High prevalence of middle cerebral artery calcification is associated with cardiovascular mortality in hemodialyzed patients: an overlooked part of arterial tree?

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High prevalence of middle cerebral artery calcification is associated with cardiovascular mortality in hemodialyzed patients. An overlooked part of arterial tree?

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Short title: Middle cerebral artery calcifications

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Abstract

Purpose: We have analyzed markers of accelerated atherosclerosis like large artery stiffness, ankle-brachial index, carotid and vertebral duplex ultrasonography and their possible associations with the incidence of intracranial calcifications, clinical course of hemodialyzed patients and cardiovascular mortality. **Methods:** A computed tomographic scan of the head was performed for any neurological indication on 100 hemodialyzed patients. Eleven intracranial arteries were analyzed for calcification score, while internal carotid arteries and vertebral arteries were excluded in cerebral artery calcification score. As a control group for assessing intracranial calcifications we have analyzed computed tomographic scans from diabetic patients who had an acute stroke. **Results:** Deceased patients had significantly higher values of augmentation index and pulse wave velocity, lower ankle-brachial index, and higher internal carotid arteries peak systolic value than survived patients. Deceased patients had significantly higher number of calcified middle cerebral arteries as well as significantly higher intracranial artery calcification score and cerebral artery calcification score. Hemodialyzed patients had significantly higher both intracranial and cerebral artery calcification scores than diabetic control group. Age and calcified middle cerebral arteries had increased HR of 1.08 and 1.36 for cardiovascular mortality. **Conclusion:** This study showed that large artery stiffness and not the presence of peripheral arterial disease or carotid artery stenosis have the prognostic role of middle cerebral arteries calcifications and cardiovascular mortality in hemodialyzed patients. The presence of middle cerebral arteries calcifications diagnosed by a non-invasive method should be considered a marker of middle-sized conduit arteries atherosclerosis, subclinical brain damage and future fatal cardiovaascular events.

Key Words: arterial stiffness; calcifications; cardiovascular; hemodialysis; intracranial arteries

Introduction

High cardiovascular (CV) risk in patients with end-stage renal disease (ESRD) is related to many traditional factors like age, hypertension, diabetes and non-traditional, dialysis-related factors like impaired calcium and phosphate balance [1]. In patients on hemodialysis (HD) the prevalence of coronary heart disease has been described to be 40% [2] while the incidence of stroke is 5-10 higher than in the general population [3]. Uremic toxins leads to development of accelerated atherosclerosis and calcification of coronary and peripheral arteries which increases CV mortality [4,5] even in very young HD patients without traditional CV risk factors [6]. Intracranial arterial calcification (IAC) has been associated with everycchronic kidney disease (CKD) stage and is worsening with progression to ESRD [7,8]. IAC is considered as an independent risk factor for stroke [9] and it is often determined in HD patients and general population by computed tomographic (CT) scan mostly in internal carotid arteries [10] or in vertebral and basilar arteries [11]. There are only few large studies on IAC and their impact on CV mortality in HD patients with opposing results [12,13] while the factors influencing calcifications are still not yet known. Early, ESRD-related, vascular aging is strongly associated with increased arterial stiffness. Decrease of arterial stiffness markers, pulse wave velocity (PWV) and augmentation index (AIx), is associated with reduction of CV mortality not only in ESRD patients but also in patients with different chronic kidney disease CKD stages [14-18]. Although increased arterial stiffness and peripheral arterial disease are independently associated to increased risk for stroke and myocardial infarction there are no data on association of arterial stiffness markers and ankle-brachial index (ABI) with IAC in HD patients. Therefore we have analyzed markers of accelerated atherosclerosis like large artery stiffness, ABI, carotid and vertebral duplex ultrasonography and their possible associations with the incidence of IAC, clinical course of HD patients and CV mortality.

Methods

Participants

In this retrospective, observational, longitudinal follow-up study 100 HD patients who had a CT scan of the head performed for any neurological indication (acute confusion in 47% cases, moto-neural symptoms in 31%, severe headache due to high blood pressure levels in 14% and a drop in conscious level in 8%) agreed to participate. Data on medical history and medication were collected from hospital documentation. Patients were selected if they have been on chronic HD for at least three months. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. Exclusion criteria were: acute stroke at the time of performing CT scan, atrial fibrillation or other chronic arrhythmias and significant hemodynamic instability during the dialysis. As a control group for assessing IAC and comparing it with HD group of patients we have analyzed CT scans from diabetic patients who had an acute stroke. These patients were age and sex matched with the group of hemodialyzed patients. Follow-up period lasted until the last enrolled patient reached the 48-months time point or till the time of death.

Image acquisition and data analysis

All CT examinations were done with a 16-slice MSCT (Brightspeed 16, General Electrics, Milwaukee, WI, USA). Images were analyzed on both bone and soft tissue windows by two experienced radiologist who were blinded for patients clinical data. Additional windowing of images during analysis was permitted. Calcium scoring was done using semiquantitative method where 0 point was given to arteries with no calcification and 1 point to arteries with any calcification. Eleven arteries; two vertebral, two internal carotid arteries, basilar artery, two middle cerebral arteries, two anterior cerebral arteries, two posterior cerebral arteries with maximum 11

points for a single patient were analyzed for intracranial artery calcification (IAC) score, while internal carotid arteries and vertebral arteries were excluded in cerebral artery calcification (CAC) score and 7 points was maximum score for a single patient. Good interobserver agreement was achieved (Cohen's a 0.74) and in cases of discrepancy, images were rescored by open discussion between two radiologists.

Hemodynamic measurements

Hemodynamic parameters and arterial stiffness measurement were performed on the mid-week dialysis day after a 2-day interdialytic interval. Due to the fact that arterial stiffness measurements are performed routinely every month in hemodialyzed patients the timing between CT examinations and measurements of arterial stiffness was synchronous. Ambulatory blood pressure monitoring (ABPM) was performed using SpaceLab 90207 (Washington, USA) on the non-fistula arm. It was started at the end of mid-week haemodialysis session and continued until the next day. The monitor was programmed to perform readings at 15-min intervals between 6 am and 10 pm (daytime), and at 30-min intervals between 10 pm and 6 am (night-time). Arterial stiffness was assessed by Tensiomed Arteriograph (Medexpert Ltd., Budapest, Hungary), a computerized and validated device using an oscillometric method which simultaneously measures PWV and AIx. PWV and AIx were determined as a mean of three measurements on the non-fistula arm. Ankle-brachial index (ABI) as a parameter of peripheral vascular disease was assessed by Nicolet VersaLab® SE Vascular Doppler System with Spectral Analysis (Golden, USA) with a cut-off value of 0.9. Spectral doppler sonography of internal carotid and vertebral arteries was performed.

Statistical methods

Statistical analysis was performed using SPSS version 23.0 (IBM Corp., USA). Normality of data distribution was tested using Kolmogorov-Smirnov test. Preliminary analyses were performed to ensure no violation of the assumptions of normality, linearity and homoscedasticity. Categorical data were expressed as numbers and frequencies. Correlations were obtained using Pearson's test

for normally distributed variables and Spearman rank correlation for non-normally distributed variables. Normally distributed variables were presented as means + standard deviations and Student's t test for independent samples was used for comparisons between two groups. Non-normally distributed data was presented as median and interquartile range and Mann-Whitney U-test was used in comparison between two groups. Analysis of variance (ANOVA) was used to detect significant differences among ≥ two groups. Categorical variables were compared using $\chi 2$- test. Survival analysis was done with Kaplan-Meier curves which were tested with log-rank test while hazard ratios were estimated with Cox proportional hazards regression. Multiple linear regression was used to explore the influence of different variables on survival and presence of MCA calcifications, while logistic regression was used for categorical dependent variables. A p value <0.05 (two-sided tests) was considered significant.

Results

Demographic and hemodynamic characteristics of hemodialyzed patients

Demographic, clinical and laboratory data of enrolled patients are demonstrated in Table 1. A total of 100 patients (68 men and 32 women) on chronic HD with a mean age of 76.3±7.2 years and mean dialysis vintage of 54.8±5.3 months were included. Approximately one third of study participants had diabetes while 94.0% had hypertension. Calcium channel antagonists and β-blockers were the most commonly prescribed antihypertensive drugs with mean of 3.93±0.2 drug per patient. Continuous ambulatory blood pressure, arterial stiffness, ABI and internal carotid and vertebral arteries PSV values are presented in Table 1.

Differences in demographic and hemodynamic characteristics between IAC score tertiles

We have divided patients in tertiles depending on different IAC score (Table 2). Patients in last two tertiles were significantly older than patients in first tertile with no differences in dialysis vintage and dialytic parameters. We have not found any significant differences between tertiles in continuous ambulatory blood pressure values and central systolic blood pressure values except higher MAP values during day and night in last two tertiles. Patients in last two tertiles had significantly higher values of AIx than patients in first tertile while patients in the last tertile had significantly higher values of PWV than in first two tertiles. Patients in last two tertiles had lower ABI than in first tertile.

Differences in demographic and hemodynamic characteristics of survived and deceased hemodialyzed patients

Patients were followed-up for a total of 48 months. The percentage of CV mortality in our group of HD patients was 34.0% (men 67.6%, women 32.4%). Seven patients have died from heart failure, 15 from stroke (8 from brain hemorrhage and 7 from brain infarction) and 12 from myocardial

infarction. Additional 2 patients had stroke (both had brain hemorrhage) and 3 had myocardial infarction but survived during the follow-up period. There were no differences in gender and smoking status between deceased and survived patients. Deceased patients were older when enrolled ($p<0.001$). However, no significant differences were observed in dialysis vintage and dialytic parameters. There were no differences in percentage of hypertensives (88.2% vs. 96.9%), diabetics (29.4% vs. 36.7%), number of hypertensive drugs per patient (3.99 vs. 3.91), number of patients on different antihypertensive drugs classes and duration of hypertension (all $p>0.05$) between two groups of patients. When patients were divided by sex and presence of diabetes, we have not found significant differences. We have not found any significant differences between deceased and survived patients in continuous ambulatory blood pressure values and central systolic blood pressure values except higher MAP values during day and night in survived patients. Deceased patients had significantly higher values of AIx and PWV, lower ABI, and higher internal carotid arteries PSV than survived patients.

Differences in IAC score of survived and deceased hemodialyzed patients

There was a significant difference in distribution of IAC between survived and deceased patients. Although we have not found differences between number of internal carotid, vertebral and basilar calcified arteries deceased patients had significantly higher number of calcified middle cerebral arteries (MCA) as well as significantly higher IAC score and CAC score. When we have compared HD patients and patients with diabetes and present stroke we have not found differences in age, sex, smoking status and percentage of hypertension. There were no differences in IAC score in these two groups of patients except higher number of calcified MCA in diabetic group of patients while HD patients had significantly higher IAC and CAC score (Table 3).

Association of demographic and hemodynamic characteristics with MCA calcification

Longer duration of hypertension, older age, higher central systolic blood pressure, AIx and PWV were associated with calcified MCA. On logistic regression older age, longer duration of hypertension and present smoking status had an OR of 0.99 [CI 0.98, 0.99], 5.2 [CI 1.6, 16.5] and 0.64 [CI 0.42, 0.98] for the presence of calcified MCA while the only hemodynamic predictors for the presence of calcified MCA were PWV and AIx with an OR of 0.63 [CI 0.43, 0.94] and 1.07 [CI 1.00, 1.14].

Association of cardiovascular mortality with IAC score

In univariate analysis older age, higher AIx and PWV, lower ABI, higher IAC score, higher CAC score and MCA calcifications and higher internal carotid arteries PSV were associated with shorter survival. Mean survival time was longer in patients without MCA calcifications (46.4 (95% CI 44.3, 48.6) vs. 31.2 (95% CI 26.9, 35.5) months, $p<0.001$; (Figure 1). When we have compared patients with other calcified cerebral arteries, namely posterior and anterior arteries, we have not found this difference in survival time as well as between sexes, patients with and without diabetes and smokers and non-smokers. In the linear regression model survival was negatively associated with age, as expected, while the strongest association was with calcified MCA. Importantly, marker of large artery stiffness PWV and its complementary marker AIx, marker of peripheral artery disease ABI and marker of internal carotid stenosis PSV have not been associated with survival in our group of patients. On multivariate Cox regression only age and calcified MCA had increased HR of 1.08 [CI 1.03, 1.13] and 1.36 [CI 1.30, 1.42] for CV mortality while in univariate Cox regression age, calcified MCA, ABI, IAC score and PSV ACIL had increased HR for CV mortality (Table 4).

Discussion

This prospective study was designed to examine the prognostic role of IAC and their associations with arterial stiffness markers, AIx and PWV, peripheral arterial disease and its marker ABI and internal carotid artery PSV for CV mortality in HD patients. The main finding of this study was significantly higher number of calcified MCA in the deceased group of patients. Changes between survived and deceased patients were mostly seen in less advanced age, lower AIx and PWV, higher ABI and lower internal carotid artery PSV in favor of survived patients. Survival was negatively associated with age while the strongest association was with calcified MCA. HR for CV mortality was significantly increased for patients with higher age and calcified MCA.

The prevalence of IAC in our HD population was even higher than in previously published data and is comparable with the prevalence of calcified coronary arteries in advanced stages of CKD [19]. We have found significantly higher prevalence of calcifications on each analyzed intracranial artery in our HD group than in general population [10] or in HD patients [11,13,22,23]. To additionally confirm our decision of selecting only MCA as a marker for increased CV mortality in our group of HD patients, and to exclude internal carotid, vertebral and basilar arteries from further analysis, we have compared IAC verified on CT-scan between HD patients and patients with diabetes and present stroke. We have found only higher number of calcified MCA in diabetic group of patients while HD patients had significantly higher IAC and CAC score. This is an additional proof that HD patients have even higher IAC score than patients with traditional, independent risk factor like diabetes. It is confirmed, based on our results, that calcified MCA is a very sensitive marker for future CV event while calcified internal carotid, vertebral and basilar arteries in HD patients are not. Power et al [12] reported high prevalence of IAC in HD patients which was not associated with ischemic stroke while Bugnicourt et al [7] reported opposing results. Our results on IAC prevalence especially MCA calcifications in HD patients are even higher than in these papers and are related with stroke and CV mortality.

CV mortality in our group of HD patients was associated with age and with the presence of MCA calcifications but interestingly it was not associated with dialysis-related, hemodynamic or arterial stiffness parameters. This is in according with studies which reported association of MCA calcifications with CV events and mortality in general population [24]. It is previously reported that MCA flow is reduced due to probably altered auto-regulation which is a consequence of hemodynamic changes during HD and results with the development of atherosclerosis and calcifications [25]. These are the possible causes why HD patients with MCA calcifications are susceptible for CV events and mortality. Although HD patients, as expected, had significantly higher values of arterial stiffness, lower ABI and higher internal carotid arteries PSV these parameters were not associated with survival. Prognostic values of large artery stiffness and its marker PWV for increased CV mortality in HD patients is well documented [17,18]. With aging and in ESRD patients with longer dialysis vintage the stiffness gradient is decreasing and pulsatile pressure is increasing in medium conduit arteries like carotid and renal arteries. As a conseqence starts remodeling and disturbance of auto-regulation which has very deleterious effects on highly perfused organs with low arteriolar resistance like brain and kidney [26]. Decreased stiffness gradient and consequently higher pressure transmission burdens peripheral arteries which associated with increased large artery stiffness determined with PWV are the most probable causes of accelerated atherosclerosis and development of calcifications of smaller, but still conduit, intracerebral arteries like MCA in our group of HD patients. Mean lumen diameter of MCA is of 2.7 mm [27] is similar to mean lumen diameter of right coronary artery of 2.8 mm and just 1.0 mm smaller than left circumflex and left anterior descending artery [28]. Therefore based on our results, where we found high percentage of myocardial infarction, we hypothesize that the presence of MCA calcifications could be similar to calcifications of coronary arteries. Furthermore, there is a possibility that calcifications of smaller conduit arteries like MCA conceal the answer on extremely high CV mortality in HD population. Although large artery stiffness and its marker PWV still

remains the gold standard in predicting future CV events and mortality especially in HD patients it is questionable are we measuring the most sensitive part of arterial tree. Although large artery stiffness had no association with survival its association with the presence of MCA calcifications is of utmost importance. These results expands the prognostic role of PWV in HD patients by showing that increased PWV is not only independently associated with shorter survival but also is a direct marker of already decreased stiffness gradient and loss of auto-regulation in highly perfused organs like brain.

This work has some limitations. First, Arteriograph records central systolic blood pressure, AIx and PWV by an oscillometric method. There is no present validation study regarding this device in patients on HD. Second, we have enrolled patients from only one dialytic unit while our sample size was probably too small. Third, unfortunatelly we did not perform a transcranial doppler by which could we assess the arterial stiffness of cerebral arteries. Therefore, by assessing presence of calcifications we could only hypothesize on its possible impact on stiffness which is a major limitation of this study. Fourth, due to aforementioned limitation we could only describe associations of MCA calcifications with increased CV mortality but we were unable to prove causality. Fifth, our group of patients underwent CT scanning due to a neurological indication. It was not a planned interval screening and the results may be influenced by indication bias. Sixth, our patients sample size is marginal for performing Cox survival analysis and the results of this study concerning MCA calcifications as a strong and independent predictor of CV mortality in HD patients should be taken with caution.

In conclusion, the present study is the first which analyzed the impact of IAC on CV mortality in HD patients. Survival and HR for CV mortality had the strongest association with age and presence of MCA calcifications. This study showed that large artery stiffness has the prognostic role of MCA calcifications and CV mortality in HD patients. The presence of ACM calcifications diagnosed by a non-invasive method should be considered a marker of middle-sized conduit arteries

atherosclerosis, subclinical brain damage and future fatal CV events. Future prospective studies with bigger sample size and detection of local cerebral arterial stiffness are needed for explaining the impact of ACM calcifications on CV outcome in HD patients.

Compliance with ethical standards:

Conflict of interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Table 1. Demographic, clinical, laboratory data, hemodynamic and arterial stiffness data of dialyzed patients

N=100	
Demographic, clinical and laboratory data	
Age (years)	76.3±7.2
Males (N/%)	68 (68.0)
BMI (kg/m^2)	24.6±4.0
Smoker (N/%)	36 (36.0)
Dialysis vintage (months)	54.8±5.3
Hypertension (Yes) (N/%)	94 (94.0)
Number of antihypertensives/person	3.93±0.2
Duration of hypertension (months)	90.0±8.3
Diabetes (Yes) (N/%)	34 (34.0)
Duration of dialysis (hours)	3.8±0.1
Ultrafiltration (mL)	2858.0±88.4
Kt/V	1.49±0.1
Residual diuresis (mL)	492.5±65.6
Weekly vitamin D load µg/week	0.88 (0.38-0.99)
Daily phosphate binder calcium load (g/day)	1.6 (0.4-2.5)
Weekly/weight erythropoietin load (IU/kg)	118 (86-140)
Hemoglobin (g/L)	103.7±1.3
Serum calcium (mmol/L)	2.2±0.1
Serum phosphate (mmol/L)	1.6±0.1
iPTH (pmol/l)	30.5±3.3
Serum glucose (mmol/L)	6.2±0.2
Serum cholesterol (mmol/L)	3.5±0.1
Triglycerides (mmol/L)	1.8±0.1
Serum uric acid (µmol/L)	339.9±5.3
Hemodynamic and arterial stiffness data of dialyzed patients	

24h SBP (mmHg)	142.4±1.7
24h DBP (mmHg)	81.1±1.3
24h MAP (mmHg)	97.2±1.9
24h PP (mmHg)	75.4±2.1
24h HR (mmHg)	64.1±1.4
Day SBP (mmHg)	144.2±1.8
Day DBP (mmHg)	82.8±1.3
Day MAP (mmHg)	98.9±1.9
Day PP (mmHg)	76.4±2.2
Day HR (mmHg)	65.1±1.5
Night SBP (mmHg)	137.6±2.0
NIght DBP (mmHg)	75.9±1.2
Night MAP (mmHg)	93.2±1.9
Night PP (mmHg)	72.9±2.1
Night HR (mmHg)	61.5±1.3
SBPL (mmHg)	148.3±3.4
AIx (%)	32.4±1.3
PWV (m/s)	10.0±0.2
PSV ACIL (cm/s)	90.7±5.8
PSV ACIR (cm/s)	82.9±4.3
PSV AVL (cm/s)	39.7±0.7
PSV AVR (cm/s)	39.9±0.8
ABI	0.95±0.01

BMI-body mass index; iPTH-intact parathyroid hormone; SBP-systolic blood pressure; PP-pulse pressure; DBP-diastolic blood pressure; MAP-mean arterial pressure; SBPL-systolic blood pressure load; HR-heart rate; AIx-augmentation index; PWV-pulse wave velocity; PSV ACIL-peak systolic flow velocity left internal carotid artery; PSV ACIR-peak systolic flow velocity right internal carotid artery; PSV AVL-peak systolic flow velocity left vertebral artery; PSV AVR-peak systolic flow velocity right vertebral artery; ABI-ankle-brachial index results are shown as mean +/- SD or median (interquartile range)

Table 2. Demographic, clinical, laboratory data, hemodynamic and arterial stiffness data between patients divided by IAC score

	IAC score 0-5 (N=22)	IAC score 6-8 (N=46)	IAC score 9-11 (N=32)	p
Demographic, clinical and laboratory data				
Age (years)	59±4.2	69±5.4	75±6.8	**<0.001**
Males (N/%)	14 (63.6)	31 (67.3)	23 (71.8)	0.93*
BMI (kg/m^2)	24.6±3.4	24.7±3.3	24.8±4.1	0.77
Smoker (N/%)	7 (31.8)	16 (35.5)	13 (40.6)	0.42*
Dialysis vintage (months)	49.2±9.1	55.2±5.7	59.1±6.2	0.23
Hypertension (Yes) (N/%)	19 (86.3)	44 (97.7)	31 (96.8)	0.19*
Number of antihypertensives/person	3.88±0.1	3.91±0.1	3.93±0.1	0.77
Duration of hypertension (months)	86.3±10.1	91.2±11.5	96.6±11.9	0.49
Diabetes (Yes) (N/%)	7 (31.8)	15 (33.3)	12 (37.5)	0.56*
Duration of dialysis (hours)	3.7±0.1	3.8±0.1	3.8±0.1	0.38
Ultrafiltration (mL)	2767.5±85.4	2981.1±87.2	3091.2±89.8	0.22
Kt/V	1.46±0.1	1.46±0.1	1.46±0.1	0.95
Residual diuresis (mL)	398.5±59.9	478.2±62.1	545.8±69.1	0.14
Weekly vitamin D load µg/week	0.88 (0.38-0.95)	0.90 (0.40-1.03)	0.89 (0.40-1.01)	0.89
Daily phosphate binder calcium load (g/day)	1.6 (0.4-2.6)	1.6 (0.4-2.5)	1.6 (0.4-2.5)	0.80
Weekly/weight erythropoietin load (IU/kg)	117 (88-139)	116 (85-138)	115 (83-138)	0.54
Hemoglobin (g/L)	103.9±2.0	102.4±1.7	105.9±2.4	0.41
Serum calcium (mmol/L)	2.2±0.1	2.2±0.1	2.2±0.1	0.82
Serum phosphate (mmol/L)	1.6±0.1	1.6±0.1	1.6±0.1	0.53
iPTH (pmol/l)	34.6±3.1	29.8±2.9	39.2±3.2	0.31
Serum glucose (mmol/L)	6.2±0.2	6.2±0.2	6.2±0.2	0.90
Serum cholesterol (mmol/L)	3.7±0.1	3.5±0.1	3.6±0.1	0.49

Triglycerides (mmol/L)	1.7±0.1	1.8±0.1	1.8±0.1	0.58
Serum uric acid (μmol/L)	342.5±5.5	340.4±5.5	341.4±5.5	0.90
Hemodynamic and arterial stiffness data				
24h SBP (mmHg)	137.2±1.4	144.5±1.8	141.1±1.7	0.23
24h DBP (mmHg)	78.2±1.2	80.3±1.3	82.9±1.5	0.26
24h MAP (mmHg)	91.4±1.7	99.5±2.1	102.1±2.2	**0.02**
24h PP (mmHg)	76.2±2.0	75.3±1.8	78.7±2.4	0.47
24h HR (mmHg)	64.3±1.4	64.0±1.4	64.0±1.4	0.95
Day SBP (mmHg)	143.2±1.7	147.2±1.8	144.3±1.8	0.21
Day DBP (mmHg)	82.5±1.5	81.7±1.4	84.2±1.5	0.18
Day MAP (mmHg)	93.3±1.6	101.8±2.5	104.5±2.6	**0.03**
Day PP (mmHg)	77.7±2.2	75.0±2.0	76.6±2.1	0.58
Day HR (mmHg)	65.2±1.5	65.1±1.5	65.1±1.5	0.95
Night SBP (mmHg)	132.1±1.8	139.2±2.1	138.9±2.0	0.15
NIght DBP (mmHg)	73.8±1.1	78.1±1.3	79.9±1.4	0.17
Night MAP (mmHg)	89.2±1.4	97.1±2.0	100.6±2.2	**0.02**
Night PP (mmHg)	75.2±2.2	75.1±2.1	79.7±2.7	0.51
Night HR (mmHg)	61.6±1.4	61.0±1.2	61.0±1.2	0.70
SBPL (mmHg)	149.2±3.9	151.5±4.1	155.7±4.5	0.06
AIx (%)	21.7±1.5	40.5±2.2	46.1±2.8	**<0.001**
PWV (m/s)	9.3±0.5	9.8±0.6	11.7±1.3	**<0.001**
PSV ACIL (cm/s)	117.3±6.9	116.7±6.3	118.2±6.1	0.78
PSV ACIR (cm/s)	73.7±3.4	77.2±3.2	82.5±3.9	0.68
PSV AVL (cm/s)	41.3±0.9	39.9±0.6	40.2±0.7	0.77
PSV AVR (cm/s)	42.0±0.9	35.1±0.7	37.9±0.8	0.55

ABI	1.22±0.01	0.87±0.01	0.79±0.01	**0.03**

IAC score-intracranial artery calcifications; BMI-body mass index; CV-cardiovascular; iPTH-intact parathyroid hormone; SBP-systolic blood pressure; PP-pulse pressure; DBP-diastolic blood pressure; MAP-mean arterial pressure; SBPL-systolic blood pressure load; HR-heart rate; AIx-augmentation index; PWV-pulse wave velocity; PSV ACIL-peak systolic flow velocity left internal carotid artery; PSV ACIR-peak systolic flow velocity right internal carotid artery; PSV AVL-peak systolic flow velocity left vertebral artery; PSV AVR-peak systolic flow velocity right vertebral artery; ABI-ankle-brachial indexresults are shown as mean +/- SD or median (interquartile range), categorical variables were compared using χ^2- test*

Table 3. Intracranial artery calcifications between hemodialyzed and diabetic patients

	Hemodialysis (N=100)	Diabetes (N=75)	p
Internal carotid artery (yes N)	98	74	0.74
Left	97	74	0.46
Right	98	74	0.74
Vertebral artery (yes N)	98	72	0.76
Left	88	69	0.39
Right	89	61	0.15
Basilar artery (yes N)	82	61	0.91
Posterior cerebral artery (yes N)	61	38	0.17
Left	37	22	0.29
Right	32	18	0.25
Anterior cerebral artery (yes N)	46	26	0.13
Left	24	16	0.68
Right	26	13	0.17
Middle cerebral artery (yes N)	54	54	**0.01**
Left	40	28	0.72
Right	35	42	**<0.01**
IAC score	7.3±0.01	6.3±0.01	**<0.001**
CAC score	2.1±0.01	1.8±0.01	**<0.01**

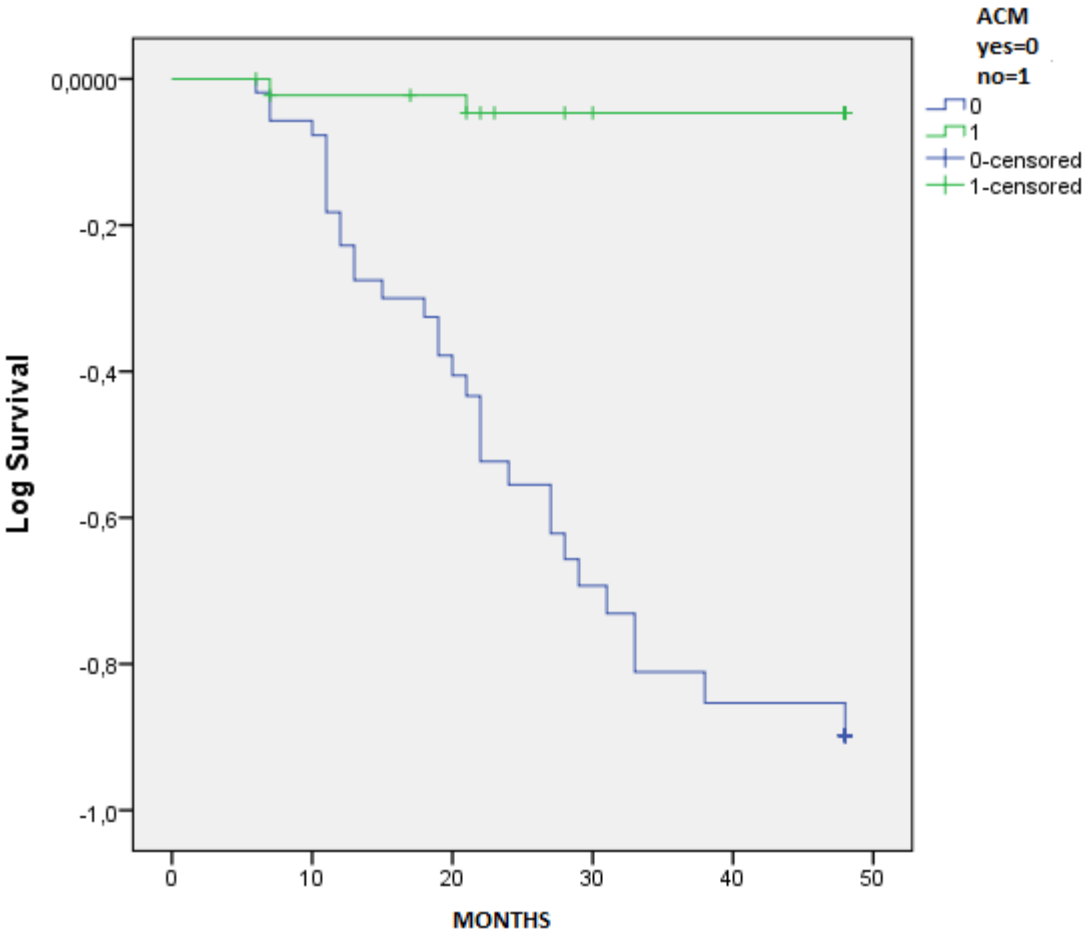
IAC score-intracranial artery calcifications; CAC score – cerebral artery calcifications; results are shown as mean +/- SD or median (interquartile range)

Table 4. Factors associated with survival

Cardiovascular mortality						
	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p	HR	95% CI	p
Age	1.32	0.72-1.52	**0.001**	1.08	0.88-1.24	**0.001**
Diabetes (yes)	0.98	0.62-1.44	0.58	0.87	0.54-1.28	0.63
IAC score	1.02	0.56-1.42	**0.04**	0.62	0.24-0.92	0.15
CAC score	1.56	1.22-1.94	0.11	1.46	1.16-1.74	0.31
AIx	1.19	0.88-1.47	0.12	1.03	0.72-1.27	0.28
PWV	1.12	0.84-1.41	0.72	1.02	0.77-1.34	0.86
PSV ACIL (cm/s)	1.26	0.83-1.48	**<0.01**	1.01	0.64-1.22	0.08
PSV ACIR (cm/s)	1.12	0.60-1.55	0.24	1.00	0.52-1.46	0.81
ABI	0.68	0.33-0.90	**<0.001**	0.35	0.12-0.58	0.13
MCA (yes)	1.82	1.32-2.14	**<0.001**	1.36	1.08-1.64	**<0.001**

AIx-augmentation index; PWV-pulse wave velocity; PSV ACIL-peak systolic flow velocity left internal carotid artery; PSV ACIR-peak systolic flow velocity right internal carotid artery; ABI-ankle-brachial index; IAC score-intracranial artery calcifications; CAC score – cerebral artery calcifications; MCA-calcified middle cerebral artery

Figure 1. Survival between patients with and without calcified cerebral medial arteries
ACM-middle cerebral arteries



Appendix

Table 1. Demographic, clinical, laboratory data, hemodynamic and arterial stiffness data between survived and deceased patients

	Deceased (N=34)	Survived (N=66)	p
Demographic, clinical and laboratory data			
Age (years)	74±6.9	61±4.7	**<0.001**
Males (N/%)	23 (67.6)	45 (68.1)	0.95*
BMI (kg/m^2)	24.9±3.5	24.5±4.3	0.57
Smoker (N/%)	14 (41.1)	22 (33.3)	0.67*
Dialysis vintage (months)	50.5±9.6	56.9±5.6	0.58
Hypertension (Yes) (N/%)	30 (88.2)	64 (96.9)	0.31*
Number of antihypertensives/person	3.99±0.1	3.91±0.1	0.89
Duration of hypertension (months)	96.6±14.8	86.6±10.1	0.58
Diabetes (Yes) (N/%)	10 (29.4)	24 (36.7)	0.49*

Duration of dialysis (hours)	3.7±0.1	3.8±0.1	0.30
Ultrafiltration (mL)	3020.6±89.9	2774.2±85.1	0.19
Kt/V	1.46±0.1	1.46±0.1	0.95
Residual diuresis (mL)	350.5±58.6	565.9±69.6	0.17
Weekly vitamin D load µg/week	0.86 (0.36-0.96)	0.90 (0.40-1.03)	0.87
Daily phosphate binder calcium load (g/day)	1.6 (0.4-2.6)	1.6 (0.4-2.5)	0.76
Weekly/weight erythropoietin load (IU/kg)	120 (89-142)	115 (83-138)	0.35
Hemoglobin (g/L)	105.5±2.1	102.7±1.6	0.32
Serum calcium (mmol/L)	2.2±0.1	2.2±0.1	0.80
Serum phosphate (mmol/L)	1.6±0.1	1.6±0.1	0.54
iPTH (pmol/l)	38.1±3.1	26.5±2.8	0.20
Serum glucose (mmol/L)	6.2±0.2	6.2±0.2	0.89
Serum cholesterol (mmol/L)	3.7±0.1	3.5±0.1	0.42
Triglycerides (mmol/L)	1.7±0.1	1.8±0.1	0.45
Serum uric acid (µmol/L)	338.9±5.2	340.4±5.5	0.88
Hemodynamic and arterial stiffness data			
24h SBP (mmHg)	138.9±1.5	144.1±1.7	0.15
24h DBP (mmHg)	78.8±1.2	82.3±1.4	0.20
24h MAP (mmHg)	91.6±1.8	100.1±2.2	**0.03**
24h PP (mmHg)	77.1±2.1	74.4±2.0	0.56
24h HR (mmHg)	64.3±1.4	64.0±1.4	0.93
Day SBP (mmHg)	140.9±1.6	145.8±1.8	0.18
Day DBP (mmHg)	80.4±1.3	84.0±1.4	0.19
Day MAP (mmHg)	93.3±1.6	101.8±2.5	**0.04**
Day PP (mmHg)	78.5±2.2	75.3±2.2	0.49

Day HR (mmHg)	65.2±1.5	65.1±1.5	0.96
Night SBP (mmHg)	133.6±1.9	139.7±2.0	0.12
NIght DBP (mmHg)	73.7±1.1	76.9±1.2	0.20
Night MAP (mmHg)	87.7±1.5	96.1±2.0	**0.04**
Night PP (mmHg)	73.5±2.1	72.6±2.0	0.84
Night HR (mmHg)	62.4±1.4	61.0±1.2	0.66
SBPL (mmHg)	157.3±3.9	143.7±3.1	0.07
AIx (%)	40.4±2.1	28.2±1.1	**<0.001**
PWV (m/s)	11.1±0.5	9.4±0.2	**<0.001**
PSV ACIL (cm/s)	117.1±6.9	77.1±4.1	**<0.01**
PSV ACIR (cm/s)	103.0±6.1	72.7±3.5	**<0.01**
PSV AVL (cm/s)	42.2±0.9	38.4±0.6	0.05
PSV AVR (cm/s)	42.8±0.9	38.5±0.7	0.05
ABI	0.85±0.01	1.01±0.01	**0.02**

BMI-body mass index; CV-cardiovascular; iPTH-intact parathyroid hormone; SBP-systolic blood pressure; PP-pulse pressure; DBP-diastolic blood pressure; MAP-mean arterial pressure; SBPL-systolic blood pressure load; HR-heart rate; AIx-augmentation index; PWV-pulse wave velocity; PSV ACIL-peak systolic flow velocity left internal carotid artery; PSV ACIR-peak systolic flow velocity right internal carotid artery; PSV AVL-peak systolic flow velocity left vertebral artery; PSV AVR-peak systolic flow velocity right vertebral artery; ABI-ankle-brachial indexresults are shown as mean +/- SD or median (interquartile range), categorical variables were compared using χ^2- test*

Table 2. Intracranial artery calcifications between survived and deceased patients

	Deceased (N=34)	Survived (N=66)	p
Internal carotid artery (yes N)	34	64	0.31
Left	34	63	0.21
Right	34	64	0.31
Vertebral artery (yes N)	34	64	0.31
Left	32	56	0.17
Right	32	57	0.24
Basilar artery (yes N)	30	52	0.24
Posterior cerebral artery (yes N)	23	38	0.53
Left	14	23	0.53
Right	13	19	0.34
Anterior cerebral artery (yes N)	15	31	0.79
Left	10	14	0.36
Right	9	17	0.94
Middle cerebral artery (yes N)	32	22	**<0.001**
Left	25	15	**<0.001**

Right	21	14	**<0.001**
IAC score	8.4±0.01	6.3±0.01	**<0.001**
CAC score	2.7±0.01	1.6±0.01	**<0.001**

IAC score-intracranial artery calcifications; CAC score – cerebral artery calcifications; results are shown as mean +/- SD or median (interquartile range)