

Original Article

Abdominal aortic calcification in dialysis patients: results of the CORD study

Eero Honkanen¹, Leena Kauppila², Björn Wikström³, Pieter L. Rensma⁴, Jean-Marie Krzesinski⁵, Knut Aasarod⁶, Francis Verbeke⁷, Per Bruno Jensen⁸, Pierre Mattelaer⁹ and Birgitte Volck⁹
on behalf of the CORD study group*

¹Division of Nephrology, Department of Medicine, Helsinki, ²Department of Rehabilitation, Helsinki University Central Hospital, Espoo, Finland, ³Department of Nephrology, Uppsala University Hospital, Uppsala, Sweden, ⁴Department of Internal Medicine, St. Elisabeth Hospital Tilburg, Tilburg, The Netherlands, ⁵Division of Nephrology, Liege University Hospital, Liege, Belgium, ⁶Department of Medicine, Trondheim University Hospital, Trondheim, Norway, ⁷Department of Nephrology, Gent University Hospital, Gent, Belgium, ⁸Odense University Hospital, Odense and ⁹Genzyme A/S, Copenhagen, Denmark

Abstract

Background. Patients with chronic kidney disease stage 5 have a high prevalence of vascular calcification, but the specific anatomical distribution and severity of abdominal aortic calcification (AAC), in contrast to coronary calcification, is less well documented. AAC may be recorded using plain radiographs. The present report is an analysis of baseline data on AAC in patients enrolled in the CORD (Calcification Outcome in Renal Disease) study.

Methods. A total of 47 centres in six European countries participated in this cross-sectional study. Inclusion criteria were age ≥ 18 years and duration of dialysis ≥ 3 months. Lateral lumbar radiography of the abdominal aorta was used to determine the overall AAC score, which is related to the severity of calcific deposits at lumbar vertebral segments L1–L4. The reliability of the method was tested by double reading of 64 radiographs (coefficient of correlation 0.9).

Results. A lateral lumbar radiograph was obtained in 933 patients. Calcification (AAC score ≥ 1) was present in 81% of the patients; its severity increased significantly from L1 to L4 ($P < 0.0001$) and affected all of these segments in 51% of patients. Independent predictors for the presence and severity of calcification were age (odds ratio [OR] 1.103/year; $P < 0.0001$), duration of dialysis (OR 1.110/year; $P = 0.002$) and history of cardiovascular disease (OR 3.247; $P < 0.0001$).

Conclusions. AAC detected by lateral lumbar radiograph is associated with several risk factors of uraemic calcification. This semi-quantitative method is more widely available and less expensive than the current procedures for studying calcification and could form part of a pre-transplant workup and cardiovascular risk stratification.

Keywords: calcification; cardiovascular disease; chronic kidney disease; dialysis; lateral lumbar radiography

Introduction

Patients with stage 5 chronic kidney disease (CKD) on dialysis have a greatly increased atherosclerotic burden, which often progresses over a relatively short period of time [1,2]. This phenomenon affects even young dialysis patients [3] and probably explains in part why cardiovascular mortality is increased 20- to 30-fold in this group compared with an age-matched population [4]. Over the past few years, numerous studies have elucidated potential pathogenetic mechanisms leading to the accelerated calcification of blood vessels (reviewed in [5]). It has also become evident that traditional risk factors for atherosclerosis, such as dyslipidaemia, hypertension, smoking, gender and age, only partly explain the calcification that seems to be more linked to the uraemic milieu and abnormalities in mineral metabolism [1,6].

Atherosclerosis in the coronary arteries and other vascular beds correlates with the extent of lesions in the aorta [7], and several studies have suggested that plain radiographs of pelvic and thigh vessels [8] and thoracic aorta [9] may be useful methods of assessment. The abdominal aorta is relatively simple to investigate radiologically, but no well-standardized method has been used in patients with end-stage renal disease (ESRD). A system for quantification of calcification was described by Kauppila *et al.* [10] in a subgroup of participants of the Framingham heart study. It relies on lateral lumbar radiographs and the calculation of the abdominal aortic calcification (AAC) score. This method was studied initially in 617 subjects and its predictive value for cardiovascular events and mortality was validated in a large cohort of 2500 subjects in the Framingham heart study [11,12]. Recently, the AAC score was

Correspondence and offprint requests to: Eero Honkanen, Division of Nephrology, Department of Medicine, Helsinki University Central Hospital, PO Box 263, FIN-00131, Helsinki, Finland. Tel: +35-8-9-471-88204; Fax: +35-8-9-417-88-400; E-mail: eero.honkanen@hus.fi

*The list of members of the CORD study group is given in the Appendix.

shown to correlate well with electron beam computer tomography (EBCT) scores of coronary arteries in chronic haemodialysis patients [13]. AAC may also be associated with all-cause and cardiovascular mortality in ESRD [14].

The Global Bone and Mineral Initiative Working Group of the Kidney Disease Improving Global Outcomes (KDIGO) managed by the National Kidney Foundation recommended screening for the presence of cardiovascular calcification with simple office-based methods to make it accessible to a greater number of nephrologists. A cardiovascular calcification index (CCI) has been developed by Muntner *et al.* [15] comprising demographic information, dialysis vintage and simple imaging procedures including plain lateral lumbar X-ray pulse pressure and an echocardiogram. These procedures are widely available, less costly and have been shown to have an acceptable sensitivity and specificity. Such testing could form the basis for determining which patients might benefit from more focused investigations.

The CORD (Calcification Outcome in Renal Disease) study is an epidemiological study in dialysis patients, aimed to quantify arterial calcification and stiffness and to identify risk factors related to these processes. In addition, the study also evaluates the progression over time and the independent predictive value of these parameters for the occurrence of cardiovascular events and mortality over a 24 months' follow-up period. The present report is an analysis of the baseline data on vascular calcification.

Subjects and methods

A total of 47 centres in Northern Europe participated in the CORD study: 14 in Belgium, 13 in the Netherlands, 6 in Sweden, 5 in Denmark, 5 in Finland and 4 in Norway. Each site collected information on age, gender, duration of dialysis, diabetic status and smoking (non-smoker, current or past smoker) of all patients on haemodialysis and peritoneal dialysis. These data served as a basis for an automated selection procedure that was used to ensure that the CORD population would be a representative sample of the overall dialysis population. A minimum of 20% of the dialysis patients in each centre was entered into the study. The inclusion criteria were patient providing informed consent, age ≥ 18 years and duration of dialysis ≥ 3 months. Exclusion criteria were significant co-morbidities that were estimated to reduce life expectancy to < 6 months and patients in whom it was impossible to measure parameters of arterial stiffness (e.g. diminished/absent pulses, atrial fibrillation and bilateral arteriovenous fistulas).

A total of 2102 patients were selected from the database to participate, and of these, 1009 did not enter the study based on the eligibility criteria outlined above. Of the remaining 1093 patients, a lateral lumbar radiograph of 933 patients was available and these formed the basis of the present study population.

The following baseline biochemical data were obtained using local routine laboratory methods at the start of the study: serum calcium, phosphorus, intact parathyroid hormone, albumin, C-reactive protein, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein

cholesterol and triglycerides. The recorded cardiovascular history included coronary events (myocardial infarction, angina pectoris, unstable angina, coronary artery bypass surgery, percutaneous coronary angioplasty and congestive heart failure); cerebrovascular events (stroke and transient ischaemic attacks) and peripheral vascular disease (intermittent claudication, abdominal aortic aneurysm, angioplasty, vascular surgery and amputation). Data on weight, height, body mass index and type and duration of dialysis were obtained as well as use of following medications: phosphate binders (use and doses of binders containing calcium, aluminium and/or sevelamer hydrochloride), vitamin D, oral anticoagulants, statins, angiotensin-converting enzyme inhibitors/angiotensin II receptor-blocking agents, beta-blockers, calcium-channel blockers and erythropoietin. Blood pressure was measured in the sitting position before haemodialysis or during peritoneal dialysis.

Lateral lumbar radiography of aorta

Lateral radiography was performed in the standing position using standard radiographic equipment. A minimum of 4 cm anterior to the lumbar spines had to be visible: the film distance was 100 cm, other adjustments were: 94 KPV, 33–200 mAs and the estimated dose of radiation was approximately 15 mGy.

Calcification of the aorta was graded using a previously validated system [10,11] in which both the location and the severity of calcific deposits at each lumbar vertebral segment (L1–L4) were evaluated. The scores were summarized using two methods: (a) the composite score for anterior–posterior severity (assigned here as the AAC) where the scores of individual aortic segments both for the anterior and posterior walls were summed (maximum score 24), and (b) the affected segments score as the total number of aortic segments showing any level of calcification is indicated (maximum score 4). The scoring system is depicted schematically in Figure 1.

Lateral lumbar radiographs were analysed centrally by two readers who were unaware of the clinical background of the patients. Double readings were performed in a subgroup of 64 patients demonstrating an excellent inter-observer agreement (intra-class coefficient of correlation 0.9).

Ethical considerations

The study design was approved by local ethics committees, and patients gave written informed consent before entering the study.

Statistical analysis

Summary statistics are reported as means \pm SE (with range, and 95% confidence intervals where appropriate) for quantitative variables and as frequencies or percentages for categorical variables. The unpaired *t*-test, Mann–Whitney *U*-test, one-way analysis of variance (ANOVA) and Kruskal–Wallis tests were used for analysis between groups where appropriate. Differences in frequency were tested using χ^2 analysis.

GRADING

- 0: no calcific deposits in front of the vertebra
- 1: small scattered calcific deposits filling less than 1/3 of the longitudinal wall of the aorta
- 2: 1/3 – 2/3 of the wall calcified
- 3: 2/3 or more of the wall calcified

Level	Affected segment	Scores for individual segments		Composite score (AAC)
		Posterior Wall Range 0-3	Anterior Wall Range 0-3	Anterior-Posterior severity Range 0-6
L1	1	1	0	1
L2	1	2	1	3
L3	1	3	2	5
L4	1	3	3	6
Total	4	9	6	15
Maximum	4	12	12	24

Fig. 1. Abdominal aorta calcification (AAC) scoring. Grading of calcification was assessed at the anterior and the posterior walls of the abdominal aorta adjacent to vertebrae L1–L4 and the composite score determined.

The independent predictive value of the following baseline parameters on the AAC score (equal to 0 or ≥ 1) were analysed using linear regression analysis with backward elimination: age (years), gender, diabetic status (yes/no), duration of dialysis (years), dialysis modality (haemodialysis/peritoneal dialysis), pulse pressure (mmHg), serum calcium (mmol/l), calcium \times phosphorous product (mmol^2/l^2) and the presence or absence of cardiovascular history. The model quality was evaluated using analysis of residual deviance. The odds ratios and their 95% confidence intervals were also reported. SAS version 8.02 statistical software package (SAS Institute, Cary, NC, USA) was used for all statistical analyses.

Results

Patient characteristics

Baseline demographics and laboratory values of the study population are shown in Tables 1 and 2 and current medications used are listed in Table 3. One patient with the low serum calcium level of 1.5 mmol/l had a period of hypocalcaemia at baseline.

Segmental ACC scores

The number of individual aortic segments affected by any calcific deposit is depicted in Figure 2. In 51% of the patients, all four segments showed deposits (score > 0), and between one and three segments were affected in 30% of patients. Interestingly, 19% of patients had no visible deposits (score = 0) in any segment. In 81% of patients who had an AAC score ≥ 1 , the localization of calcific deposits was analysed for the individual segments (L1–L4): 54% of patients had calcifications at level L1, 67% at L2, 75% at

Table 1. Baseline patient characteristics

Characteristic	Value
Mean (range) age (years)	61.4 (19–89)
Gender (%)	
Male	60.8
Female	39.2
Mean (range) mass index (kg/m^2)	25.1 (15.4–46.4)
Diabetes (%)	
With	22.9
Without	77.1
Tobacco use (%)	
Yes	18.5
No	81.5
History of cardiovascular disease (%)	
Yes	43.7
No	56.3
Type of dialysis (%)	
Haemodialysis	83.9
Peritoneal dialysis	16.1
Mean (range) duration of dialysis (months)	38.2 (3–363)

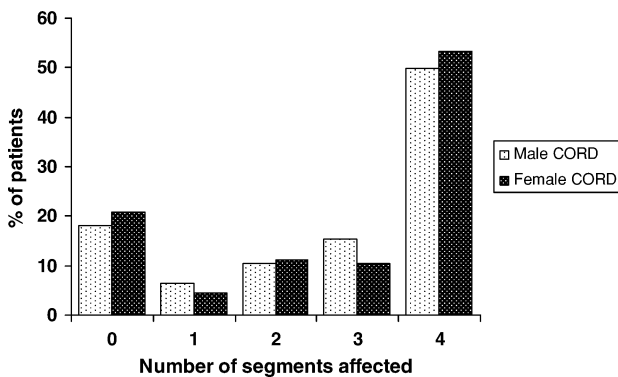
Table 2. Blood pressure and laboratory values

Parameter	Mean (range)
Systolic blood pressure (mmHg)	146 (72–218)
Diastolic blood pressure (mmHg)	79 (30–141)
Pulse pressure (mmHg)	67 (17–131)
Serum calcium (mmol/l)	2.4 (1.5–3.0)
Serum phosphorus (mmol/l)	1.7 (0.4–3.4)
Calcium phosphorus product (mmol^2/l^2)	4.0 (0.9–8.3)
S-PTH int (ng/l)	281 (1.0–2505)
Serum C-reactive protein (mg/l)	11 (0–253)
Total serum cholesterol (mmol/l)	4.2 (1.7–9.0)
Serum LDL cholesterol (mmol/l)	2.2 (0.01–6.4)
Serum HDL cholesterol (mmol/l)	1.3 (0.5–3.7)
Serum triglycerides (mmol/l)	1.8 (0.4–17.0)

S-PTH int = intact parathyroid hormone, LDL = low-density lipoprotein, HDL = high-density lipoprotein.

Table 3. Current medication of the study population

Agent	Percentage of patients	Mean (range) dose (mg)
Phosphate binders		
Calcium containing	73	2026 (200–10 000)
Aluminium containing	4	1734 (400–6000)
Sevelamer	48	4866 (800–16 000)
Vitamin D analogues	52	
Oral anticoagulants	14	
Statins	35	
Angiotensin-converting enzyme inhibitors or angiotensin II receptor blocking agents	39	
Beta blocking agents	48	
Calcium channel blocking agents	27	
Erythropoiesis stimulating agents	93	

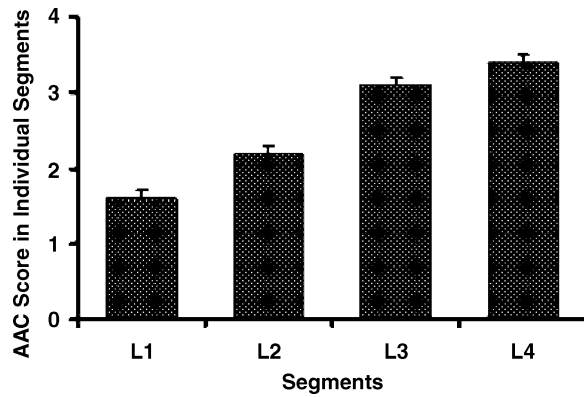
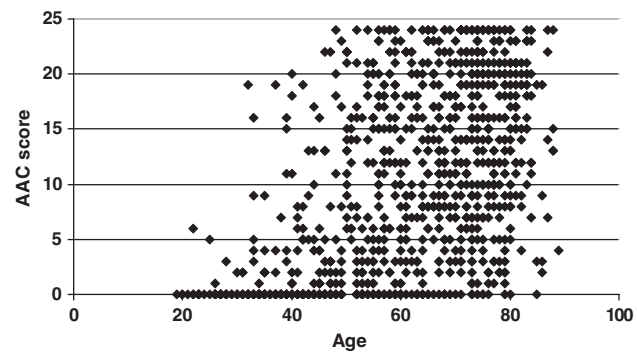
**Fig. 2.** Number of aortic segments affected by calcific deposits.

L3 and 76% at L4, indicating that calcification developed in a distal to proximal direction.

The proportion of patients with minimal or no calcification, defined as number of affected segments equal to 0 or 1, decreased with age: 54% of the patients <50 years, 27% of patients aged 51–60 years and <10% in those >60 years (in whom typically all segments L1–L4 were affected). Accordingly, age correlated with the number of affected aortic segments ($r = 0.59$; $P < 0.0001$). Patients in whom all four aortic segments were affected had been on dialysis for a longer period of time compared to those in whom only 0–2 segments were affected (40 ± 2 months versus 33 ± 2 months, respectively; $P = 0.006$).

ACC scores

The mean (\pm SE) AAC score of the study population was 10.3 ± 0.3 . No significant gender differences were observed; the mean scores for men and women were 10.2 ± 0.3 and 10.4 ± 0.4 , respectively. At a mean age of 61 years, 81% of the CORD patients had calcific deposits in the abdominal aorta (score ≥ 1). The AAC scores of individual aortic segments of the CORD population (Figure 3) increased stepwise from 1.6 ± 0.1 at level L1 up to 3.4 ± 0.1 at level L4 ($P < 0.0001$; ANOVA).

**Fig. 3.** Abdominal aortic calcification (AAC) scores in segments L1–L4 ($n = 933$; $P < 0.0001$).**Fig. 4.** Abdominal aortic calcification (AAC) scores in individual patients in relation to their age.

Factors associated with ACC scores

There was no significant relationship between AAC and smoking status, systolic or diastolic blood pressure, phosphorus, lipids or CRP (simple regression analysis). The relationship between age and AAC scores of individual patients is shown in Figure 4. Overall, calcification scores increased rapidly with age ($r = 0.51$, $P < 0.0001$). Although 31% (70 of 226) patients at the age of ≥ 50 years had severe calcification (AAC score > 4), 11% (37 of 336) patients at the age of ≥ 70 years had little or no calcification (AAC score ≤ 4) (Figure 5). Patients with a history of cardiovascular disease had higher AAC scores than those without (13.9 ± 0.4 versus 7.9 ± 0.4 ; $P < 0.0001$). Multiple logistic regression analysis was used to investigate independent predictors of the presence of calcification (AAC score > 1). The following factors were excluded by the backward elimination: gender ($P = 0.3$), diabetic status ($P = 0.4$), pulse pressure ($P = 0.2$), dialysis modality ($P = 0.2$), baseline serum calcium ($P = 0.7$) and calcium \times phosphorus product ($P = 0.1$). Independent predictors of AAC included in the final model were age (per 1 year increase; odds ratio [OR] 1.103; 95% confidence interval [CI] 1.082–1.116; $P < 0.0001$), duration of dialysis (per 1 year increase; OR 1.110; CI 1.040–1.191; $P = 0.002$) and positive history of cardiovascular disease (OR 3.247; CI 1.976–5.319; $P < 0.0001$).

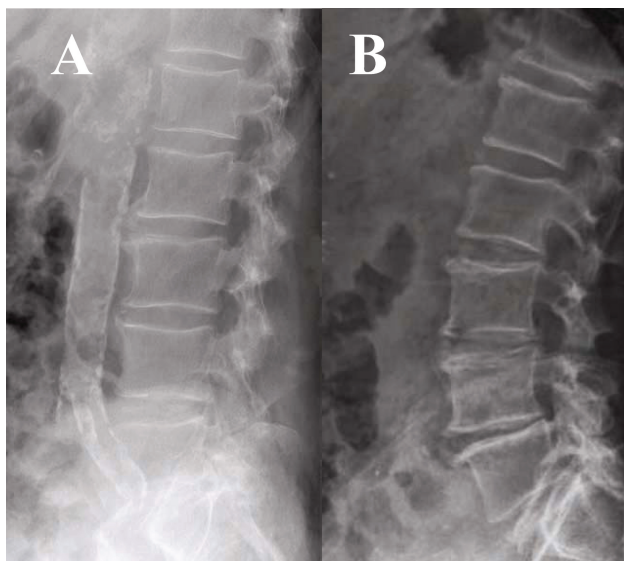


Fig. 5. Plain X-ray of (A) a 59-year-old patient with abundant abdominal aortic calcification (AAC = 21) and (B) a 73-year-old patient with no calcific deposits in the abdominal aorta (AAC = 0).

Discussion

The present multicentre, cross-sectional study comprised 933 patients with dialysis-dependent CKD. AAC was investigated using plain lateral radiographs, which are widely available, easy to use, relatively inexpensive and involve low exposure to radiation. To our knowledge, this is the largest radiological documentation of arterial calcification in dialysis patients. The main findings were severe premature calcification of the abdominal aorta that was related to age, duration of dialysis and history of cardiovascular disease. Aortic calcification was most severe in front of the fourth lumbar segment and decreased towards the higher lumbar levels. Only one in five patients had no visible calcification in the abdominal aorta, whereas >50% had calcification in all four segments, indicating severe calcification.

Several radiological methods, such as EBCT, multislice spiral CT and plain radiographs, have been used to investigate aortic calcification [16,17]. Such methods are costly and are primarily used for clinical research purposes in nephrology. A few studies have systematically investigated plain radiographs as a means of assessing calcification in dialysis patients [18,19]. None of these methods have been accepted as a gold standard in cardiovascular risk assessment (reviewed in [20]). The current study investigated X-rays of the abdominal aorta. In Belgium and the Netherlands, a special goal was to include up to 50% of peripheral hospitals. Without the more specific equipment available in university centres, a simple lateral lumbar X-ray affords them an easy inexpensive method for the initial screening of cardiovascular risk in their patients. The scoring system applied is a validated method developed on the basis of lateral lumbar X-rays from the general population in the Framingham heart study [10], where it was proven to be predictive for cardiovascular risk and outcome [11,12]. The

baseline prevalence of calcification in that cohort, which had a mean age of 54 years, was 37% in men and 27% in women and increased significantly during the 25 years of follow-up. Kiel *et al.* [21] investigated 554 subjects using the same methodology and observed that, over a period of 25 years, AAC increased sixfold in men and eightfold in women in whom the change correlated to the degree of bone loss.

Several studies suggest that aortic calcification correlates with the findings in coronary arteries, which in turn predict all-cause mortality [5,13]. In line with these studies are the findings that the severity of AAC is also an important indicator of cardiovascular disease and mortality. Calcification scored using the same system as in the present study was strongly related to the development of congestive heart failure, coronary heart disease and cardiovascular events in the general population [11,12]. AAC remained as an independent predictor of risk even after the adjustment for traditional cardiovascular risk factors such as diabetes, older age, male gender, family history of coronary heart disease, systolic blood pressure, left ventricular hypertrophy, smoking, dyslipidaemia and body mass index [11]. In the present study, a history of cardiovascular events was associated with 224% increased odds of calcification. Interestingly, Okuno and co-workers reported recently on a cohort of 515 haemodialysis patients showing that the presence of AAC was significantly associated with both all-cause and cardiovascular mortality during a mean follow-up of 51 months [14].

There was a significant age-related increase in AAC in the present study, a finding that has previously been shown in both non-renal [10,22] and renal [23] patients. In the general population, calcific deposits in the posterior aortic wall have been shown to occur most commonly at the level of L4 and in the anterior wall at levels L3 and L4 [24]. In the present study of ESRD patients, the most pronounced calcification was also detected at level L4, suggesting that the distribution of AAC is similar, but more extensive and premature in ESRD.

Although some reports on the general population [22] have suggested that men are particularly prone to calcification, no significant sex-related difference was observed in the present study. The duration of dialysis correlates with calcification in the coronary [23], carotid and peripheral arteries [8], but the association is less clear in the thoracic aorta [23]. In the present study, there was a significant relation between dialysis vintage and AAC: each year on dialysis increased the odds for AAC ≥ 1 by 11%. However, pulse pressure did not predict AAC scores, which is in line with the recent study by Bellasi and co-workers [13], where no association was found between pulse pressure and coronary artery calcification.

In the CORD study, 19% of patients had no visible calcification in their abdominal aorta, even though some of them were >80 years of age. These findings are in line with certain previous observations [2,22], and it has been suggested that these individuals rarely develop calcification at follow-up [2,25,26]. However, in a recent longitudinal study, Asmus *et al.* [27] followed 72 haemodialysis patients, of whom 41 used calcium-containing phosphate binders and 31 used sevelamer hydrochloride. A subset of

these patients (15%) had no coronary or thoracic aortic calcification at baseline, but their calcification developed during 2 years of observation and was most prevalent in those receiving calcium-containing binders. Thus, it remains to be proven if the 'non-calcified' patients have some typical biochemical and/or genetic features that protect them from calcification. The analysis of the aortic X-rays at the 24-month follow-up of the CORD study will provide further insight into this question.

The present cross-sectional study has some limitations. The increased vascular calcification and its relationship to age and dialysis vintage are well known. In a recent study [13] on 140 prevalent haemodialysis patients with a mean age of 55 years and dialysis vintage of 2.7 years, the mean AAC was 4.4, i.e. much lower than that in the present study on North European patients. Importantly, patients with severely reduced life expectancy were excluded. Furthermore, only those patients in whom parameters of arterial stiffness by applanation tonometry could be recorded were included; this measure was impossible in some patients with severe vascular disease and/or atrial fibrillation. Most likely this resulted in a favourable selection bias and the actual calcification burden of dialysis patients may be even more profound.

In conclusion, severe calcification of the abdominal aorta as detected by lateral lumbar radiography was found in this large cohort of dialysis patients from Northern Europe. The pattern of distribution was similar to previously reported findings in the general population in the Framingham heart study, with the most severe lesions detected at the L4 level decreasing towards L1. Importantly, a subset (19%) of dialysis patients had no evidence of calcification whereas the majority had extensive calcification involving the entire length of the abdominal aorta. Since AAC correlates with calcification at other sites (e.g. coronary arteries) and has been shown to have significant prognostic significance for cardiovascular events and mortality, this easy and inexpensive method may prove to be a useful alternative for CT-based techniques in epidemiological studies in patients with CKD. Furthermore, it may serve as a part of the cardiovascular risk assessment and as a guide to more sophisticated examinations as recently recommended by an international expert group [28]. The ongoing CORD study will provide valuable information about the relationships between AAC, arterial compliance, their evolution during dialysis or after transplantation and their prognostic significance.

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Appendix

Belgium:

Dr M. Dhaene, RHMS Badour; Dr A. Chachati, CHR Huy; Dr P. Cambier, CHR Citadelle Liege; Prof. JM. Krzesinski, CHU Liege; Dr E. Bertrand, CHR Seraing; Prof. M. Jadoul, UCL St. Luc Bruxelles; Dr M. Wauthier, St. Pierre Hospital Ottignies; Dr J. J. Lafontaine, Clinique du Sud Luxembourg Arlon; Dr I. Vandewiele, Heilig Hart Hospital Roeselare; Dr K. Claes, UZ Gasthuisberg Leuven; Dr J. De Meester, Onze Lieve Vrouweziekenhuis Aalst; Dr B. De Moor, Virga Jesse Hospital Hasselt; Dr F. Verbeke, Gent University Hospital; Dr J. C. Stolar, RHMS Tournai.

The Netherlands:

Dr J.A. Bijlsma, Dianet Dialysecentrum Amsterdam; Dr P.L. Rensma, Sint Elizabeth Ziekenhuis Tilburg; Dr H.G. Peltenburg, Groene Hart Ziekenhuis Gouda; Dr I. Keur, Academisch Medisch Centrum Amsterdam; Dr F.J. van Ittersum, VU Medisch Centrum Amsterdam; Dr C.J.A.M. Konings, Catharina Ziekenhuis Eindhoven; Dr L.A.M. Frenken, Atrium Medisch Centrum Heerlen; Dr H.W. van Hamersvelt, Universitair Medisch Centrum St. Radboud Nijmegen; Dr C.A. Verburgh, Kennemer Gasthuis, Haarlem; Dr Y.W.J. Sijkens, Leids Universitair Medisch Centrum Leiden; Dr W.A. Bax, Medisch Centrum Alkmaar; Dr W.D. Kloppenburg, Martini Ziekenhuis Groningen; Dr C.A.J.M. Gaillard, Meander Medisch Centrum Amersfoort.

Denmark:

Dr P. B. Jensen, Odense University Hospital; Dr J. Dam Jensen, Aarhus University Hospital; Dr J. Hagstrup Christensen, Aalborg Hospital/Aarhus University Hospital; Dr S. Ladefoged, Copenhagen University Hospital; Dr K. E. Otte, Fredericia & Kolding Hospitals.

Norway:

Dr K. Aasarød, Trondheim University Hospital; Dr H. Viko, Ullevål University Hospital; Dr L. Gøransson, Stavanger University Hospital; Dr E. Svarstad, Haukeland University Hospital.

Sweden:

Dr M. Haarhaus, Linköping University Hospital; Dr G. Welander, Karlstad Central Hospital; Dr G. Sterner, Malmö University Hospital; Prof. A. Alvestrand, Karolinska University Hospital; Dr B. Wikström, Uppsala University Hospital.

Finland:

Dr H. Saha, Tampere University Hospital; Dr E. Honkanen, Helsinki University Hospital; Dr K. Metsärinne, Turku University Hospital; Dr P. Karhapää, Kuopio University Hospital; Dr R. Ikäheimo, Oulu University Hospital.

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