 to $\leq 0\%$	10 (6.7)	15 (10.0)	<i>16.7</i>	9 (6.0)	15 (10.0)	<i>16.0</i>
Total (%)	<i>12.0</i>	<i>15.3</i>	27.3	<i>12.7</i>	<i>17.3</i>	30.0
> 0 to $\leq 30\%$	10 (6.7)	7 (4.7)	<i>11.3</i>	11 (7.3)	6 (4.0)	<i>11.3</i>
$> 30\%$	8 (5.3)	6 (4.0)	<i>9.3</i>	6 (4.0)	10 (6.7)	<i>10.7</i>
Total (%)	<i>12.0</i>	<i>8.7</i>	20.7	<i>11.3</i>	<i>10.7</i>	22.0

Non-responders were further divided by $> 30\%$ increase in U_{PCR} and a < 75 mg/dL decrease in TC. Responders were divided by a $> 30\%$ decrease in U_{PCR} and a > 125 mg/dL decrease in TC. Numbers are represented as frequency (%).

The values in italic indicate the % responders and non-responders per parameter (vertical for TC; horizontal for U_{PCR}).

The bold values indicate the proportion of patients in the combined response group (for example, proportion of patients showing a decrease in both U_{PCR} and TC).

in both U_{PCR} and TC are predictors of eGFR changes during statin therapy in diabetic and non-diabetic patients with proteinuria.

In the PLANET trials, treatment with rosuvastatin did not reduce U_{PCR} at a population level, whereas a significant reduction in U_{PCR} was observed in the atorvastatin group. Moreover, unlike atorvastatin-treated patients, patients in the rosuvastatin group showed an evident decline in renal function. However, a substantial number of patients in the rosuvastatin group did have a reduction in U_{PCR} , which was associated with less decline in renal function. This finding suggests that, although rosuvastatin did not lower proteinuria at a population level, rosuvastatin may result in beneficial renal effects in a specific proportion of patients. Thus, the faster eGFR decline with rosuvastatin is likely explained by the fact that many patients did not show a fall in proteinuria and relatively more patients showed a considerable increase in U_{PCR} , compared with atorvastatin-treated patients. Hence, the reduction in proteinuria may be used as an early marker to identify individuals who are more likely to show a reduction in renal risk during atorvastatin or rosuvastatin therapy.

The PLANET trials showed that differential proteinuria-lowering effects of the two statins were attained at similar cholesterol-lowering effects, suggesting that the proteinuria-lowering effects are dissociated from the lipid-lowering

effects [5]. This *post hoc* analysis supports these results by demonstrating a lack of correlation between changes in TC and U_{PCR} . Interestingly, $\sim 25\%$ of patients either did not show a reduction in U_{PCR} but showed a response in TC or vice versa, a finding that is consistent in both rosuvastatin and atorvastatin groups. The underlying mechanisms of this discordance in response are unknown but could be related to differences in drug disposition in different tissues within an individual [11, 12]. Additionally, individual patient characteristics such as inflammatory status could have influenced U_{PCR} response to a lesser or greater extent than TC response or vice versa. Of note, the extent of discordance was comparable for the different statins and was also observed when LDL-C instead of TC response was analysed. It could be possible that a true correlation between U_{PCR} and TC response could not be detected due to random variability in urinary protein excretion and lipid measurements. This is, however, unlikely since we have previously shown that variation in albuminuria response is reproducible upon re-exposure, suggesting that the individual albuminuria response is a true pharmacologic response and not a random phenomenon [13, 14].

This is not the first drug class for which it is shown that the response in multiple renal risk markers within an individual is discordant. Previous studies already showed that a reduction in blood pressure during renin-angiotensin-aldosterone system

Table 2. Baseline characteristics of the intention to treat population stratified by groups of change in proteinuria and cholesterol from baseline to Week 14 (n = 504)

	$\Delta TC \leq -100$ mg/dL $\Delta U_{PCR} \leq 0\%$	$\Delta TC \leq -100$ mg/dL $\Delta U_{PCR} > 0\%$	$\Delta TC > -100$ mg/dL $\Delta U_{PCR} \leq 0\%$	$\Delta TC > -100$ mg/dL $\Delta U_{PCR} > 0\%$	P-value
Number of patients	112 (22.2)	100 (19.8)	134 (26.6)	158 (31.3)	
U_{PCR} change ^a	-35.6 (-41.1 to -29.7)	45.2 (36.7 to 54.2)	-38.6 (-43.9 to -32.7)	52.3 (43.4 to 61.7)	<0.001
Cholesterol change ^b	-128.6 (26.8)	-136.9 (34.4)	-65.2 (28.1)	-64.2 (27.0)	<0.001
Age (years)	54.7 (12.6)	54.0 (11.9)	53.1 (13.5)	52.6 (13.6)	0.592
Gender, n (%)					0.134
Women	35 (31.2)	42 (42.0)	37 (27.6)	53 (33.5)	
Men	77 (68.8)	58 (58.0)	97 (72.4)	105 (66.5)	
Race, n (%)					0.625
Caucasian	102 (91.1)	87 (87.0)	117 (87.3)	134 (84.8)	
Black	4 (3.6)	8 (8.0)	5 (3.7)	9 (5.7)	
Hispanic	4 (3.6)	4 (4.0)	9 (6.7)	8 (5.1)	
Other	2 (1.8)	1 (1.0)	3 (2.1)	6 (3.8)	
Diagnosis of diabetes, n (%)	71 (63.4)	66 (66.0)	74 (55.2)	88 (55.7)	0.220
Systolic BP (mmHg)	137.4 (16.1)	134.5 (16.7)	136.3 (15.4)	132.4 (15.9)	0.057
Diastolic BP (mmHg)	80.2 (9.3)	79.8 (9.5)	79.2 (10.1)	80.3 (7.9)	0.752
Body mass index (kg/m ²)	31.2 (6.3)	32.5 (7.8)	29.8 (6.2)	30.0 (6.3)	0.007
Haemoglobin (g/L)	142.0 (15.5)	138.7 (14.9)	139.5 (18.1)	139.1 (16.4)	0.444
HbA1c (%)	7.1 (1.5)	7.1 (1.6)	6.7 (1.5)	6.7 (1.5)	0.089
TC (mg/dL)	274.4 (49.6)	301.6 (60.0)	222.8 (33.0)	230.6 (43.6)	<0.001
HDL-C (mg/dL)	50.0 (14.2)	49.2 (14.2)	49.3 (14.4)	50.0 (16.8)	0.958
LDL-C (mg/dL)	171.2 (43.0)	196.9 (53.9)	137.3 (27.9)	140.7 (31.8)	<0.001
Triglycerides (mg/dL)	274.3 (190.5)	273.1 (171.3)	182.7 (128.7)	196.8 (139.2)	<0.001
Serum CRP (mg/dL)	0.5 (0.5)	0.4 (0.4)	0.5 (0.7)	0.5 (0.9)	0.180
eGFR (mL/min/1.73 m ²) ^c	71.6 (25.0)	75.0 (33.3)	73.2 (22.3)	74.3 (29.3)	0.799
U_{PCR} (mg/g)	1327 (1188–1482)	1276 (1133–1437)	1182 (1071–1305)	1104 (1007–1210)	0.058
Treatment allocation, n (%)					<0.001
Rosuvastatin 10 mg	22 (19.6)	23 (23.0)	48 (35.8)	66 (41.8)	
Rosuvastatin 40 mg	44 (39.3)	46 (46.0)	36 (26.9)	57 (36.1)	
Atorvastatin 80 mg	46 (41.1)	31 (31.0)	50 (37.3)	35 (22.2)	

A negative concordant response is defined as no reduction in TC ($\Delta TC > -100$ mg/dL) and no reduction in U_{PCR} ($\Delta U_{PCR} > 0\%$). A positive concordant response is defined by a decrease in total cholesterol ($\Delta TC \leq -100$ mg/dL) and a decrease in U_{PCR} ($\Delta U_{PCR} \leq 0\%$). Numeric variables are presented as mean (SD) if normally distributed. U_{PCR} is presented as mean (95% CI). Categorical variables are presented as frequency (%).

^aPercentage change at Week 14 as compared with baseline.

^bAbsolute change at Week 14 as compared with baseline.

^cCalculated with the Modification of Diet in Renal Disease study equation.

BP, blood pressure; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol.

(RAAS) inhibition was not accompanied by a reduction in albuminuria in ~40% of patients. In addition, sodium-glucose cotransporter-2 inhibitors also exert multiple effects that can vary within an individual [15].

Similar to the anti-proteinuric effects that were observed during treatment with RAAS blockers [16, 17] and statins [18, 19], a reduction in U_{PCR} or TC induced by either rosuvastatin or atorvastatin was associated with less eGFR decline compared with a lack of response in either of these parameters. This illustrates the importance of monitoring proteinuria as well as cholesterol response in proteinuric patients after initiation of statins. Further prospective clinical trials are obviously needed to demonstrate whether specific targeting of proteinuria with statins will improve renal outcomes.

A limitation of this study inherent to the design of the PLANET trials and the *post hoc* nature of this analysis is that there is no placebo adjustment. It is important to note that the PLANET trials were not primarily aimed to investigate the dependence of renal outcome on various levels of lipid-lowering and anti-proteinuric responses. The observed responses could be the result of a regression to the mean phenomenon. Therefore,

the results can only be interpreted as hypothesis generating. Furthermore, arbitrary thresholds of U_{PCR} and TC were used to identify different response groups. However, similar categories of U_{PCR} response were used in previous studies [7, 8]. Moreover, stratification of response groups by quartiles of TC and U_{PCR} changes (absolute or percentage) yielded similar results. Finally, our analysis did not include hard clinical outcomes, and there was a relatively short follow-up period to assess changes in eGFR.

Previously we found that atorvastatin but not rosuvastatin reduced proteinuria and slowed renal function decline. These population-level findings cannot be directly extrapolated to an individual patient level. The current analysis shows that both in the rosuvastatin and the atorvastatin groups a substantial number of patients (more in the atorvastatin group than in both rosuvastatin groups) can be identified with a fall in proteinuria. Furthermore, proteinuria response to statin therapy can be discordant from cholesterol response within an individual. Both individual responses in proteinuria and cholesterol are independently associated with a more stable eGFR, suggesting that changes in both proteinuria and cholesterol should be individually monitored to identify who will benefit from statin therapy.

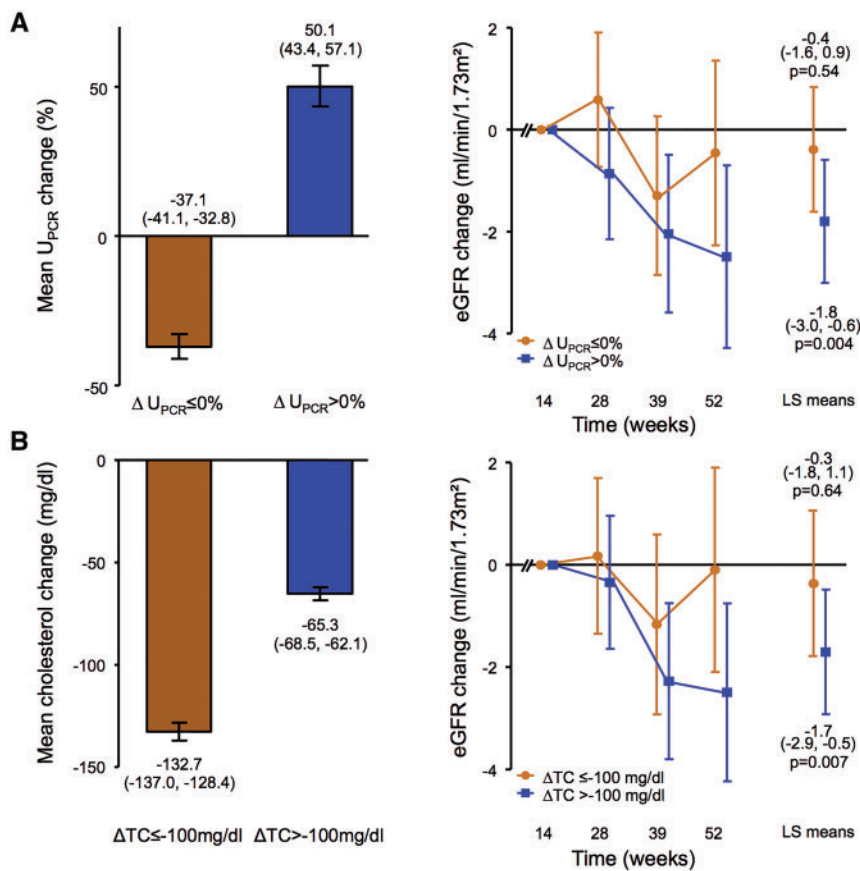


FIGURE 2: Change in eGFR from Weeks 11 to 52 according to U_{PCR} change and TC change from baseline to Week 14. **(A)** Mean U_{PCR} change and subsequent eGFR change in U_{PCR} responders ($\Delta U_{PCR} \leq 0\%$) and U_{PCR} non-responders ($\Delta U_{PCR} > 0\%$). **(B)** Mean TC change and subsequent eGFR change in cholesterol responders ($\Delta TC \leq -100$ mg/dL) and cholesterol non-responders ($\Delta TC > -100$ mg/dL). **(C)** Least square (LS) means of eGFR change from Weeks 11 to 52 according to combined U_{PCR} and TC change from baseline to Week 14.

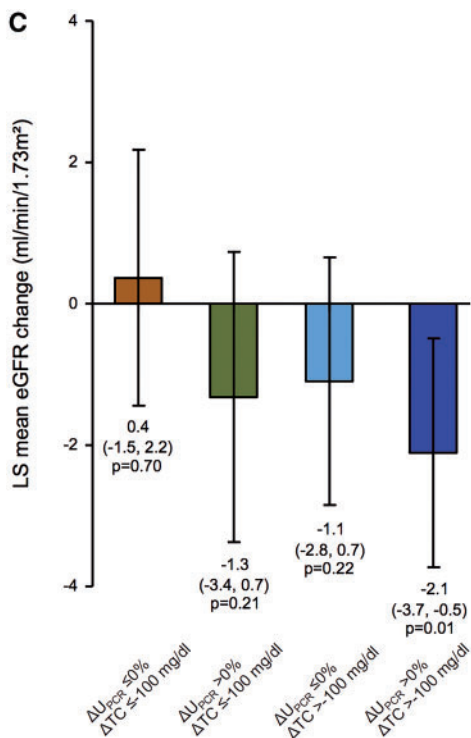


FIGURE 2c: Continued

SUPPLEMENTARY DATA

Supplementary data are available at [ndt online](http://ndt.online).

ACKNOWLEDGEMENTS

We thank all investigators, patients and support staff. We would also like to thank the members of the steering committee and the safety committee. The supplement lists the steering committee, the safety committee and the investigators of PLANET I and II.

FUNDING

The PLANET studies were sponsored by AstraZeneca. Funding for this analysis was received from Innovative Medicines Initiative (IMI) Biomarker Enterprise to Attack Diabetic Kidney Disease (BEAt-DKD) programme. The BEAt-DKD project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No. 115974. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and European Federation of Pharmaceutical Industries and Associations (EFPIA). H.J.L.H. is supported by a Vidi grant from the Netherlands Organisation for Scientific Research (917.15.306).

AUTHORS' CONTRIBUTIONS

H.-H.P., D.d.Z. and H.J.L.H. made contributions to the conception and design of the study and the acquisition of data. N.M.A.I. and H.J.L.H. conducted the analyses. N.M.A.I., H.J.L.H. and M.J.P. participated in drafting the article. M.J.P., H.J.L.H., D.d.Z. and H.-H.P. performed revisions for important intellectual content.

CONFLICT OF INTEREST STATEMENT

N.M.A.I. and M.J.P. report no conflicts of interest. D.d.Z. is consultant for and received honoraria (to employer) from AbbVie, Astellas, Eli-Lilly, Chemocentryx, Fresenius and Janssen. H.-H.P. is consultant for and received honoraria from AbbVie, Novartis and Astra Zeneca. H.J.L.H. is consultant for AbbVie, Astellas, Astra Zeneca, Boehringer Ingelheim, Fresenius, Janssen and Merck and has a policy that all honoraria are paid to his employer. The manuscript or portions thereof are not under consideration by another journal or electronic publication and have not been previously published.

REFERENCES

1. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L *et al.* Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170, 000 participants in 26 randomised trials. *Lancet* 2010; 376: 1670–1681
2. Taylor F, Huffman MD, Macedo AF *et al.* Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2013; CD004816; doi: 10.1002/14651858.CD004816.pub5.
3. Palmer SC, Navaneethan SD, Craig JC *et al.* HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. *Cochrane Database Syst Rev* 2014; CD007784; doi: 10.1002/14651858.CD007784.pub2.
4. Haynes R, Lewis D, Emberson J *et al.* Effects of lowering LDL cholesterol on progression of kidney disease. *J Am Soc Nephrol* 2014; 25: 1825–1833
5. de Zeeuw D, Anzalone DA, Cain VA *et al.* Renal effects of atorvastatin and rosuvastatin in patients with diabetes who have progressive renal disease (PLANET I): a randomised clinical trial. *Lancet Diabetes Endocrinol* 2015; 3: 181–190
6. Levey AS, Bosch JP, Lewis JB *et al.* A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* 1999; 130: 461–470
7. Eijkelkamp WB, Zhang Z, Remuzzi G *et al.* Albuminuria is a target for renoprotective therapy independent from blood pressure in patients with type 2 diabetic nephropathy: post hoc analysis from the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial. *J Am Soc Nephrol* 2007; 18: 1540–1546
8. Holtkamp FA, de Zeeuw D, de Graeff PA *et al.* Albuminuria and blood pressure, independent targets for cardioprotective therapy in patients with diabetes and nephropathy: a post hoc analysis of the combined RENAAL and IDNT trials. *Eur Heart J* 2011; 32: 1493–1499
9. Dafni U. Landmark analysis at the 25-year landmark point. *Circ Cardiovasc Qual Outcomes* 2011; 4: 363–371
10. Toffaletti JG, McDonnell EH. Variation of serum creatinine, cystatin C, and creatinine clearance tests in persons with normal renal function. *Clin Chim Acta* 2008; 395: 115–119
11. Blanco-Colio LM, Tunon J, Martin-Ventura JL *et al.* Anti-inflammatory and immunomodulatory effects of statins. *Kidney Int* 2003; 63: 12–23
12. Epstein M, Campese VM. Pleiotropic effects of 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitors on renal function. *Am J Kidney Dis* 2005; 45: 2–14
13. Petrykiv SI, de Zeeuw D, Persson F *et al.* Variability in response to albuminuria-lowering drugs: true or random? *Br J Clin Pharmacol* 2016; 83: 1197–1204
14. Petrykiv SI, Laverman GD, Zeeuw D *et al.* The albuminuria lowering response to dapagliflozin is variable and reproducible between individual patients. *Diabetes Obes Metab* 2017; 19: 1363–1370
15. Petrykiv S, Sjostrom CD, Greasley PJ *et al.* Differential effects of dapagliflozin on cardiovascular risk factors at varying degrees of renal function. *Clin J Am Soc Nephrol* 2017; 12: 751–759
16. Brenner BM, Cooper ME, de Zeeuw D *et al.* Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; 345: 861–869
17. Parving HH, Lehnert H, Brochner-Mortensen J *et al.* The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001; 345: 870–878
18. Tonolo G, Velussi M, Brocco E *et al.* Simvastatin maintains steady patterns of GFR and improves AER and expression of slit diaphragm proteins in type II diabetes. *Kidney Int* 2006; 70: 177–186
19. Bianchi S, Bigazzi R, Caiazza A *et al.* A controlled, prospective study of the effects of atorvastatin on proteinuria and progression of kidney disease. *Am J Kidney Dis* 2003; 41: 565–570

Received: 29.1.2018; Editorial decision: 1.5.2018