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Association between individual cholesterol and proteinuria response and exposure to atorvastatin or rosuvastatin

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Abstract

Aim: The PLANET trials showed that atorvastatin 80 mg but not rosuvastatin at either 10 or 40 mg reduced urinary protein to creatinine ratio (UPCR) at similar effects on LDL-cholesterol. However, individual changes in both UPCR and LDL-cholesterol during treatment with these statins varied widely between patients. This inter-individual variability could not be explained by patients' physical or biochemical characteristics. We assessed whether the plasma concentrations of both statins were associated with LDL-cholesterol and UPCR response.

Materials and methods: The PLANET trials randomized patients with a UPCR of 500-5000 mg/g and fasting LDL-cholesterol >2.33 mmol/L to a 52-week treatment with atorvastatin 80 mg, rosuvastatin 10 mg or 40 mg. For the current analysis, patients with available samples at week 52 and treatment compliance >80% by pill count were included (N = 295). The main outcome measurements were percentage change in UPCR and absolute change in LDL-cholesterol (delta LDL) from baseline to week 52.

Results: Median (interquartile range) plasma concentration at week 52 for atorvastatin 80 mg was 3.9 ng/mL (IQR: 2.1 to 8.7), for rosuvastatin 10 mg 1.0 ng/mL (IQR: 0.7 to 2.0) and for rosuvastatin 40 mg 3.5 ng/mL (IQR: 2.0 to 6.8). Higher plasma concentration of statin was associated with larger LDL-cholesterol reductions at week 52 [rosuvastatin r = −0.40 (P < .001); atorvastatin r = −0.28 (P = .006)]. The plasma concentration of both statins did not correlate with UPCR change [rosuvastatin r = 0.07 (P = .30); atorvastatin r = 0.16 (P = .13)].

Conclusions: Individual variation in plasma concentrations of rosuvastatin and atorvastatin was associated with LDL-cholesterol changes in patients. The individual variation in UPCR change was not associated with the plasma concentration of both statins.

KEYWORDS
albuminuria, atorvastatin, chronic kidney disease, drug exposure, LDL-cholesterol, PLANET, rosuvastatin, statins

1 | INTRODUCTION

Lipid-lowering therapy is part of the guideline recommended treatment for cardiovascular protection in patients with diabetes and chronic kidney disease.[1] The effects of statins on kidney function remain unclear. Some studies show a renoprotective profile of a particular statin whereas other studies have suggested that some statins may exert harmful effects.[2-6]

The PLANET trials were designed to assess the effects of atorvastatin and rosuvastatin on proteinuria and estimated glomerular filtration rate (eGFR). The trials showed that not all statins are similar in their effects on renal variables even at equipotent lipid-lowering effects.[7] PLANET showed that atorvastatin but not rosuvastatin decreased mean proteinuria, while mean eGFR decline was less with atorvastatin than with rosuvastatin despite similar cholesterol-lowering efficacy.[7] A post hoc analysis of these trials showed a large variation in individual patient responses in proteinuria and lipid variables for both statins, which could not be explained by clinical patient characteristics.[8] Drug concentrations of these statins or their active metabolites have been shown to

play a role in the variation of lipid-lowering effects.[9,10] Such data are not available for the proteinuria response to these statins.

To provide more insight into the underlying mechanisms of the individual variation in response to statins, we investigated whether drug plasma concentration of atorvastatin, rosuvastatin or their metabolites were a determinant of the individual albuminuria and LDL-cholesterol response. We also assessed which patient characteristics were associated with the variation in drug concentration.

2 | MATERIALS AND METHODS

2.1 | Study design and protocol

Combined data from the PLANET I and PLANET II trials were used for this analysis. The design and primary results of both trials were reported previously.[7] In short, the PLANET trials were randomized, double-blind, 52-week, parallel-group, multicentre, phase 3 studies. Eligible patients were randomly assigned to treatment with atorvastatin 80 mg/day, rosuvastatin 10 mg/day or rosuvastatin 40 mg/day

TABLE 1 Demographics and baseline characteristics of the included population. Data are presented as mean (SD) unless otherwise noted. Plasma concentrations are presented as median and interquartile range

	Atorvastatin 80 mg/day	Rosuvastatin 10 mg/day	Rosuvastatin 40 mg/day
n	92	90	113
Age, years	52.66 (13.64)	55.60 (12.73)	54.04 (12.21)
Gender (female) (%)	29 (31.5)	38 (42.2)	33 (29.2)
Race (%)			
Black	6 (10.5)	6 (11.5)	6 (8.7)
Caucasian	48 (84.2)	40 (76.9)	58 (84.1)
Hispanic	3 (5.3)	3 (5.8)	2 (2.9)
Other	0 (0.0)	3 (5.8)	3 (4.3)
BMI	31.19 (8.03)	30.82 (5.87)	30.26 (6.02)
Systolic BP (mm Hg)	138.30 (15.26)	133.73 (16.92)	136.27 (15.45)
Diastolic BP (mm Hg)	81.02 (8.63)	79.00 (8.47)	80.75 (9.40)
eGFR (ml/min/1.73m^2)	75.87 (29.51)	75.53 (25.37)	75.93 (28.25)
Total cholesterol (mmol/l)	4.28 (1.40)	4.58 (1.88)	3.93 (1.00)
LDL-cholesterol (mmol/l)	2.14 (1.02)	2.37 (1.65)	1.78 (0.75)
HDL-cholesterol (mmol/l)	1.23 (0.42)	1.36 (0.40)	1.30 (0.41)
Urinary protein to creatinine ratio (mg/g)[a]	1081 [684-1829]	1074 [694-1807]	1315 [777-1831]
Urinary albumin to creatinine ratio (mg/g)[a]	852 [456-1296]	813 [538-1333]	965 [616-1418]
Plasma concentration			
Rosuvastatin (ng/ml)	-	1.03 (0.67-1.97)	3.53 (1.98-6.77)
Atorvastatin (ng/ml)	3.87 (2.05-8.65)	-	-
Desmethylrosuvastatin (ng/ml)	-	0.24 (0.08-0.48)	0.45 (0.21-0.98)
Rosuvastatin lacton (ng/ml)	-	0.13 (0.07-0.28)	0.07 (0.04-0.13)
X2-OH-Atorvastatin (ng/ml)	7.38 (2.57-22.1)	-	-
X4-OH-Atorvastatin (ng/ml)	1.65 (0.70-3.74)	-	-

Abbreviations: BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate.
[a]Urinary protein to creatinine ratio and urinary albumin to creatinine ratio are reported as median (IQR).

for 52 weeks after an 8-week lead-in period in which dietary advice was given, existing hypertensive treatment was optimized and statins were discontinued if applicable. The study protocols of the PLANET trials are registered with clinicaltrials.gov (PLANET I: NCT00296374 and PLANET II: NCT00296400). The trials were performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol was approved by independent ethics committee. All participants signed written informed consent before the start of any study-specific procedure.

2.2 | Patients

PLANET I enrolled 325 patients with type 1 or type 2 diabetes and PLANET II enrolled 220 evaluable patients without diabetes (total N = 545). Both PLANET trials included patients aged ≥18 years with a urine protein to creatinine ratio (UPCR) between 500-5000 mg/g and fasting LDL-cholesterol of 2.33 mmol/L or more, and who were receiving treatment with an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) for at least 3 months before the first screening visit. Key exclusion criteria were HbA1c ≥ 11%, statin intolerance, severe hypertension and type 3 hyperlipoproteinaemia or if the patient used immunosuppressive drugs to treat proteinuria or renal disease within 3 months before the first screening visit. For the current analysis, 295 patients were available (169 in PLANET I and 126 in PLANET II). In total, 247 patients were not included for the following reasons: 178 had no plasma

sample available at week 52, 44 did not adhere to therapy (<80% compliance by pill count) and 25 subjects were excluded for other reasons.

2.3 | Measurements

Height was collected once at the start of the screening. Vital signs including blood pressure, weight and pulse rate, urine samples (collected at three consecutive morning voids before the study visit) and biochemistry, including but not limited to albumin, bilirubin, creatinine, blood urea nitrogen and a lipid panel consisting of LDL, HDL and total cholesterol, were collected at baseline and at week 4, 8, 14, 26, 39 and 52 in fasted condition on the morning of the study visit.

At each visit, patients collected three consecutive first morning void urine samples for measurement of urinary protein, albumin and creatinine. UPCR and urinary albumin to creatinine ratio (UACR) were calculated as the geometric mean from the three first morning void urine collections. The change in UPCR and UACR was defined as the log ratio of the week 52 value divided by the baseline UPCR or UACR value. A log transformation was applied to take into account the skewed distribution. eGFR was calculated with the Modification of Diet in Renal Disease Equation.[11] All clinical chemistry laboratory analyses were performed at central laboratories (Covance, Indianapolis, IN, USA, and Geneva, Switzerland).

Plasma concentrations of atorvastatin and rosuvastatin plus metabolites were measured with liquid chromatography mass
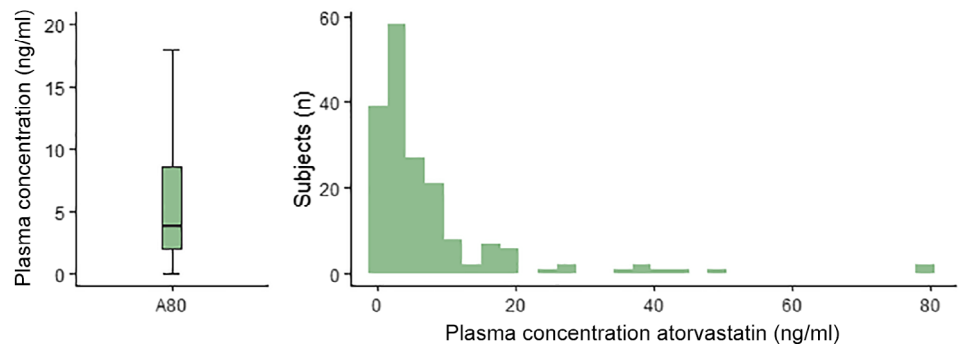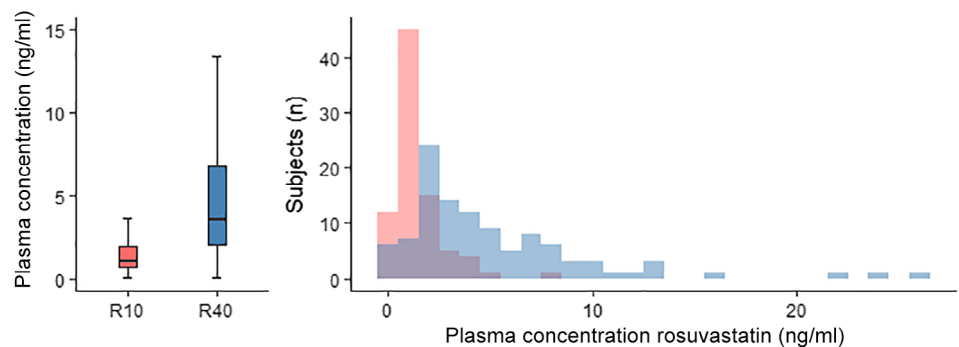

FIGURE 1 Large variation in plasma concentration between individuals during treatment with atorvastatin 80 mg, rosuvastatin 10 mg or rosuvastatin 40 mg

spectrometry (LC/MS-MS). For atorvastatin and its active metabolites detection took place using a Sciex API 4000 mass spectrometer in positive ionization MRM mode. For rosuvastatin and its active metabolites detection took place using a Sciex API 6500 mass spectrometer in positive ionization MRM mode. The mass spectrometric data were acquired and processed using Analyst (Applied Biosystems). Standard curves were constructed employing linear regression with $1/x2$ weighting. Plasma concentrations of both statins were performed by QPS (QPS laboratory, Groningen, the Netherlands).

2.4 | Statistical analysis

Changes in UPCR and UACR were calculated as % change and change in lipids by absolute change both from baseline to end of the study. We used descriptive statistics to report baseline demographic information. Pearson correlation was used to assess the relationship between drug concentrations of atorvastatin, rosuvastatin and change in LDL-cholesterol and percentage change UPCR and UACR. Two-sided P-values <.05 indicated statistical significance.

We imputed missing values of plasma concentrations <LLOQ (lower limit of quantification) with the lowest measured concentration below LLOQ. Multiple linear regression models were used to explore the relationships between the response variable (plasma concentrations) and the explanatory variables (clinical demographics and clinical chemistry). For the first model, each variable was tested as univariate and included in the multivariate model when the P-value was ≤.10. Using backwards elimination and forward inclusion, the best model was selected. Data were analyzed with R version 3.4.3 (The R Foundation for Statistical Computing Platform: i386-w64-mingw32/i386 [32-bit]). RStudio version 1.1.383 was used.

3 | RESULTS

Clinical and biochemical characteristics as well as statin plasma concentrations are presented in Table 1. The mean eGFR was 76 mL/min/1.73m^2 for all three dose groups, median UPCR ranged between 1074 and 1315 mg/g and mean LDL-cholesterol ranged between 1.8 and 2.4 mmol/L for the three dose groups.

Figure 1 shows a wide variation in the plasma concentrations among individual patients. This was observed for the different statins and dose groups. The rosuvastatin plasma concentration of 88 patients assigned to the 10 mg dose (44% of all patients receiving rosuvastatin) overlapped with the plasma concentration of patients assigned to the 40 mg dose.

The mean change in LDL-cholesterol at week 52 for atorvastatin 80 mg was −2.07 mmol/L (95% CI −4.2 to −0.18 mmol/L) and for the rosuvastatin group (10 and 40 mg) it was −2.0 mmol/L (95% CI −4.47 to 0.22; Figure 2). The mean change in UPCR at week 52 was −13.2% (95% CI −24.2 to −0.5) for atorvastatin 80 mg and for the rosuvastatin (10 and 40 mg) group combined it was 4.1% (95% CI −7.3 to 16.8; Figure 2). The mean change in UACR at week 52 was for atorvastatin 80 mg was −19.3% (95% CI −31.2 to −5.3) and for

the rosuvastatin (10 and 40 mg) group combined it was −5.4% (95% CI −17.2 to 8.1; Figure 2).

To assess whether the exposure of the statins correlated with lipid and UPCR responses, we correlated the plasma concentration at week
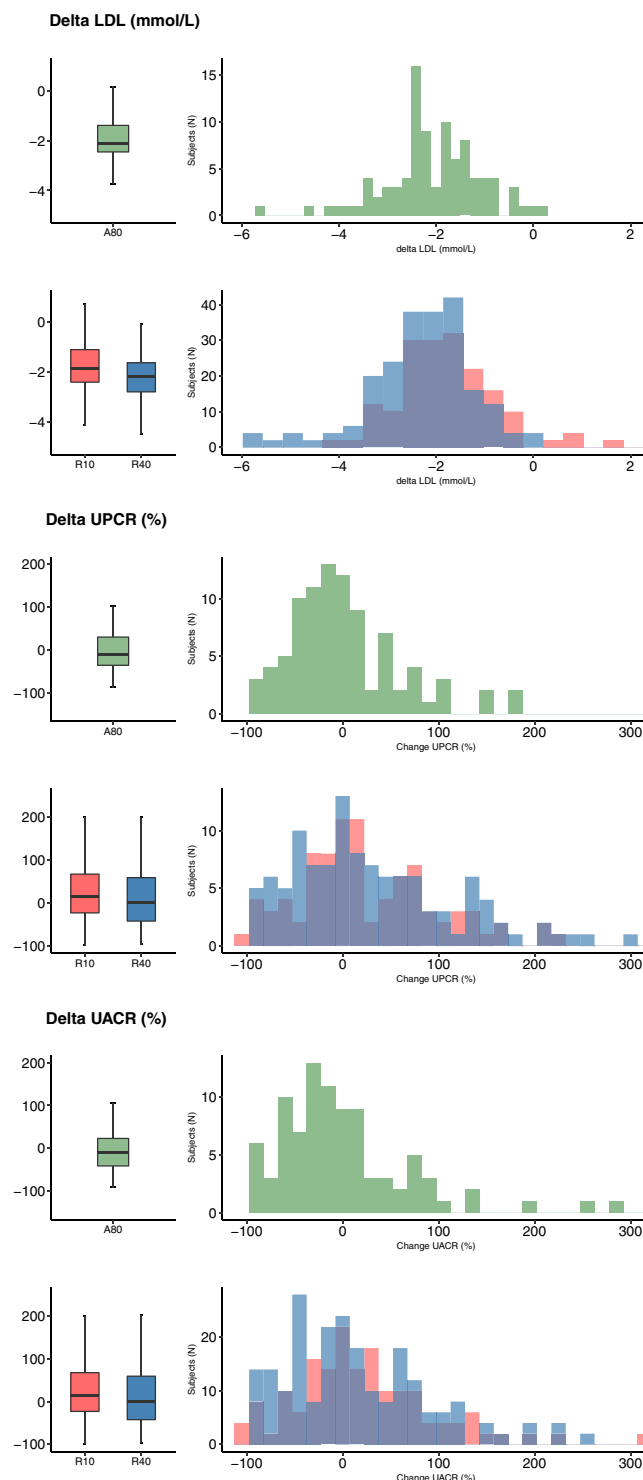

FIGURE 2 Large variation between individuals in change from baseline in LDL, urinary protein to creatinine ratio (UPCR) and urinary albumin to creatinine ratio (UACR) at week 52 during treatment with atorvastatin 80 mg (A80), rosuvastatin 10 mg (R10) and rosuvastatin 40 mg (R40)

TABLE 2 Pearson correlations between plasma concentrations of atorvastatin and rosuvastatin and delta LDL-cholesterol (mmol/l) and log delta urinary protein to creatinine ratio (UPCR) and urinary albumin to creatinine ratio (UACR) at week 52

	LDL change		UPCR change		UACR change	
	Pearson correlation	P-value	Pearson correlation	P-value	Pearson correlation	P-value
Atorvastatin	−0.28	.006	.16	.13	.14	.16
Rosuvastatin	−0.40	<.001	.07	.30	.03	.70

52 with those responses. Higher plasma concentration of statin was associated with larger LDL-cholesterol reductions at week 52 [rosuvastatin r = −0.40 (P < .001); atorvastatin r = −0.28 (P = .006); Table 2]. The variation in plasma concentration of both atorvastatin and rosuvastatin did not correlate with UPCR or UACR changes (Table 2 and Figure 3). The metabolites of both statins tended to

correlate with LDL-cholesterol change (Table S1). None of the metabolites correlated with UPCR or UACR change.

Finally, we assessed which patient characteristics were associated with the variation in plasma concentrations of the statins. None of the assessed patient characteristics were associated with variation in atorvastatin plasma concentration (Table 3). For rosuvastatin, lower eGFR
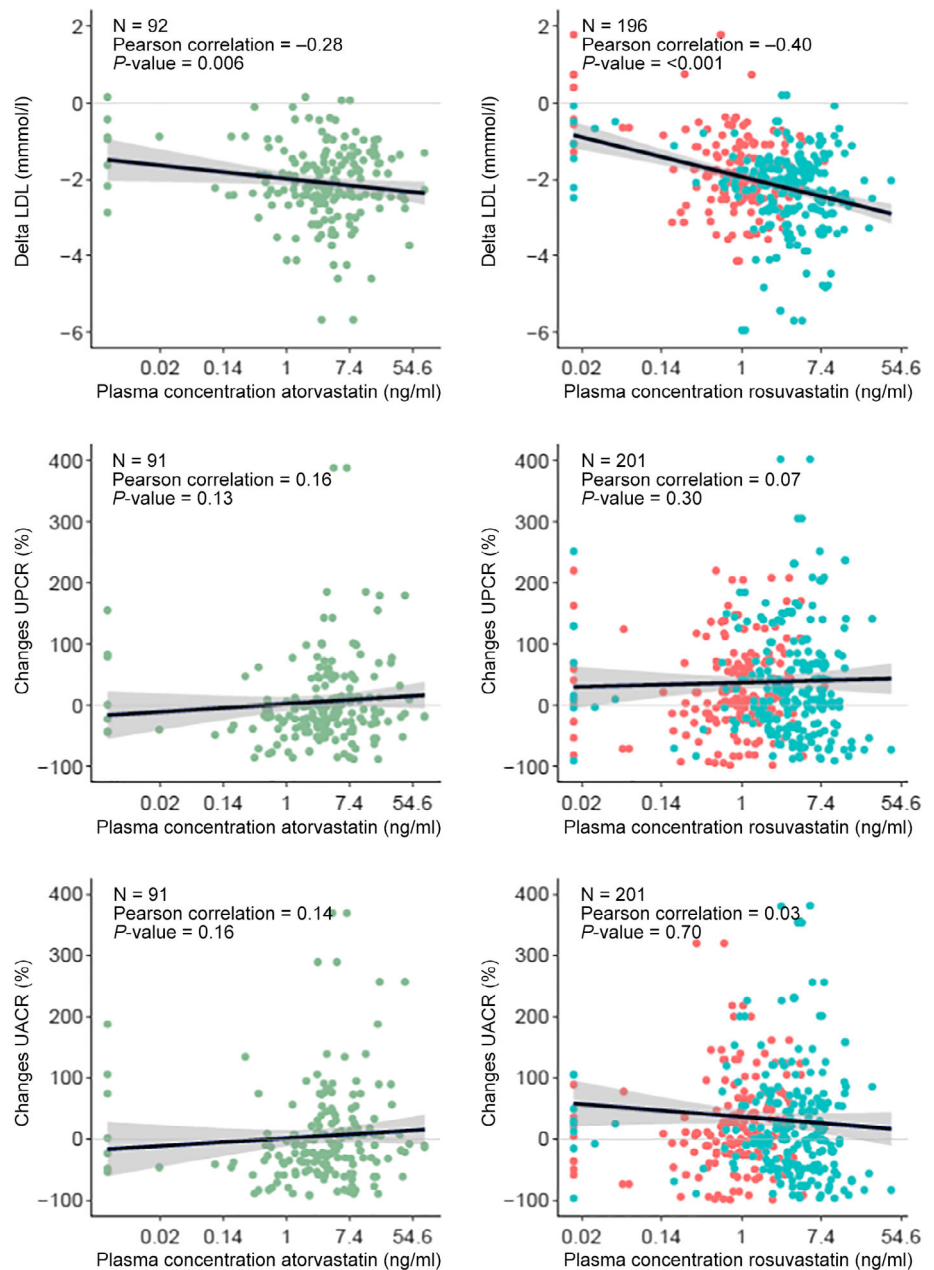

FIGURE 3 Plasma concentrations of atorvastatin (left panels) or rosuvastatin (right panels, R10 = red, R40 = blue) correlated with change from baseline in LDL-cholesterol (top panels) but not with change from baseline in urinary protein to creatinine ratio (UPCR) (middle panels) and urinary albumin to creatinine ratio (UACR) (bottom panels)

TABLE 3 Patient characteristics associated with plasma concentrations of atorvastatin 80 mg and rosuvastatin 10 and 40 mg at week 52

	Atorvastatin 80 mg/day				Rosuvastatin 10 and 40 mg/day			
	Univariate		Multivariate		Univariate		Multivariate[a]	
	β	P-value	β	P-value	β	P-value	β	P-value
Age (per year)	.02	.13	-	-	.01	.20	-	-
Gender	.31	.40	-	-	−.31	.27	-	-
BMI (baseline)	.01	.62	-	-	.01	.53	-	-
Bilirubin (μmol/l)	.03	.39	-	-	**.07**	**.06**	-	-
eGFR (per ml/min/1.73m^2)	−.00	.40	-	-	**−.00**	**.03**	**−.01**	**.04**
Serum albumin (g/l)	−.33	.34	-	-	**.68**	**.03**	**.63**	**.05**
Total protein (g/l)	.00	.76	-	-	−.02	.44	-	-
Urea nitrogen (mmol/l)	.08	.10	-	-	**.09**	**.01**	-	-

Note: P-value and β for p-values <0.1 are shown as bold.
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate.
[a]The R^2 of the multivariate model for rosuvastatin 0.21.

and higher serum albumin were independently associated with higher plasma concentration (Table 3).

4 | DISCUSSION

In this study we tested whether the large individual variation in lipid lowering as well as proteinuria lowering response to two different statins (atorvastatin and rosuvastatin) was associated with the achieved individual plasma statin levels in proteinuric patients with or without diabetes. We found that variations in plasma levels of the statins were associated with the variation in LDL-cholesterol-lowering effect. The large variation in proteinuria lowering was not associated with variations in plasma drug levels of either atorvastatin or rosuvastatin.

The large between-individual variation in plasma concentrations of atorvastatin and rosuvastatin is consistent with findings from other statin trials.[9,12,13] We found a marked overlap in plasma concentrations among patients assigned to rosuvastatin 10 mg and 40 mg, indicating that the individual exposure of a patient at low dose rosuvastatin can exceed the exposure of an individual treated with a four times higher dose. These data suggest that individual characteristics determine the plasma level of a statin. We found that a lower eGFR was associated with a higher rosuvastatin plasma concentration. Although hepatic clearance is the major route of rosuvastatin clearance, rosuvastatin is in part also excreted by the kidneys and the lower eGFR level may reflect diminished renal clearance. High serum albumin was also associated with higher plasma concentration. We speculate that because of the high protein binding of rosuvastatin, the free fraction decreases when serum albumin increases. As bound rosuvastatin cannot readily leave the capillaries, total plasma rosuvastatin may increase. As rosuvastatin is subject to both hepatic and, more importantly, renal elimination, the potentially lower fraction of unbound drug can also reduce the clearance leading to a higher total plasma concentration of rosuvastatin over time. Little is known from the literature about the association between plasma concentration and LDL response at an individual patient level.

Multiple dose finding studies with both atorvastatin and rosuvastatin have reported strong dose-dependent effects of statins on LDL-cholesterol.[14,15] Specifically, pharmacokinetic studies with rosuvastatin showed an approximately linear relationship between dose and area under the rosuvastatin concentration time curve for doses ranging from 5 to 80 mg.[16,17] However, these studies assessed the dose exposure relationship at a population level but not the exposure response at an individual patient level. We found that lower plasma concentrations of the statins were associated with a lower LDL-cholesterol response at an individual patient level. Given that higher doses are associated with higher plasma concentrations, this finding indicates that to enhance the LDL-cholesterol-lowering effect a higher dose is probably required.

There are to our knowledge no data in the literature regarding a dose-response or exposure-response relationship of a statin on proteinuria lowering (or increase). We found that both statins had clearly varying effects on proteinuria and albuminuria: atorvastatin lowers both proteinuria and albuminuria whereas rosuvastatin does not, both measured at a population level. However, at an individual level, both statins show a wide range of responses varying from distinct proteinuria lowering to increases.[8]

The potential mechanisms mediating albuminuria-lowering effects are unclear although various hypotheses have been postulated. Among other things, it has been suggested that statins may protect podocytes, reduce endothelial dysfunction, or reduce tubulointerstitial injury.[18]

We did not observe a correlation between the individual plasma concentration of both statins and proteinuria or albuminuria. The lack of correlation indicates that the systemic exposure is not a reflection of the individual response. It is possible that intra-renal exposure is a better indicator of the individual proteinuria response. Nevertheless, we cannot exclude the possibility that random variations in proteinuria obscure a true association, although the large sample size in this study provided sufficient power to detect even modest correlations.

This study has limitations. First, this was a post hoc exploratory study. The study was not designed to characterize the statin exposure and albuminuria response. This is reflected by the fact that dosing times of individual patients were not available. Although all study medications were administered as per protocol in the morning and samples were taken in trough conditions, we are unable to ascertain the duration between study drug administration and blood sampling. The current findings should be externally validated or investigated in a dedicated clinical trial. Second, the variation in plasma concentration for atorvastatin was smaller than for rosuvastatin because only a single dose of atorvastatin was investigated. The smaller inter-individual variation in plasma concentration of atorvastatin limits the statistical power to detect an association with pharmacodynamic response variables. We measured plasma concentrations as a proxy for systemic exposure. However, the LDL-cholesterol-lowering effect of statins is caused by the intracellular binding to the HMG-CoA receptor. Intrahepatic concentrations of both drugs may have led to stronger associations with LDL-cholesterol response. Finally, both atorvastatin and rosuvastatin have active metabolites. Active metabolites were not associated with LDL-cholesterol response. Because we were not able to assess the degree of metabolism for both statins at an individual level, this complicates and possibly underestimates the strength of the correlation between total active compound of atorvastatin or rosuvastatin with the pharmacodynamic response.

In conclusion, individual variation in plasma concentrations of both atorvastatin and rosuvastatin was associated with the variation in LDL-cholesterol but not proteinuria or albuminuria changes during treatment with these statins.

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CONFLICT OF INTEREST

The PLANET trials were sponsored by AstraZeneca.
MYAMK and JS report no conflicts of interest. DdZ is consultant for and received honoraria from AbbVie, Fresenius, Janssen, Bayer and Mundipharma. HJLH is consultant for and received honoraria from AbbVie, Astellas, Astra Zeneca, Boehringer Ingelheim, Fresenius, Janssen, and Merck and has a policy that all honoraria are paid to his employer.

AUTHOR CONTRIBUTIONS

DdZ and HJLH made contributions to the conception and design of the study and the acquisition of data. MYAMK was responsible for collecting data and plasma concentration measurements. MYAMK, JS and HJLH performed statistical analyses. MYAMK and HJLH wrote the first draft. All authors contributed to revisions for important intellectual content.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.