Effect of atorvastatin on inflammation and outcome in patients with type 2 diabetes mellitus on hemodialysis

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Statins have multiple effects, including anti-inflammatory actions, lowering C-reactive protein levels, and reducing coronary events. We performed a *post hoc* analysis of the randomized placebo-controlled 4D Study that had evaluated the efficacy and safety of atorvastatin in 1255 patients with type 2 diabetes mellitus who were on maintenance hemodialysis. Here we determined the relationship between atorvastatin treatment, C-reactive protein, and the outcome of patients who had pre-specified and adjudicated endpoints of all-cause mortality, composite vascular endpoint, myocardial infarction, sudden death, and stroke. Atorvastatin had no significant effect on the risk of composite vascular endpoint or death relative to placebo in any quartile of baseline C-reactive protein. These baseline levels were not significantly different between the treated and placebo group and remained stable at 6 months on atorvastatin but significantly increased in those patients on placebo. All of the patients with baseline C-reactive protein in the fourth quartile had a significantly increased risk of deaths and in composite vascular endpoint compared to patients in the first quartile. The mean value of two consecutive C-reactive protein measurements was associated with significant increases in the risk of sudden death, stroke, all-cause mortality and composite vascular endpoint. Our results show that C-reactive protein was highly predictive of outcome, but atorvastatin treatment was not associated with reduced relative risks in the composite vascular endpoint or mortality in patients on hemodialysis with or without inflammation.

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To improve vascular risk stratification in dialysis patients regular assessment of high-sensitivity C-reactive protein (CRP) is recommended.[1] This recommendation has been issued despite a lack of specific antiinflammatory treatment strategies that could result from such screening. Studies in stable patients with coronary heart disease and normal kidney function as well as in patients with acute coronary syndromes have raised the possibility that the clinical benefit of statins are related to their antiinflammatory effect.[2,3] Statins have been shown to lower CRP in a variety of patient populations.[4,5] This raises the question whether a statin would be an especially effective cardiovascular event-lowering drug in hemodialysis patients depending on the degree of inflammation as indicated by baseline CRP. More than 20 out of 100 diabetic hemodialysis patients die per year[6] and identifying treatments that decrease inflammation and high CRP may translate into a significant reduction of cardiovascular events.[7]

We performed a *post hoc* analysis of the 4D study (German Diabetes Dialysis Study—Die Deutsche Diabetes Dialyse Studie),[8] which evaluated the efficacy and safety of atorvastatin in 1255 patients with type 2 diabetes mellitus on maintenance hemodialysis treatment. The purpose of this study was to evaluate (1) the effect of atorvastatin treatment on CRP serum concentrations,[5] (2) the relationship between baseline CRP and cardiovascular endpoints (for example sudden death, myocardial infarction, and stroke), (3) the relationship between changes of CRP upon follow-up and cardiovascular events, and (4) the effect of atorvastatin on cardiovascular endpoints in subgroups stratified according to CRP at baseline.

RESULTS

Of 1255 patients, 1249 had a baseline, 1204 had a post-baseline, and 1202 had the two CRP measurements. Results from 633 patients on placebo and 616 patients on atorvastatin at baseline and 605 on placebo and 599 on atorvastatin after a median of 182 days (interquartile range 177–185 days, referred here as 6 months) were available for

analysis. The mean follow-up periods were 3.96 years (median 4.0 years) and 3.91 years (median 4.08 years) in patients receiving atorvastatin or placebo, respectively.

During follow-up, 465 patients reached the composite vascular endpoint (CVE, cardiac death, nonfatal myocardial infarction, and stroke). Fatal and nonfatal myocardial infarction, and stroke occurred in 200 and 99 patients, respectively. Overall 612 patients died, of whom 160 died of sudden death.

The characteristics of study participants grouped according to baseline CRP are shown in Table 1.

Effect of atorvastatin on CRP

Median baseline CRP was high (overall median: 5.0 mg/l) and did not differ significantly between groups ($P=0.170$; placebo group: quartile 1, 2.5 mg/l; median, 5.5 mg/l; mean: 10.99 ± 17.7 mg/l; quartile 3, 12.4 mg/l; atorvastatin group: quartile 1, 2.2 mg/l; median, 4.6 mg/l; mean 10.91 ± 20.4 mg/l; quartile 3, 12.45 mg/l).

During treatment with atorvastatin CRP remained stable ($P=0.706$) (change from baseline: quartile 1, −3.1 mg/l; median, −0.2 mg/l; quartile 3, 2.9 mg/l) whereas it increased during placebo treatment ($P=0.001$; change from baseline: quartile 1, −2.7 mg/l; median, 0.4 mg/l; quartile 3, 4.9 mg/l). Therefore, post-baseline CRP was lower ($P=0.002$) in atorvastatin-treated (median, 4.4 mg/l) compared to placebo-treated patients (median, 6.0 mg/l) as was the change from baseline ($P=0.012$). The distribution of CRP at baseline and at follow-up is shown in Figure 1.

Baseline CRP and the risk of sudden death, stroke, myocardial infarction, composite vascular endpoint, and all-cause mortality

The risk of experiencing a CVE and of dying from any cause increased by 10 and 25%, respectively, per unit increase in log-transformed CRP (hazard ratio (HR): 1.10; 95% confidence interval (CI): 1.01–1.18; $P=0.023$; HR: 1.25; 95% CI: 1.17–1.33; $P<0.001$, respectively). One unit increase in logarithmically transformed CRP was equal to a 2.72-fold increase in absolute values. No statistically significant association between baseline CRP and single components of the CVE was detected (risk of sudden death—HR: 1.13; 95% CI: 1.00–1.29; $P=0.060$; stroke—HR: 1.11; 95% CI: 0.94–1.32; $P=0.233$; myocardial infarction—HR: 1.12; 95% CI: 1.00–1.26; $P=0.056$). Results of analyses with quartiles of baseline CRP are shown in Figure 2a and b, and Table 2.

Table 1 | Baseline patient characteristics according to quartiles of baseline CRP (⩽2.3, >2.3 to 5, >5 to 12.4, and >12.4 mg/l)

CRP	Quartile 1 ⩽2.3 mg/l *n*=316	Quartile 2 >2.3 to ⩽5 mg/l *n*=310	Quartile 3 >5 to ⩽12.4 mg/l *n*=312	Quartile 4 >12.4 mg/l *n*=311	*P*-value
Age (years)	66.4 ± 8.1	65.6 ± 8.2	65.9 ± 8.1	64.8 ± 8.6	0.270
Gender (male/female)	155/161	177/133	160/152	180/131	0.169
Ever smoking (% (*n*))	36 (114)	40 (123)	38 (119)	48 (149)	0.089
Body mass index (kg/m^2)	26.6 ± 4.5	27.5 ± 4.7	28.1 ± 5.1	28.0 ± 4.9	<0.001
Systolic blood pressure (mm Hg)	146 ± 23	148 ± 22	145 ± 21	143 ± 21	0.012
Diastolic blood pressure (mm Hg)	76 ± 11	77 ± 11	75 ± 11	75 ± 11	0.139
Ultrafiltration volume[a] (kg)	2.21 ± 1.17	2.12 ± 1.12	2.30 ± 1.19	2.38 ± 1.30	0.066
Arteriovenous fistula (% (*n*))	95 (301)	95 (294)	93 (288)	90 (281)	0.029
Time receiving dialysis (months)	8.2 ± 6.6	8.1 ± 6.8	8.3 ± 7.1	8.4 ± 7.1	0.972
History of[b]					
Arrhythmia (% (*n*))	17 (53)	17 (54)	18 (56)	23 (71)	0.088
Myocardial infarction, CABG[c], PCI[d], or CHD[e] (% (n))	30 (96)	30 (93)	26 (81)	31 (95)	0.564
Congestive heart failure[f] (% (*n*))	31 (97)	36 (111)	36 (113)	39 (120)	0.088
Stroke or TIA[g] (% (*n*))	16 (52)	18 (56)	19 (58)	18 (56)	0.902
Peripheral vascular disease (% (*n*))	39 (122)	42 (130)	46 (142)	52 (161)	0.010
Hemoglobin (g/100 ml)	11.0 ± 1.3	11.1 ± 1.4	10.9 ± 1.3	10.6 ± 1.3	<0.001
HbA1c[h] (%)	6.57 ± 1.21	6.68 ± 1.29	6.74 ± 1.19	6.90 ± 1.32	0.011
Phosphate (mg/l)	6.06 ± 1.56	5.91 ± 1.52	5.95 ± 1.57	6.21 ± 1.77	0.127
Albumin (g/100 ml)	3.89 ± 0.28	3.87 ± 0.27	3.80 ± 0.31	3.72 ± 0.32	<0.001
LDL cholesterol (mg/100 ml)	126 ± 28	128 ± 31	126 ± 29	122 ± 31	0.057
CRP (mg/l) (median (25th and 75th percentile))	1.3 (0.9–1.7)	3.5 (2.9–4.2)	7.5 (6.1–9.6)	22.8 (16–34.9)	—

P-values for comparison between groups of patients according to baseline CRP quartiles were derived from a general linear model for continuous variables or logistic regression for categorical variables both adjusted for age and gender, as appropriate.
Data are given as mean ± standard deviation. To convert hemoglobin values to millimoles per liter, multiply by 0.62. To convert values for phosphate to millimoles per liter, multiply by 0.32. To convert values for LDL cholesterol to millimoles per liter, multiply by 0.03.
[a]The ultrafiltration volume was calculated based on the body weight before and after dialysis at the randomization visit.
[b]Types of disease and intervention are not mutually exclusive.
[c]Coronary artery bypass grafting surgery.
[d]Percutaneous coronary intervention.
[e]Coronary heart disease, documented by coronary angiography.
[f]Predominantly New York Heart Association II.
[g]Transient ischemic attack.
[h]Glycated hemoglobin.