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Original Article

Predictors of atherosclerotic events in patients on haemodialysis: *post hoc* analyses from the AURORA study

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ABSTRACT

Background. Patients on haemodialysis (HD) are at high risk for cardiovascular events, but heart failure and sudden death are more common than atherosclerotic events. The A Study to Evaluate the Use of Rosuvastatinin Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) trial was designed to assess the effect of rosuvastatin on myocardial infarction and death from any cardiac cause in 2773 HD patients. We studied predictors of the atherosclerotic cardiovascular events in AURORA.

Methods. We readjudicated all deaths and presumed myocardial infarctions according to the criteria used in the Study of Heart and Renal Protection (SHARP); these were specifically developed to separate atherosclerotic from non-atherosclerotic cardiovascular events. The readjudicated atherosclerotic end point included the first event of the following: non-fatal myocardial infarction, fatal coronary heart disease, non-fatal and fatal non-haemorrhagic stroke, coronary revascularization procedures and death from ischaemic limb disease. Stepwise Cox regression analysis was used to identify the predictors of such events.

Results. During a mean follow-up of 3.2 years, 506 patients experienced the new composite atherosclerotic outcome. Age, male sex, prevalent diabetes, prior cardiovascular disease, weekly dialysis duration, baseline albumin [hazard ratio (HR) 0.96; 95% confidence interval (CI) 0.94–0.99 per g/L increase], high-sensitivity C-reactive protein (HR 1.13; 95% CI 1.04–1.22 per mg/L increase) and oxidized low-density lipoprotein (LDL) cholesterol (HR 1.09; 95% CI 1.03–1.17 per 10 U/L increase) were selected as significant predictors in the model. Neither LDL cholesterol nor allocation to placebo/rosuvastatin therapy predicted the outcome.

Conclusions. Even with the use of strict criteria for end point definition, non-traditional risk factors, but not lipid disturbances, predicted atherosclerotic events in HD patients.

Keywords: atherosclerosis, coronary artery disease, haemodialysis, statins, vascular calcification

INTRODUCTION

Although survival in patients on haemodialysis (HD) has improved during the last two decades [1, 2], adjusted mortality rates are still high [1]. In prevalent dialysis patients, cardiovascular disease (CVD) is the leading cause of death, accounting for ∼40% of all deaths [1, 2].

The use of strategies to lower low-density lipoprotein (LDL) cholesterol, including statins, as prevention against coronary heart disease (CHD) and other atherosclerotic vascular diseases

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is well-established in the general population [3]. In patients with chronic kidney disease (CKD), however, and particularly in patients on maintenance dialysis, sudden cardiac death and heart failure predominate [4–6], and traditional risk factors for atherosclerosis, such as hyperlipidaemia, appear to play a less prominent role. Instead, non-traditional risk factors, including uraemic toxins, markers of mineral bone disorder and vascular calcification, inflammation, oxidative stress and fluid overload [6], have been associated with increased CVD risk in this population. Nevertheless, traditional cardiovascular risk factors (e.g. hypertension and dyslipidaemia), as well as atherosclerotic diseases, are commonly observed in HD patients [7, 8].

Two large randomized controlled trials, the A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) and Die Deutsche Diabetes Dialyse Studie (4D), were designed to test whether statin treatment could improve cardiovascular morbidity and mortality in HD patients [9, 10]. Both failed to demonstrate a significant benefit of LDL-lowering therapy on the primary vascular end points. Although the lack of interaction between treatment allocation and dialysis status at baseline (yes/no) in the Study of Heart and Renal Protection (SHARP) contradicted a subgroup difference, no significant treatment effect of simvastatin plus ezetimibe was observed when the dialysis subgroup was considered in isolation [11]. In AURORA, which so far is the largest randomized statin trial conducted solely in patients on dialysis, the primary outcome was a composite end point of atherosclerotic and non-atherosclerotic cardiovascular events. The reported percentage of deaths attributable to CHD was three times the percentage reported in 4D and four times the reported incident rate in the dialysis subgroup in SHARP [11]. Although inclusion criteria and treatment strategy varied slightly between the three trials (Table 1), the dissimilarities in outcome incidence have been attributed to differences in coding rules used to ascribe deaths to CHD in these trials.

In order to separate atherosclerotic from non-atherosclerotic cardiovascular events in AURORA, we readjudicated all fatal events and non-fatal coronary events according to criteria specifically developed to separate atherosclerotic from non-atherosclerotic cardiovascular events in kidney disease, i.e. the same criteria that were used in SHARP. The aim of the present study was to assess predictors of a combined atherosclerotic cardiovascular end point similar to the main outcome in SHARP.

MATERIALS AND METHODS

Study cohort and the design of the AURORA trial

The design, baseline data and main results of the AURORA trial have been published previously [9, 12]. In short, in 2003–04, 2773 male and female prevalent HD patients (treated for ≥3 months), aged 50–80 years, from 280 centres in 25 countries across the world were randomized 1:1 to receive either rosuvastatin 10 mg/day or placebo. The mean follow-up time was 3.2 years. The primary composite end point was time to a major cardiovascular event, defined as non-fatal myocardial infarction, non-fatal stroke or death from cardiovascular causes. A sudden, unexpected death was attributed to CHD (definite or suspected) if there was inadequate information to ascribe a non-cardiovascular cause. All events were adjudicated by an independent end point committee blinded to treatment allocation. The study (clinicaltrials.gov identifier number NCT00240331) was conducted in accordance with the ethical principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Conference of Harmonization and local regulatory requirements at all participating centres.

Readjudication of fatal and non-fatal events

In 2014 and 2015, all fatal events and all events originally classified as definite or suspected non-fatal myocardial infarctions were readjudicated according to criteria identical to those used in SHARP [11]. Non-fatal and fatal coronary events were classified as definite, probable or possible. A death was attributed to acute CHD if diagnosed by postmortem examination and no other probable cause of death was revealed, or on the basis of clinical criteria. Typical (chest pain) or atypical (pulmonary oedema, syncope or shock) coronary symptoms were a prerequisite for the clinical diagnosis of all CHD, and ECG and myocardial biomarkers were reviewed according to strict criteria. In order to be attributed to CHD, death must have occurred within 28 days of the coronary event and no other cause of death must have been recorded. A sudden, unexpected death was not assigned a coronary cause unless supported by ECG, biomarkers or autopsy. Using the overriding principles set out by the International Statistical Classification of Disease and Related Health Problems 10th Revision (ICD-10), 'the disease or injury which initiated the chain of morbid events leading directly to death' was recorded as the cause of death.

The readjudications were completed by two experienced clinicians who were blinded to treatment allocation, other exposure data and the original event adjudication. In case of doubts, the event was discussed by two consultants. Also, random cases were evaluated by both consultants to ensure coherent adjudication.

The new composite atherosclerotic end point comprised the first event of the following: definite, probable or possible non-fatal myocardial infarction or fatal CHD, coronary revascularization procedures and non-fatal or fatal non-haemorrhagic or unspecified stroke. In addition, death from peripheral artery disease (PAD) was included in the end point.

Statistical analyses

Originally, 805 primary events were required for 87% power to reveal a 19.5% lower incidence rate in the AURORA treatment group [9]. The readjudication process resulted in a considerably lower number of events. Thus, the statistical power to assess the treatment effect of rosuvastatin on the new end point was reduced. However, we chose to run the intention-to-treat analysis, using an unadjusted Cox regression model and producing a Kaplan–Meier survival curve. All other analyses in the present study were done in the entire AUROA cohort with no regards to treatment allocation.

Data are presented as mean [standard deviation (SD)] or number (%) as appropriate. Differences in baseline risk factors between patients who did or did not experience the new

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Table 1. Study design of the main trials assessing the effect of LDL cholesterol-lowering agents in patients on dialysis

	Inclusion criteria	Treatment strategy	Pre-defined end points
AURORA	LDL cholesterol of any value Men and women aged 50–80 years ESRD and chronic HD for ≥3 months	Rosuvastatin 10 mg versus placebo	Primary end point Time to MACE (non-fatal myocardial infarction, non-fatal stroke, death from a cardiovascular cause) Secondary end points All-cause mortality Cardiovascular event-free survival Death from a cardiovascular cause Death from a non-cardiovascular cause Coronary or peripheral revascularization Procedure for stenosis or thrombosis of the vascular access[a]
SHARP	LDL cholesterol of any value Men and women ≥40 years History of CKD Blood creatinine ≥150 μmol/L in men or ≥130 μmol/L in women On dialysis (HD or peritoneal dialysis)	Ezetimibe 10 mg/simvastatin 20 mg versus placebo	Primary end point Time to major atherosclerotic event (non-fatal myocardial infarction, coronary death, non-haemorrhagic stroke, arterial revascularization procedure) Secondary end points Each separate component of the primary end point Major vascular event (primary end point, non-coronary cardiac death, haemorrhagic stroke) Commencement of chronic dialysis or kidney transplantation
4D	Fasting LDL cholesterol ≥2.1 and ≤4.9 mmol/L Men and women aged 18–80 years Chronic HD for ≤2 years	Atorvastatin 20 mg versus placebo	Primary end point Time to MACE (fatal myocardial infarction, sudden death, death from congestive heart failure, death from diagnostic or therapeutic procedure due to coronary artery disease, death from another coronary cause, non-fatal myocardial infarction, non-fatal or fatal stroke) Secondary end points All-cause mortality Cardiovascular event (cardiovascular death, myocardial infarction, coronary intervention procedure) Cerebrovascular event (stroke, transient ischaemic attack) Death from non-cardiovascular causes stratified by cause Changes in lipid levels relative to baseline

LDL, low-density lipoprotein; ESRD, end-stage renal disease; HD, haemodialysis; MACE, major adverse cardiac event; CKD, chronic kidney disease.
[a]Arteriovenous fistula or graft used for chronic HD.

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composite end point were assessed using two-tailed independent samples *t*-tests or χ^2 tests, as appropriate.

Crude incidence rates of each atherosclerotic end point were calculated as events per 1000 person years at risk.

Cox proportional hazard regression analyses were run to assess the impact of baseline risk factors on the composite atherosclerotic end point. We calculated the univariate hazard ratios (HRs) and 95% confidence intervals (CIs) for the following potential predictors: demographics (sex, age, geographic region) comorbidity (diabetes, history of CVD, history of CHD), lipids [total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides], other traditional risk factors (body weight and height, body mass index, current smoking, systolic and diastolic blood pressure, pulse pressure), dialysis-specific risk factors (HD vintage, weekly duration of HD treatment, dialysis quality measured as *Kt*/*V*), other non-traditional or uraemia-specific risk factors and inflammation markers [phosphate, calcium, albumin, haemoglobin, haematocrit and high-sensitivity C-reactive protein (hsCRP)]. Oxidized LDL cholesterol and apolipoprotein (Apo) B/Apo A1 ratio may be characterized as markers of lipid disturbances or inflammation and were also assessed as predictors. Finally, current medication use (β-blockers, inhibitors of the renin–angiotensin system, sevelamer) and randomized treatment allocation (rosuvastatin versus placebo) were entered into univariate Cox models.

All variables with a $P < 0.1$ for univariate association with the atherosclerotic end point were included in a backwards stepwise Cox regression model to obtain the independent risk factors.

The same procedure was repeated for each subgroup of events: CHD (fatal or non-fatal myocardial infarction and/or coronary revascularization), non-haemorrhagic or unspecified stroke (fatal or non-fatal) and death from PAD.

Non-linear associations with the main end point were assessed in univariate Cox regression models for each predictor categorized into quartiles.

The proportional hazard assumption for each Cox model was checked using a global test of scaled Schoenfeld residuals against time. Analyses were run using IBM SPSS Statistics Software version 20 (IBM Corp., Armonk, NY, USA) and Stata Statistical Software 11 (StataCorp LP, College Station, TX, USA). Two-sided P-values <0.05 were considered statistically significant.

RESULTS

Baseline risk factors

Baseline characteristics for patients according to whether they did or did not experience the new composite end point are presented in Table 2. The 506 patients who had at least one atherosclerotic event during follow-up were more frequently men, older and had a higher prevalence of diabetes and previous CVD at baseline than the 2267 patients with no reported atherosclerotic event. However, lipid values other than HDL cholesterol, systolic blood pressure and frequency of current smoking did not differ significantly between the two groups. The event group had significantly lower albumin and higher levels of markers of inflammation and oxidative stress including hsCRP, oxidized LDL and Apo B/Apo A1 ratio. These patients also had longer HD treatment per week, whereas dialysis vintage and quality were similar. Patients from Western Europe were over-represented in the end point group compared with the group without atherosclerotic events, whereas the opposite was found for patients from South America.

The combined atherosclerotic end point and predictor assessment

There were 506 patients who experienced at least one atherosclerotic event. Some patients had more than one non-fatal event. The numbers of first event within each subgroup of atherosclerotic disease, as well as crude incidence rates, are given in Table 3. The composite end point included 120 non-fatal and 78 fatal CHD events, 180 coronary revascularization procedures, 71 non-fatal and 28 fatal non-haemorrhagic and unspecified strokes and 29 deaths due to PAD.

There was no significant effect of allocation category (rosuvastatin or placebo) on the new end point (Figure 1 and Table 4).

The univariate and multivariable associations between traditional and non-traditional risk factors and the readjudicated atherosclerotic end point are displayed in Table 4. LDL cholesterol was not significantly associated with the end point in univariate analyses. Thus, neither LDL cholesterol nor treatment allocation was included in the multivariable model. Significant association with the composite end point was found for HDL cholesterol, Apo B/Apo A1 ratio and oxidized LDL in univariate analyses. In multivariable analysis age, male sex, diabetes and prevalent CVD significantly predicted the atherosclerotic end point, whereas no parameters reflecting hyperlipidaemia were independent predictors. Hypoalbuminaemia, increased hsCRP and oxidized LDL cholesterol were independent non-traditional predictors of the combined end point. Patients from South America had a lower HR for the combined end point than patients from other geographical regions. A non-linear association was found between dialysis vintage and the atherosclerotic end point, with dialysis vintage in the second quartile (1.0–2.3 years) predicting significantly reduced risk of events compared with the fourth quartile (>4.4 years), and a non-significant trend towards higher event risk in the first quartile. In multivariable analysis with the categorized dialysis vintage variable, estimates were essentially unchanged, apart from weekly HD duration losing and phosphate gaining statistical significance (data not shown). No other variables exhibited a non-linear association with the end point. Collinearity/multicollinearity did not affect any of the multivariable analyses.

Predictors of CHD, ischaemic stroke and death from PAD

During follow-up, 384 persons had at least one non-fatal or fatal myocardial infarction and/or underwent coronary revascularization (Tables 3 and 5). In univariate Cox regression analyses, several traditional (age, sex, previous CHD and CVD, diabetes, body weight and height, low diastolic blood pressure and low HDL cholesterol) and non-traditional (dialysis duration, hsCRP and low albumin) risk factors predicted

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Table 2. Baseline characteristics of the patients who did and did not experience the combined atherosclerotic end point during follow-up

	Patients with end point ($n = 506$)	Patients without end point ($n = 2267$)	P-value
Sex, male, *n* (%)	353 (69.8)	1370 (60.4)	<0.001
Age, years	66.6 ± 8.5	63.7 ± 8.6	<0.001
Randomized to rosuvastatin, *n* (%)	253 (50.0)	1136 (50.0)	0.96
Region, *n* (%)			<0.001
Western Europe	308 (60.9)	1108 (48.9)	
Eastern Europe	107 (21.1)	480 (21.2)	
Asia	10 (2.0)	72 (3.2)	
South America	23 (4.5)	323 (14.2)	
Other	58 (11.4)	284 (12.5)	
Systolic blood pressure, mmHg	136 ± 25	137 ± 24	0.23
Diastolic blood pressure, mmHg	74 ± 13	76 ± 13	<0.001
Height, cm	167.9 ± 9.4	166.7 ± 9.8	0.014
Weight, kg	72.6 ± 14.4	70.5 ± 15.7	0.004
Body mass index, kg/m^2	25.7 ± 4.7	25.3 ± 5.0	0.11
Current smoking, *n* (%)	83 (16.4)	346 (15.3)	0.52
Previous CHD, *n* (%)	355 (70.2)	1069 (47.2)	<0.001
Previous CVD, *n* (%)	299 (59.1)	806 (35.6)	<0.001
Diabetes, *n* (%)	182 (36.0)	549 (24.2)	<0.001
Cholesterol, mmol/L	4.60 ± 1.12	4.52 ± 1.09	0.17
LDL cholesterol, mmol/L	2.63 ± 0.91	2.56 ± 0.89	0.13
HDL cholesterol, mmol/L	1.13 ± 0.37	1.17 ± 0.40	0.043
Triglycerides, mmol/L	1.82 ± 1.11	1.74 ± 1.07	0.16
Oxidized LDL cholesterol, U/L	36.0 ± 15.9	33.8 ± 13.2	0.004
Apolipoprotein B/apolipoprotein A1 ratio	0.73 ± 0.26	0.69 ± 0.25	0.001
β-Blocker, *n* (%)	206 (40.7)	826 (36.6)	0.09
ACEi or ARB, *n* (%)	194 (38.3)	826 (36.6)	0.47
Dialysis vintage, years	3.48 ± 3.82	3.50 ± 3.86	0.90
Dialysis time per week, h	12.1 ± 1.6	11.8 ± 1.8	<0.001
Kt/V midweek session	1.20 ± 0.33	1.20 ± 0.29	0.68
Phosphate, mmol/L	1.82 ± 0.54	1.79 ± 0.55	0.25
Calcium, mmol/L	2.33 ± 0.20	2.34 ± 0.22	0.39
Haemoglobin, g/dL	11.8 ± 1.47	11.6 ± 1.62	0.021
Albumin, g/dL	39.2 ± 3.2	39.8 ± 3.5	<0.001
hsCRP, mg/L	1.15 ± 1.18	0.97 ± 1.15	0.001
Sevelamer, *n* (%)	84 (16.6)	422 (18.7)	0.27

Values are given as mean (standard deviation) or *n* (%) as appropriate.
CHD, coronary heart disease; CVD, cardiovascular disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; hsCRP, high-sensitivity C-reactive protein.

Table 3. Subgroups of atherosclerotic diseases; number of events, follow-up time and crude incidence rates

	Number of events	Follow-up time, months	Number of events per 1000 patient years (95% CI)
Combined atherosclerotic outcome	506	100 891	61.0 (55.7–66.3)
CHD			
Non-fatal myocardial infarction	123	104 677	14.1 (11.6–16.6)
Fatal myocardial infarction	108	113 390	11.4 (9.3–13.6)
Coronary revascularization	203	109 034	22.3 (19.3–25.4)
Ischaemic stroke			
Non-fatal ischaemic stroke	85	105 659	9.7 (7.6–11.7)
Fatal ischaemic stroke	33	113 390	3.5 (2.3–4.7)
Death from peripheral atherosclerotic disease	50	113 390	5.3 (3.8–6.8)

Some patients had several non-fatal events. The first event within each diagnosis subgroup has been counted.
CI, confidence interval; CHD, coronary heart disease.

CHD. An elevated Apo B/Apo A1 ratio was also associated with this end point (Table 5). LDL cholesterol was not a significant predictor of CHD [HR per mmol/L increase 1.03 (95% CI 0.92–1.15; P = 0.59)], and neither was randomization category (P = 0.96). Both univariate and multivariable analyses of predictors for CHD mimicked the results for the combined atherosclerotic end point, but the Apo B/Apo A1 ratio remained significantly associated with CHD in the fully adjusted models. Furthermore, elevated serum phosphate independently predicted CHD.

There were only 116 patients who had at least one episode of non-haemorrhagic or unspecified stroke (non-fatal or fatal), and 50 patients died from PAD, limiting the power to study these outcomes in isolation. Age and hypoalbuminaemia independently predicted stroke in the multivariable Cox regression

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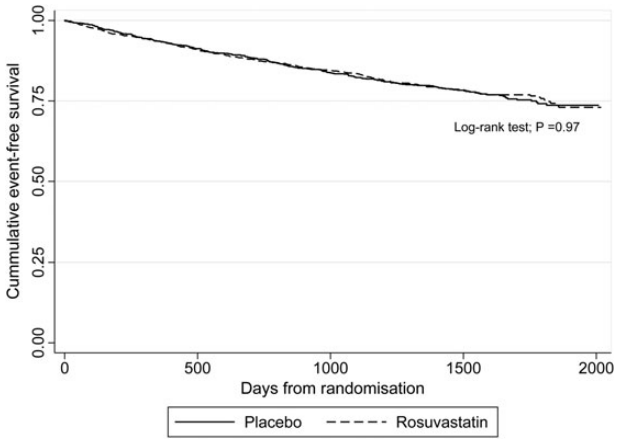

FIGURE 1: Kaplan–Meier survival curves for the new atherosclerotic end point in the two treatment allocation groups (rosuvastatin versus placebo).

analysis (Table 6). High serum phosphate strongly predicted death from PAD, as did prevalent diabetes, previous CVD, hypoalbuminaemia, higher LDL cholesterol and higher hsCRP (Table 7).

DISCUSSION

In a large cohort of prevalent HD patients, we found that elevated LDL cholesterol was not selected as a predictor of the new composite atherosclerotic end point, despite a strict definition of atherosclerosis according to the SHARP criteria. Traditional risk factors were mainly non-modifiable (higher age, sex, diabetes and a history of CVD). Moreover, the model identified non-traditional risk factors, including hypoalbuminaemia and biomarkers of oxidative stress and inflammation, as significant predictors of atherosclerotic events, similar to previously

Table 4. Univariate and multivariable adjusted HRs and 95% CIs for the combined, readjudicated atherosclerotic end point (506 events)

	Univariate models			Multivariable model		
	HR	95% CI	P-value	HR	95% CI	P-value
Sex, male	1.46	(1.21–1.77)	<0.001	1.49	(1.21–1.83)	<0.001
Age, per 5 years	1.24	(1.18–1.31)	<0.001	1.15	(1.09–1.22)	<0.001
Region			<0.001			0.023
Western Europe	1.30	(0.99–1.73)	0.064	1.27	(0.95–1.71)	0.11
Eastern Europe	1.12	(0.81–1.54)	0.50	1.23	(0.88–1.71)	0.23
Asia	0.65	(0.33–1.27)	0.21	0.98	(0.49–1.96)	0.96
South America	0.46	(0.28–0.74)	0.001	0.63	(0.38–1.04)	0.072
Other	Ref.			Ref.		
Allocation rosuvastatin versus placebo, y/n	1.00	(0.84–1.19)	0.97			
Systolic blood pressure, per 10 mmHg	0.99	(0.95–1.02)	0.53			
Diastolic blood pressure, per 5 mmHg	0.94	(0.91–0.97)	<0.001			
Pulse pressure, per 5 mmHg	1.02	(0.99–1.04)	0.14			
Body weight, per 5 kg	1.03	(1.00–1.06)	0.056			
Body height, per 5 cm	1.05	(1.00–1.09)	0.062			
Body mass index, per kg/m^2	1.01	(0.99–1.03)	0.29			
Current smoking, y/n	1.09	(0.86–1.38)	0.48			
Previous CHD, y/n	2.74	(2.26–3.32)	<0.001			
Previous CVD, y/n	2.63	(2.20–3.14)	<0.001	1.93	(1.59–2.34)	<0.001
Diabetes, y/n	1.93	(1.61–2.32)	<0.001	1.76	(1.45–2.14)	<0.001
Cholesterol, per mmol/L	1.01	(0.93–1.09)	0.82			
LDL cholesterol, per mmol/L	1.03	(0.93–1.13)	0.58			
HDL cholesterol, per mmol/L	0.76	(0.60–0.96)	0.023			
Triglycerides, per mmol/L	1.03	(0.95–1.11)	0.51			
Oxidized LDL cholesterol, per 10 U/L	1.07	(1.01–1.14)	0.017	1.09	(1.03–1.17)	0.006
Apolipoprotein B /apolipoprotein A1 ratio, per unit	1.77	(1.28–2.45)	0.001			
β-Blocker, y/n	1.14	(0.95–1.36)	0.16			
ACEi or ARB, y/n	1.07	(0.90–1.28)	0.44			
Dialysis vintage, per year	1.00	(0.98–1.02)	0.96			
Dialysis time per week, per h	1.05	(1.01–1.11)	0.031	1.07	(1.01–1.12)	0.018
Kt/V midweek session, per unit	0.85	(0.62–1.16)	0.29			
Phosphate, per mmol/L	1.14	(0.97–1.34)	0.11			
Calcium, per mmol/L	0.80	(0.53–1.20)	0.27			
Haematocrit, per %	2.95	(0.46–18.8)	0.25			
Haemoglobin, per g/dL	1.03	(0.98–1.09)	0.26			
Albumin, per g/L	0.93	(0.91–0.95)	<0.001	0.96	(0.94–0.99)	0.008
hsCRP, per mg/L	1.19	(1.11–1.27)	<0.001	1.13	(1.04–1.22)	0.002
Sevelamer, y/n	0.84	(0.67–1.07)	0.16			

HR, hazard ratio; CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; hsCRP, high-sensitivity C-reactive protein.
The significant predictors assessed by a stepwise multivariable Cox regression analysis (which originally included all variables with $P < 0.1$ in univariate analysis) are listed.

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Table 5. Univariate and multivariable adjusted HRs and 95% CIs for CHD (fatal or non-fatal myocardial infarction or coronary revascularization; 384 events)

	Univariate models			Multivariable model		
	HR	95% CI	P-value	HR	95% CI	P-value
Sex, male	1.79	(1.43–2.25)	<0.001	1.80	(1.41–2.30)	<0.001
Age, per 5 years	1.22	(1.15–1.29)	<0.001	1.13	(1.06–1.20)	<0.001
Region			<0.001			0.002
Western Europe	1.17	(0.86–1.59)	0.32	1.18	(0.86–1.62)	0.30
Eastern Europe	0.99	(0.70–1.42)	0.97	1.12	(0.78–1.62)	0.53
Asia	0.77	(0.39–1.52)	0.45	1.00	(0.49–2.03)	0.99
South America	0.21	(0.10–0.43)	<0.001	0.28	(0.14–0.59)	0.001
Other	Ref.					
Allocation rosuvastatin versus placebo, y/n	1.01	(0.82–1.23)	0.96			
Systolic blood pressure, per 10 mmHg	0.97	(0.93–1.02)	0.24			
Diastolic blood pressure, per 5 mmHg	0.92	(0.88–0.96)	<0.001	0.96	(0.92–1.00)	0.042
Pulse pressure, per 5 mmHg	1.02	(0.99–1.05)	0.21			
Body weight, per 5 kg	1.04	(1.01–1.07)	0.028			
Body height, per 5 cm	1.06	(1.01–1.12)	0.029			
Body mass index, per kg/m^2	1.01	(0.99–1.03)	0.25			
Current smoking, y/n	1.13	(0.87–1.48)	0.36			
Previous CHD, y/n	3.10	(2.47–3.88)	<0.001	1.70	(1.10–2.64)	0.017
Previous CVD, y/n	2.83	(2.31–3.48)	<0.001			
Diabetes, y/n	1.92	(1.56–2.36)	<0.001	1.46	(1.11–1.91)	0.007
Cholesterol, per mmol/L	1.01	(0.92–1.11)	0.83			
LDL cholesterol, per mmol/L	1.03	(0.92–1.15)	0.59			
HDL cholesterol, per mmol/L	0.69	(0.52–0.92)	0.010			
Triglycerides, per mmol/L	1.04	(0.95–1.13)	0.40			
Oxidized LDL cholesterol, per 10 U/L	1.06	(0.99–1.14)	0.085			
Apolipoprotein B/apolipoprotein A1 ratio, per unit	1.91	(1.32–2.76)	0.001	1.66	(1.11–2.49)	0.014
β-Blocker, y/n	1.20	(0.98–1.47)	0.082			
ACEi or ARB, y/n	1.12	(0.91–1.37)	0.29			
Dialysis vintage, per year	0.98	(0.96–1.01)	0.27			
Dialysis time per week, per h	1.06	(1.01–1.12)	0.033			
Kt/*V* midweek session, per unit	0.98	(0.69–1.39)	0.90			
Phosphate, per mmol/L	1.18	(0.98–1.41)	0.081	1.28	(1.06–1.55)	0.010
Calcium, per mmol/L	0.69	(0.43–1.10)	0.11			
Haematocrit, per %	4.07	(0.48–34.5)	0.20			
Haemoglobin, per g/dL	1.04	(0.97–1.12)	0.23			
Albumin, per g/L	0.95	(0.92–0.98)	<0.001			
hsCRP, per mg/L	1.17	(1.08–1.27)	<0.001	1.12	(1.03–1.22)	0.009
Sevelamer, y/n	0.86	(0.66–1.21)	0.26			

HR, hazard ratio; CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; hsCRP, high-sensitivity C-reactive protein.
The significant predictors assessed by a stepwise multivariable Cox regression analysis (which originally included all variables with $P < 0.1$ in univariate analysis) are listed.

published predictors of all major cardiovascular events in AURORA [13].

In the general population, atherosclerosis dominates as the pathological substrate for CVD. CHD is the major cause of cardiovascular morbidity and mortality, and the Framingham risk score is a validated tool for risk prediction [14]. The same tool has been evaluated to be less useful in patients with CKD not on dialysis [15]. In patients on chronic HD, cardiac diseases such as heart failure [16, 17] and sudden death [4] surpass the classic atherosclerotic disorders. Nevertheless, coronary pathology is common in advanced stages of CKD [5, 8, 17, 18], and atherosclerotic diseases infer a worse prognosis in this patient group than in non-CKD patients [19, 20]. Therefore, assessment of predictors of this subset of CVD is of considerable importance also in patients on maintenance dialysis.

Available data about predictors of atherosclerotic CVD in dialysis patients is limited, with studies often considering cardiovascular events overall [16, 21, 22] or relying on less accurate death registry reports [23, 24]. Furthermore, there are no agreed criteria on which to distinguish atherosclerotic from non-atherosclerotic CVD in trials [9–11, 25]. Partly, these variations reflect challenges in diagnosing atherosclerotic events in HD patients [26]. For example, dialysis patients with acute coronary syndrome often have atypical symptoms [26, 27], ST elevations are observed less frequently [26, 28], and myocardial biomarkers have low sensitivity and specificity to diagnose the disease [29].

Despite the effort to separate non-atherosclerotic from atherosclerotic events that was made in the present study, there may be a substantial overlap and no clear-cut differences between these diseases in prevalent dialysis patients. Vascular calcification, which is associated with CVD and mortality, is common [30, 31]. Coronary atherosclerotic lesions are characterized by marked calcifications consisting of hydroxylapatite and calcium-phosphate, increased media thickness and reduced lumen area [32]. Phosphate is among the promoters of progressive calcification and a strong predictor of adverse

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Table 6. Univariate and multivariable adjusted HRs and 95% CIs for ischaemic stroke (116 events)

	Univariate models			Multivariable model		
	HR	95% CI	P-value	HR	95% CI	P-value
Sex, male	0.97	(0.67–1.40)	0.86			
Age, per 5 years	1.21	(1.08–1.34)	0.001	1.15	(1.03–1.29)	0.013
Region			0.55			
Western Europe	1.47	(0.80–2.71)	0.22			
Eastern Europe	1.24	(0.62–2.48)	0.55			
Asia	NA					
South America	0.92	(0.38–2.18)	0.84			
Other	Ref.					
Allocation rosuvastatin versus placebo, y/n	1.07	(0.75–1.54)	0.71			
Systolic blood pressure, per 10 mmHg	1.04	(0.96–1.12)	0.31			
Diastolic blood pressure, per 5 mmHg	1.02	(0.95–1.09)	0.64			
Pulse pressure, per 5 mmHg	1.03	(0.98–1.07)	0.33			
Body weight, per 5 kg	1.02	(0.96–1.08)	0.54			
Body height, per 5 cm	1.02	(0.93–1.13)	0.65			
Body mass index, per kg/m^2	1.01	(0.97–1.05)	0.66			
Current smoking, y/n	1.44	(0.92–2.26)	0.11			
Previous CHD, y/n	1.62	(1.12–2.35)	0.011			
Previous CVD, y/n	1.73	(1.20–2.49)	0.003			
Diabetes, y/n	1.68	(1.14–2.47)	0.009			
Cholesterol, per mmol/L	1.00	(0.85–1.19)	0.97			
LDL cholesterol, per mmol/L	1.01	(0.83–1.24)	0.92			
HDL cholesterol, per mmol/L	1.18	(0.76–1.82)	0.46			
Triglycerides, per mmol/L	0.94	(0.79–1.13)	0.52			
Oxidized LDL cholesterol, per 10 U/L	1.10	(0.98–1.24)	0.11			
Apolipoprotein B /apolipoprotein A1 ratio, per unit	1.09	(0.52–2.26)	0.83			
β-Blocker, y/n	1.07	(0.74–1.56)	0.71			
ACEi or ARB, y/n	1.09	(0.75–1.58)	0.66			
Dialysis vintage, per year	1.03	(0.99–1.07)	0.22			
Dialysis time per week, per h	1.07	(0.97–1.18)	0.18			
Kt/V midweek session, per unit	0.70	(0.36–1.37)	0.30			
Phosphate, per mmol/L	0.94	(0.66–1.33)	0.73			
Calcium, per mmol/L	0.82	(0.35–1.90)	0.64			
Haematocrit, per %	1.66	(0.03–80.3)	0.80			
Haemoglobin, per g/dL	1.03	(0.91–1.16)	0.65			
Albumin, per g/L	0.89	(0.85–0.94)	<0.001	0.91	(0.86–0.96)	<0.001
hsCRP, per mg/L	1.11	(0.95–1.29)	0.20			
Sevelamer, y/n	0.94	(0.59–1.52)	0.81			

HR, hazard ratio; CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; hsCRP, high-sensitivity C-reactive protein; NA, not applicable due to low number of events.
The significant predictors assessed by a stepwise multivariable Cox regression analysis (which originally included all variables with $P < 0.1$ in univariate analysis) are listed.

outcome in dialysis patients [33]. In our study, phosphate did not predict the composite end point, but independently predicted CHD and death from PAD. This is in agreement with the reported discoveries of calcium-phosphate rich coronary plaques that may differ from atherosclerotic plaques in non-CKD patients. There is substantial evidence suggesting that risk scoring as well as preventive interventions in this patient group cannot be adopted directly from guidelines developed for other risk groups [34, 35].

The fact that oxidized LDL cholesterol was significantly associated with atherosclerotic events is of interest. Oxidatively modified LDL cholesterol particles exhibit proinflammatory and proatherogenic effects in vessel walls, including chemoattractant, cytotoxic and cytokine stimulatory effects. Monocytes have effective uptake mechanisms for these modified LDL cholesterol molecules, facilitating the formation of foam cells [36]. Conflicting data have been published regarding levels of oxidized LDL in dialysis patients. Whereas one study reports nearly 10 times higher levels [37], others have reported no difference [38] or even lower values [39] in dialysis patients compared with healthy individuals. Furthermore, whether oxidized LDL cholesterol primarily is a marker of lipid disturbances or indicates oxidative stress has not yet been agreed upon [39, 40]. Nevertheless, in our study LDL cholesterol was associated with death from PAD, and Apo B/Apo A1 ratio predicted CHD. A recent meta-analysis that included placebo-controlled statin trials in patients on maintenance dialysis, confirmed an hsCRP lowering effect from statin treatment [41]. A *post hoc* analysis from the 4D study demonstrated significant risk reduction by atorvastatin in HD patients with pre-treatment LDL cholesterol level in the highest quartile. At baseline, this group also had lower serum albumin and higher hsCRP [42]. Therefore, it cannot be ruled out that both an atherogenic lipoprotein profile and chronic inflammation are risk factors that may be available for intervention in a subset of prevalent HD patients.

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Table 7. Univariate and multivariable adjusted HRs and 95% CIs for death from peripheral atherosclerotic disease (50 events)

	Univariate models			Multivariable model		
	HR	95% CI	P-value	HR	95% CI	P-value
Sex, male	1.00	(0.56–1.77)	1.00			
Age, per 5 years	1.52	(1.27–1.82)	<0.001	1.38	(1.14–1.68)	0.001
Region			0.64			
Western Europe	2.54	(0.77–8.31)	0.13			
Eastern Europe	2.51	(0.71–8.89)	0.15			
Asia	NA					
South America	2.02	(0.48–8.50)	0.34			
Other	Ref.					
Allocation rosuvastatin versus placebo, y/n	1.27	(0.73–2.23)	0.40			
Systolic blood pressure, per 10 mmHg	1.01	(0.90–1.14)	0.84			
Diastolic blood pressure, per 5 mmHg	0.90	(0.80–1.01)	0.056			
Pulse pressure, per 5 mmHg	1.05	(0.99–1.13)	0.14			
Body weight, per 5 kg	1.03	(0.95–1.13)	0.50			
Body height, per 5 cm	0.99	(0.85–1.14)	0.84			
Body mass index, per kg/m^2	1.03	(0.97–1.08)	0.37			
Current smoking, y/n	1.04	(0.50–2.22)	0.92			
Previous CHD, y/n	13.04	(4.69–36.25)	<0.001			
Previous CVD, y/n	7.18	(3.59–14.36)	<0.001	4.34	(2.11–8.89)	<0.001
Diabetes, y/n	3.55	(2.03–6.18)	<0.001	3.16	(1.77–5.65)	<0.001
Cholesterol, per mmol/L	1.26	(1.00–1.59)	0.054			
LDL cholesterol, per mmol/L	1.39	(1.05–1.83)	0.020	1.33	(1.03–1.72)	0.029
HDL cholesterol, per mmol/L	0.58	(0.26–1.30)	0.19			
Triglycerides, per mmol/L	1.10	(0.91–1.34)	0.34			
Oxidized LDL cholesterol, per 10 U/L	1.18	(1.00–1.40)	0.052			
Apolipoprotein B/apolipoprotein A1 ratio, per unit	2.97	(1.23–7.18)	0.016			
β-Blocker, y/n	0.77	(0.42–1.39)	0.38			
ACEi or ARB, y/n	0.61	(0.32–1.15)	0.12			
Dialysis vintage, per year	0.98	(0.90–1.06)	0.56			
Dialysis time per week, per h	0.97	(0.83–1.14)	0.75			
Kt/V midweek session, per unit	0.41	(0.14–1.18)	0.096			
Phosphate, per mmol/L	1.92	(1.23–3.02)	0.004	2.37	(1.50–3.75)	<0.001
Calcium, per mmol/L	1.29	(0.37–4.57)	0.69			
Haematocrit, per %	0.44	(0.00–168.1)	0.79			
Haemoglobin, per g/dL	0.97	(0.81–1.16)	0.76			
Albumin, per g/L	0.87	(0.81–0.94)	0.001	0.92	(0.84–1.00)	0.048
hsCRP, per mg/L	1.50	(1.24–1.81)	<0.001	1.39	(1.12–1.72)	0.003
Sevelamer, y/n	0.47	(0.19–1.19)	0.11			

HR, hazard ratio; CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; hsCRP, high-sensitivity C-reactive protein; NA, not applicable due to low number of events.
The significant predictors assessed by a stepwise multivariable Cox regression analysis (which originally included all variables with $P < 0.1$ in univariate analysis) are listed.

The AURORA cohort consisted of prevalent HD patients who had been on maintenance dialysis for median 28.0 months [12]. Dialysis vintage has been shown to predict progression of vascular calcification [43–45], whereas traditional risk factors, including LDL cholesterol, do not increase with increasing duration of HD treatment [46]. One may speculate that 'traditional' atherosclerosis associated with traditional risk factors becomes less common, whereas vascular calcification, not readily accessible for established preventive measures, becomes increasingly important with increasing time on HD.

We found a significantly lower risk of CHD and atherosclerotic events in patients dialysed in South America compared with the other geographic regions. This phenomenon probably reflects differences in diagnosis and reporting of CHD in this region, as well as a higher incidence of other causes of death during the study period.

The incidence rate of ischaemic stroke is high in HD patients [47, 48]. Older age and diabetes have consistently been reported to be associated with ischaemic stroke in HD cohorts [47, 48]. In the present study, only high age and hypoalbuminaemia were selected as predictors, but the number of strokes was low, and the results should be interpreted with caution.

Important strengths of our study were the large cohort of well-characterized, prevalent HD patients from 25 different countries worldwide. Furthermore, each event was readjudicated by clinicians according to validated criteria. However, residual confounding due to measurement error, unmeasured risk factors and the lack of adjustment for time-varying covariates during follow-up constitutes important limitations. The observational study design, and in particular the use of statistical models that selected predictors in an automated fashion, precludes causal inferences, and the lack of associations between traditional risk factors and the atherosclerotic end point should be interpreted with caution. As discussed above, a clear separation between atherosclerotic and non-atherosclerotic events is difficult in patients on dialysis, and misclassifications may have

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interfered with our results. Therefore, we cannot exclude the possibility that a clinically significant association between hyperlipidaemia and a subset of atherosclerotic events may exist in prevalent HD patients. Moreover, our results may not be generalizable to younger dialysis populations with shorter HD vintage.

In conclusion, this *post hoc* analysis from the AURORA trial confirmed that modifiable traditional risk factors including lipid disturbances did not predict atherosclerotic cardiovascular events in prevalent HD patients. The events were adjudicated with the use of strict and validated criteria. Markers of inflammation and oxidative stress were significant predictors, and future studies should further evaluate the relevance of these markers and whether they may be targets for novel treatment strategies in patients on dialysis.

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CONFLICT OF INTEREST STATEMENT

None declared.

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