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ORIGINAL ARTICLE

Aortic pulse wave velocity in haemodialysis patients is associated with the prescription of active vitamin D analogues

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Abstract
Background Cardiovascular disease remains the most common cause of death for haemodialysis patients. In addition to traditional cardiovascular risk factors, haemodialysis patients have additional risk factors, including vascular calcification. Pulse wave velocity (PWV) is a measurement of arterial stiffness, and we wished to determine whether PWV is affected by different factors in haemodialysis patients compared to the general population.
Methods Aortic PWV was measured in 303 adult patients attending for routine outpatient dialysis.
Results 303 patients, 63.4 % male, mean age 68.5 ± 15.8 years, 47.5 % diabetic with a body mass index of 25.8 ± 5.3 kg/m^2, were studied. Systolic blood pressure (SBP) was 148.7 ± 28.6 mmHg and diastolic 80.4 ± 15.3 mmHg. Aortic PWV was 9.73 ± 2.08 m/s, and was correlated with SBP (β 0.015, F 5.29, $p = 0.023$), log serum parathyroid hormone (PTH) (β 1.58, F 13.85, $p < 0.001$) and prescription of alfacalcidol (β −1.11, F 6.81, $p = 0.010$). 197 patients had corresponding ECHO cardiograms, and in this cohort PWV was associated with SBP (β 0.017, F 7.49, $p = 0.006$), log serum parathyroid hormone (β 0.85, F 5.99, $p < 0.015$) and prescription of alfacalcidol (β −0.8, F 4.18, $p = 0.042$), left ventricular mass index (LVMI) (β 0.01, F 11.4, $p = 0.001$), and log serum triglycerides (β 1.43, F 4.79, $p = 0.03$).
Conclusions We found that PWV, a measurement of arterial stiffness, was associated with both traditional cardiovascular risk factors, including SBP and LVMI, but also non-traditional risk factors such as prescription of active vitamin D analogues, suggesting a potential link between vascular calcification and arterial stiffness in haemodialysis patients.

Keywords Hypertension · Haemodialysis · Parathyroid hormone · Vitamin D · Pulse wave velocity

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Background

The mortality of haemodialysis patients remains high, with survival rates similar to those of some solid organ malignancies. Cardiovascular disease continues to be the major cause of this excess mortality. Whereas atheromatous coronary artery disease with cholesterol rich plaque formation is the predominant cardiovascular risk factor for the general population, haemodialysis patients typically develop arteriosclerosis with medial vascular calcification and increased risk of death due to heart failure, stroke and cardiac arrhythmias [1, 2].

Arterial stiffness is one of the first detectable manifestations of arteriosclerosis. Pulse wave velocity (PWV) is the most validated non-invasive method of assessing arterial stiffness, and as such is considered the gold standard measurement [3, 4]. Aortic stiffness is recognised as an important risk factor for cardiovascular mortality in both the general population and also patients with chronic kidney disease [5]. In order to determine if there were different factors associated with aortic stiffness in patients on haemodialysis compared to the general population, we

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reviewed aortic PWV measurements in a cohort of established haemodialysis outpatients.

Patients and methods

The records of 303 adult patients with chronic kidney disease stage 5 who were undergoing outpatient haemodialysis treatment thrice weekly and had reliable pulse wave velocity (PWV) measurements taken before the dialysis session were reviewed. PWV measurement was attempted in all outpatient haemodialysis patients under the care of the Royal Free Hospital, but it was not possible to have reliable PVW measurements in patients with atrial fibrillation, other cardiac arrhythmias, those patients with fistulae in both arms, and those in whom no recordable upper arm blood pressure recording was possible. Aortic-brachial pulse wave velocity was measured using the Tensio Clinic Ateriograph which has been validated against direct invasive measurements [6], and also been shown to be the most reproducible of the currently available devices for measuring PWV [7]. The distance between jugular notch and symphysis pubis was measured with a specially designed measuring device, and after patients had rested pulse wave velocity measurements were made in the recumbent position in the non-fistula arm. The upper arm circumference was measured and the appropriately sized blood pressure arm cuff chosen. Aortic augmentation index (AoAXi), brachial artery augmentation index (BrAXi), and diastolic relaxation index (DRA) were corrected for heart rate.

Patients were dialysed thrice weekly, targeted to achieve an on-line clearance of $\geq$1.4 (Fresenius 4008/5008, Fresenius, Bad Homburg, Germany; Dialog+, B Braun Medical Inc, Melsungen, Germany), mean session time 3.96 $\pm$ 0.38 h, using polysulfone dialyzers (Nipro, Osaka, Japan) [8] with ultrapure quality dialysate, and anticoagulated with tinzaparin (Leo Laboratories, Market Harborough, UK), median dose 2,500 IU [9]. Regarding the vascular access, 86 (28.4 %) patients dialysed using central venous catheters [10], 205 (67.7 %) by arteriovenous fistulae and 12 (3.9 %) by arteriovenous grafts. Dialysate temperature was set at 35–35.5 °C, and dialysate sodium regularly checked by flame photometry (Flame photometer 943, Instrumentation Laboratory, Warrington, UK) with appropriate aqueous standards, to ensure quality control [11]. Mean dialysis session time was 3.96 $\pm$ 0.38 h, using a mean dialysate sodium of 137.3 $\pm$ 1.2 mmol/l, potassium 1.9 $\pm$ 0.5 mmol/l, and calcium 1.3 $\pm$ 0.2 mmol/l, with a set dialysate bicarbonate of 32 mmol/l, 3 mmol/l of acetate and 0.5 mmol/l of magnesium.

Standard biochemical investigations were measured using an automated multichannel analyser, with albumin measured by the bromcresol green method (Roche Integra, Roche diagnostics, Lewes, UK), and C reactive protein used the same assay as the UK National Amyloid Centre [12]. Standard 2 dimensional echocardiograms were performed on a non-dialysis day (Philips IE33, Philips Medical Systems, Eindhoven, The Netherlands) [13] in a subset of 197 patients and 137 (45.2 %) patients had attended for cardiac stress testing using adenosine triphosphate myocardial perfusion scintigraphy on a non-dialysis day [14]. Echocardiograms and isotope heart stress tests were performed as part of patient assessment for transplantation and introduction of the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines [15].

This retrospective audit complied with the UK National Health Service (NHS) guidelines for audit and clinical service development. Measurement of pulse wave velocity was introduced into clinical practice in 2011 and measured as part of an audit of blood pressure control in haemodialysis patients.

Statistical analysis

Results are expressed as mean $\pm$ standard deviation, median and interquartile range, or percentage. Simple correlation analysis was used to determine associates of PVW, with non-parametric variables log transformed when entered into a step back multiple regression model if $p < 0.1$, and retained if significant and confidence limits did not cross the line of unity, unless variables improved the model fit. Statistical analysis was performed using Graph Pad Prism (version 6.0, Graph Pad, San Diego, CA, USA) and SPSS (version 17, University Chicago, USA). Results are expressed as mean and standard deviation or, median and interquartile range, unless otherwise stated. Statistical significance was taken at or below the 5 % level.

Results

Data was available on 303 patients (male 63.4 %, mean age 68.5 $\pm$ 15.8 years, weight 71.4 $\pm$ 16.7 kg, body mass index 25.8 $\pm$ 5.3 kg/m^2, with a median dialysis vintage of 32.5 (14–60) months). 47.5 % of the patients were coded as being diabetic, with either a fasting plasma glucose $\geq$7.0 mmol/l (126 mg/dl) or 2-h plasma glucose $\geq$11.1 mmol/l (200 mg/dl) being recorded in their medical records. 79.5 % had a past medical history of hypertension, 29.0 % ischaemic heart disease, 19.8 % peripheral vascular disease, 14.9 % cerebrovascular disease and 5.3 % had undergone previous parathyroid surgery. The mean systolic blood pressure (SBP) was 148.7 $\pm$ 28.6 mmHg, diastolic blood pressure (DBP) 80.4 $\pm$ 15.3 mmHg, and pulse pressure (PP) 68.2 $\pm$ 20.3 mmHg. As for antihypertensive

medications, 27.4 % were prescribed angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), 26.4 % beta-blockers and 21.5 % calcium channel blockers. In addition, 60.1 % were prescribed aspirin, 13.2 % clopidogrel and 2.3 % were anticoagulated with coumarins.

Mean haemoglobin was 111.7 ± 14.5 g/l, with a serum albumin of 39.6 ± 4.1 g/l, median C reactive protein 4 (2–13) mg/l, calcium 2.27 ± 0.17 mmol/l, corrected calcium 2.44 ± 0.15 mmol/l, phosphate 1.48 ± 0.47 mmol/l, alkaline phosphatase 97 (72–138) IU/l, CRP mg/l and parathyroid hormone (PTH) 27.0 (13.9–53.4) pmol/l. The median dose of alfacalcidol prescribed was 2 (0.75–4.5) µg/week. 53.1 % of patients were prescribed calcium containing phosphate binders [median dose 1,000 (0–1,500) g/day], 16.2 % sevelamer, 13.5 % lanthanum carbonate and 8.5 % cinacalcet [all median dose 0 (0–0)]. Vitamin D (25 hydroxy vitamin D3) levels were measured and 181 (59.7 %) patients with reduced concentrations were prescribed 20,000 IU/week of cholecalciferol.

Serum total cholesterol (TChol) was 3.98 ± 1.1 mmol/l, high density lipoprotein (HDL) 1.27 ± 0.48 mmol/l, low density lipoprotein (LDL) 2.83 ± 0.9 mmol/l and triglycerides 1.3 (0.9–1.9) mmol/l, with 58.4 % prescribed HMG CoA 3 reductase inhibitors (statins).

Aortic PWV was 9.73 ± 2.08 m/s, with a heart rate of 73.3 ± 13.6 beats/min, giving a corrected aortic PWV 9.67 ± 2.99 (for a heart rate of 70). Aortic systolic blood pressure was 149.2 ± 46.8 mmHg, and augmentation indices corrected for heart rate were 3.77 ± 31.9 and 39.1 ± 20.7 % for the brachial and aortic arteries respectively, with a diastolic relaxation area of 40.2 ± 24.6 %.

Left ventricular (LV) mass was calculated in 197 patients and corrected for body surface area, using standard equations [15, 16], with a mean LV mass of 265.7 ± 93.6 g, and LVmass index of 147.5 ± 48.6 g/cm^2, with a relative wall thickness of 0.52 ± 0.15. No patient was reported to have severe valvular calcification, but minor degrees of valvular calcification were not reported. 137 (45.2 %) patients had attended for cardiac stress testing using adenosine triphosphate myocardial perfusion scintigraphy, and 39.4 % of these tests were reported to show reversible cardiac ischaemia. Dialysis adequacy was targeted to achieve a minimum on-line Kt/V of >1.4 [17].

Simple correlation analysis showed that there was no correlation between pulse wave velocity and haemoglobin, serum albumin or C reactive protein, although a number of variables were statistically associated with PWV (Table 1). Nonparametric variables were log transformed as appropriate and a linear regression model was created for all patients, using all variables with a simple correlation of $p < 0.01$. A stepwise regression analysis was then performed with elimination of variables that were not statistically significant, unless they improved the fit of the model. PWV was associated with SBP, serum PTH and prescription of alfacalcidol (Tables 2, 3). Another model was created by restricting the analysis to only those patients with echocardiography-derived LVmass index (Tables 2, 3). Co-linearity was checked by simple plotting of variables and checking correlations; the correlation between serum PTH and alfacalcidol prescription was somewhat weak with an r^2 value of 0.023. As both alfacalcidol and PTH were present in both models, patients were re-analysed according to alfacalcidol prescription and quartiles of serum PTH concentrations (Tables 4, 5). PWV was greater in those patients not prescribed alfacalcidol (Fig. 1), despite similar patient demographics, body size, blood pressure and left ventricular mass (Table 4), prescription of antihypertensive medications (ACEI/ARBs 30 vs. 26.6 %, β blockers 33.3 vs. 24.6 %), and prescription of calcium based binders (41.7 vs. 51.5 %), all $p > 0.05$. Although PTH was lower in the group not prescribed alfacalcidol, there was no difference in PVW, blood

Table 1 Simple Pearson correlation analysis for pulse wave velocity

Variable	Pearson r	p
Left ventricular mass	0.236	0.001
Systolic blood pressure	0.229	0.000
Left ventricular mass index	0.206	0.004
Pulse pressure	0.205	0.000
Body mass index	0.172	0.003
Prescription of HMG-CoA 3 reductase inhibitors (statins)	0.164	0.004
History of peripheral vascular disease	0.160	0.005
History of diabetes mellitus	0.158	0.006
Diastolic blood pressure	0.157	0.006
Log serum triglycerides	0.155	0.007
Prescription of alfacalcidol	−0.150	0.009
Age	0.149	0.010
Weight	0.147	0.010
Prescription of cholecalciferol	−0.131	0.023
History of hypertension	0.128	0.026
Sex (female vs. male)	−0.124	0.031

Table 2 Linear regression models for pulse wave velocity (PVW) measured in 303 patients

	β	SEM	F	95 % CL	p
log PTH	1.58	0.42	13.9	0.74 to 2.42	<0.001
SBP	0.02	0.01	5.3	0.03 to 0.023	0.023
1α	−1.11	0.04	6.81	−1.94 to −0.27	0.01
log TG	1.37	0.69	4.0	1.99 to 01	0.048

Model fit $r^2 = 0.47$, adjusted $r^2 = 0.18$

Table 3 Linear regression models for pulse wave velocity (PVW) restricted to 197 patients with echocardiography-derived left ventricular mass index (LVMI)

	β	SEM	F	95 % CL	p value
log PTH	0.85	0.35	6.0	0.16 to 1.53	0.005
SBP	0.02	0.01	7.5	0.01 to 0.03	0.006
LVMI	0.01	0.00	11.4	0.01 to 0.07	0.001
1α	−0.8	0.39	4.2	−1.56 to −0.27	0.04
logTG	1.43	0.65	4.79	0.14 to 2.72	0.03

Model fit $r^2 = 0.37$, adjusted $r^2 = 0.19$

CL confidence limits, *SBP* systolic blood pressure, *PTH* serum parathyroid hormone, *TG* triglycerides, *1α* prescription of calcitriol

Table 4 Demographics of 60 patients not prescribed alfacalcidol vs. 243 prescribed alfacalcidol

	No alfacalcidol	Alfacalcidol	p
Age, years	69.6 ± 1.9	65.8 ± 1.1	0.09
Male sex (%)	63.3	63.1	1.00
Diabetes (%)	51.7	46.3	0.56
Dialysis vintage months	1.33 ± 0.07	1.46 ± 0.04	0.10
Weight, kg	69.5 ± 1.8	71.9 ± 1.1	0.33
Body mass index, kg/m^2	25.2 ± 0.6	25.9 ± 0.4	0.33
Ejection fraction (%)	53.3 ± 1.7	54.4 ± 0.9	0.16
Left ventricular mass, g	262.5 ± 15.5	266.5 ± 7.5	0.82
Left ventricular mass index, g/cm^2	147.5 ± 8.1	147.5 ± 3.9	0.99
Heart rate, beats/min	71.4 ± 1.5	73.7 ± 0.9	0.24
Systolic blood pressure, mmHg	147.2 ± 3.9	149.0 ± 1.8	0.66
Diastolic blood pressure, mmHg	79.2 ± 2.1	80.7 ± 1.0	0.52
Albumin, g/l	39.1 ± 0.6	39.8 ± 0.3	0.29
Cholesterol, mmol/l	4.0 ± 0.1	4.0 ± 0.1	0.77
Parathyroid hormone, pmol/l	16 9 (4–30.5)	30.9 (17.2–56.2)	0.005*
Calcium, mmol/l	2.43 ± 0.02	2.44 ± 0.01	0.21
Phosphate, mmol/l	1.44 ± 0.06	1.49 ± 0.03	0.45

Dialysis vintage was log transformed

Results expressed as percentage, mean ± standard error of the mean (SEM), median and interquartile range

Uncorrected p values displayed and * $p < 0.05$ after correction for multiple testing

pressure or left ventricular mass between patient quartiles according to serum PTH (Table 5). There was a trend for the highest PTH quartile to be younger, but heavier and have lower serum phosphate. However after correcting for multiple statistical analyses, these differences were no longer significant.

Discussion

Patients with chronic kidney disease develop arterial stiffening well before progression to CKD stage 5 [5]. Pulse wave velocity is currently considered the "gold" standard non-invasive measurement of arterial stiffness, due to the reliability of the measurements [3, 4]. We measured aortic PWV, as this is more reproducible compared to carotid-femoral measurements [7, 18].

In the general population, PWV has been shown to increase with age, while there is no significant difference of PWV between men and women [19]. In our cohort, we only found a simple univariate association between age and increasing PWV. Although several smaller studies in dialysis patients have observed increasing PWV with age [1, 20, 21], this finding is not universal, particularly with larger cross sectional studies [22]. As expected, PWV was associated with systolic and diastolic blood pressures and pulse pressure, and left ventricular mass. In addition PWV was also, on univariate analysis, associated with past medical history of hypertension and peripheral vascular disease. While some studies in dialysis patients have reported increased PWV in women [23], our measurements initially suggested a higher PWV in women but after adjustment for heart rate and body size there were no differences.

Some reports have noted increased PWV in diabetic dialysis patients [20, 22], but although we found diabetes to be associated with PWV on univariate analysis we could not confirm this association on multivariate analysis. This may reflect the greater prevalence of impaired glucose metabolism in our inner city catchment population, and the greater prevalence of type 2 diabetes in younger dialysis patients from ethnic minority groups. Our cohort did not show an effect of the type of vascular access on PWV, although there are studies suggesting that PWV is reduced by the presence of an arteriovenous fistula [24]. Other studies have also reported reduced PWV with use of angiotensin converting enzyme inhibitors, angiotensin receptor blockers and calcium channel blockers compared to beta blockers [3, 25]. In our cross sectional analysis, there was no observed effect of any antihypertensive agent, or of the number of antihypertensive medications on PWV. The association of PWV with dyslipidaemia [3, 26] was also not confirmed by our results, since we did not find any association with total cholesterol, high density or low density lipoprotein. This may have been due to the relatively large number of our patients prescribed statins, and on simple correlation there was an affect with statin prescription. However on further analysis there was an association with triglycerides, which supports the observations of an earlier study [27].

Table 5 Demographics of patients characterised by serum parathyroid hormone (PTH) concentration quartiles

PTH, pmol/l	<13.9	13.9–27.0	27.1–53.4	>53.4	p value
Age, years	68.8 ± 1.7	69.3 ± 1.9	70.3 ± 1.8	58.0 ± 1.7	<0.001*
Male sex (%)	62.7	65.4	62.3	63.5	0.98
Diabetes (%)	41.3	53.8	53.6	41.9	0.22
Dialysis vintage, months	1.39 ± 0.07	1.37 ± 0.02	1.5 ± 0.06	1.51 ± 0.06	0.30
Weight, kg	67.2 ± 1.8	72.3 ± 1.9	70.2 ± 1.8	76.3 ± 2.1	0.015
BMI, kg/m^2	24.9 ± 0.6	25.1 ± 0.6	25.2 ± 0.6	27.2 ± 0.6	0.068
ej (%)	55.1 ± 1.3	54.8 ± 1.6	54.6 ± 1.9	56.2 ± 1.6	0.94
LVmass, g	256.4 ± 13.5	282.5 ± 14	257.8 ± 14.3	261.7 ± 12.4	0.44
LVMI, g/cm^2	148.2 ± 7.0	154.3 ± 6.8	145.5 ± 7.6	140.0 ± 6.7	0.52
HR, beats/min	73.3 ± 1.4	70.7 ± 1.5	74.5 ± 1.7	74.5 ± 1.7	0.26
SBP, mmHg	147.1 ± 3.6	150.7 ± 2.9	148.1 ± 3.1	148.4 ± 3.7	0.82
DBP, mmHg	79.0 ± 1.9	80.4 ± 1.6	77.5 ± 1.8	84.5 ± 1.9	0.039
Albumin, g/l	39.5 ± 0.5	38.7 ± 0.4	39.9 ± 0.2	40.6 ± 0.4	0.042
Cholesterol, mmol/l	3.87 ± 0.11	3.91 ± 0.13	4.0 ± 0.13	3.3 ± 0.14	0.38
PWV, m/s	9.62 ± 0.25	9.58 ± 0.23	9.97 ± 0.24	9.79 ± 0.24	0.66
Calcium, mmol/l	2.26 ± 0.02	2.26 ± 0.02	2.28 ± 0.02	2.16 ± 0.02	0.72
Phosphate, mmol/l	1.38 ± 0.5	1.47 ± 0.05	1.45 ± 0.06	1.28 ± 0.05	0.029

Dialysis vintage in months log transformed

BMI body mass index, *ej* cardiac echo derived ejection fraction, *LVMI* left ventricular mass index, *HR* heart rate, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *PWV* pulse wave velocity

Results expressed as percentage, mean ± SEM, median and interquartile range

p values for one way anova with Holm-Sidek correction and then * $p < 0.05$ after correction for multiple testing

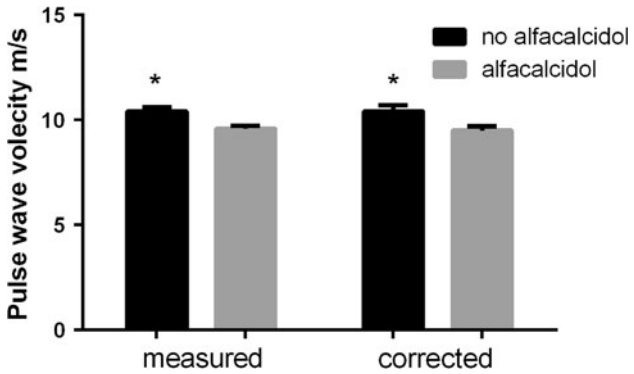

Fig. 1 Measured pulse wave velocity, and pulse wave velocity corrected for heart rate in patients prescribed and not prescribed alfacalcidol. Data expressed as mean ± SEM. *$p < 0.05$ after correction for multiple analyses

Chronic dialysis patients are at risk of medial vascular calcification, and arterial stiffness [20, 28]. Although the biology of vascular calcification remains complex [29], the risks appear to be increased both when bone turnover is suppressed and also at high turnover states [30]. We did not systematically perform X-rays or computerized tomography (CT) scans on our patients and as such cannot comment on radiological calcification scores and PWV. Due to the limited number of patients with valvular calcification on echocardiography we did not observe any association between PWV and valvular calcification. Previous reports have suggested an association between PWV and PTH [31, 32]. In our cohort there was no relationship with PTH on simple univariate analysis, and no difference between PTH quartiles. There was a trend for the highest PTH quartile group to be heavier, on one hand, which is reported to be associated with increased PVW, but on the other hand they were younger, which is associated with lower PVW. As such there was a trend for PVW to be higher for those patients in the higher PTH quartiles compared to those in the lower quartiles, and PTH did achieve significance in our multiple linear regression models. However in every day clinical practice alfacalcidol dosing is based on review of the trend in serum PTH, calcium and phosphate. Hence alfacalcidol therapy may be lowered or withdrawn in patients with low PTH values in an attempt to prevent further PTH suppression and low bone turnover, and this may explain the differences in serum PTH levels in those patients who were or were not prescribed calcitriol. Previous studies suggesting a relationship with PTH and PVW did not analyse the effect of medications. Patients not prescribed active vitamin D analogues had increased pulse wave velocity, and several large cohort studies have observed increased mortality in those patients not prescribed active vitamin D analogues [33, 34]. Gla-matrix

protein which inhibits vascular calcification is regulated by vitamin K, and possibly vitamin D3. Many dialysis patients in the UK are deficient in 25 hydroxy-vitamin D3, as sunlight levels are generally inadequate for most of the year, particularly for ethnic minority groups. As such our policy is to provide replacement cholecalciferol, and we could therefore not demonstrate any association between 25 hydroxy vitamin D3 serum concentrations and PWV. Increased arterial vessel stiffness due to vascular calcification could therefore link our results with previous reports of increased mortality in those patients not prescribed active vitamin D analogues. As such pulse wave velocity in haemodialysis patients is associated with non-traditional risk factors associated with bone-mineral disorders of dialysis patients. Further studies are required to determine whether newer markers of vascular calcification are associated with the increased PWV observed in dialysis patients.

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Conflict of interest The authors have no conflict of interest.

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