

# Risk Stratification in Dialysis Patients: Coronary Artery Calcification Score Combined with High Sensitive C-Reactive Protein and Framingham Score for Cardiovascular Risk Prediction in Asymptomatic Subjects

Katarzyna Janda<sup>1</sup>, Marcin Krzanowski<sup>1</sup>, Paulina Dumnicka<sup>2</sup>, Maria Kapusta<sup>3</sup>, Piotr Klimeczek<sup>4</sup>, Eve Chowaniec<sup>1</sup>, Przemysław Miarka<sup>1</sup>, Mieczysław Pasowicz<sup>4</sup> and Władysław Sułowicz<sup>1</sup>

<sup>1</sup>Department of Nephrology, Jagiellonian University, Medical College, Cracow, Poland

<sup>2</sup>Department of Medical Diagnostics, Jagiellonian University, Medical College, Cracow, Poland

<sup>3</sup>Chair of Clinical Biochemistry, Jagiellonian University, Medical College, Cracow, Poland

<sup>4</sup>Center for Diagnosis, Prevention and Telemedicine, John Paul II Hospital, Cracow, Poland

## Abstract

**Introduction:** Vascular calcification independently predicts cardiovascular disease, the major cause of death in Chronic Kidney Disease (CKD) patients. Coronary Artery Calcium Score (CACS) is a marker for atherosclerotic plaque burden, vascular calcification and has been shown to be a predictor of incidence of myocardial infarction and death from Cardiovascular (CV) disease.

**Objectives:** The aim of the study was to evaluate factors influencing CV mortality in a group of Peritoneal Dialysis (PD) patients during a six year observation period.

**Patients and methods:** The study included 53 patients with no symptoms of CV disease (25 women, 28 men; mean age of 52 ± 12 years) treated with PD for a median period of 24 months. Baseline Framingham Risk Score (FRS) was assessed and CACS was measured using Multi-Row Spiral Computed Tomography (MSCT). Laboratory measurements included high sensitive C-reactive protein (hsCRP), osteoprotegerin (OPG), fibroblast growth factor 23 (FGF23), osteopontin (OPN), osteocalcin (OC), intact parathyroid hormone (iPTH), total calcium (Ca) and phosphates (Pi). The data concerning mortality was collected over a 6 year period.

**Results:** During the six year observation period, 24 (45%) patients died, including 19 due to CV causes. Median overall survival was 72 months (lower quartile, 17 months). CACS was a significant predictor of all-cause and CV mortality both in simple analysis (HR=1.03 per 100 Agatston units, p=0.02 and HR=1.05, p=0.003), as well as in a multiple model adjusted for age of patients, dialysis duration, weekly creatinine clearance, Ca x Pi, iPTH, OPG, hsCRP and FRS (HR=1.04, p=0.02 and HR=1.05, p=0.01). The value of 800 Agatston units significantly differentiated the group into those with higher and lower risk for CV death (p=0.04). Age and FGF23 concentration were independent predictors of CACS. Also, hsCRP and FRS significantly predicted all-cause and CV mortality in simple Cox regression (HR=1.04, p=0.002 and HR=1.04, p=0.003; HR=1.14, p=0.047 and HR=1.23, p=0.01) as well as in a multiple model (HR=1.05, p=0.002 and HR=1.05, p=0.01; HR=1.23, p=0.01 and HR=1.33, p=0.004). Adding CACS to FRS and hsCRP significantly improved the prediction of cardiovascular mortality (p=0.02).

**Conclusions:** Coronary calcium imaging is a non-invasive method of CV risk stratification that can accurately identify high-risk asymptomatic dialysis patients at the start of dialysis. The assessment of CACS together with inflammatory markers and conventional CV risk factors (FRS) may contribute to early diagnosis, prevention and reduction of deaths from CV disease in dialysis patients. Among the markers of bone disease, FGF-23 (a regulator of phosphorus metabolism) may be an early predictor of vascular calcification among dialysis patients.

**Keywords:** Calcium scoring; Cardiovascular mortality; Fibroblast growth factor 23; Framingham risk score; Osteoprotegerin; Peritoneal dialysis

## Introduction

Vascular calcification independently predicts cardiovascular (CV) disease, the major cause of death in Chronic Kidney Disease (CKD) patients. Coronary Artery Calcium Score (CACS) is a marker for atherosclerotic plaque burden and has been shown to predict the incidence of myocardial infarction and death from CV disease. CKD leads to increased calcium score secondary to accelerated progression of atherosclerosis, as well as changes in calcium homeostasis [1]. Vascular calcification is one of the major problems among CKD patients and contributes to the increased risk of CV events by a variety of mechanisms including increased arterial stiffness due to medial calcification or plaque vulnerability linked with atherosclerotic calcification [2]. Risk factors for atherosclerosis and coronary artery disease, including age, sex, dyslipidemia, diabetes, obesity, smoking habit, high blood pressure, family history of early onset CV disease,

inflammation and renal function are used to predict absolute risk for CV disease both in CKD patients and general population [3]. Emerging nontraditional risk factors for risk assessment include high sensitive C-reactive protein (hsCRP), fibrinogen, lipoprotein A, interleukin-6 (IL-6) and plasminogen activator inhibitor (PAI-1). The

**\*Corresponding author:** Katarzyna Janda, Department of Nephrology, Jagiellonian University, Medical College, 31-501 Krakow, Kopernika 15c Str., Poland, Tel: +48-124247800; Fax: +48-124247941; E-mail: [kasiajanda@op.pl](mailto:kasiajanda@op.pl)

Received February 18, 2014; Accepted March 22, 2014; Published March 29, 2014

**Citation:** Janda K, Krzanowski M, Dumnicka P, Kapusta M, Klimeczek P, et al. (2014) Risk Stratification in Dialysis Patients: Coronary Artery Calcification Score Combined with High Sensitive C-Reactive Protein and Framingham Score for Cardiovascular Risk Prediction in Asymptomatic Subjects. J Clin Exp Cardiol 5: 296. doi:10.4172/2155-9880.1000296

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role of inflammation in the pathogenesis of several complications of CKD is well documented [4]. In particular, several markers have been associated with CV morbidity and vascular calcification. They include: hsCRP, IL-6, markers of oxidative stress as well as bone turnover with some evidence of a cause-effect relationship [5-7].

Coronary calcification is a marker of atherosclerosis and evaluation of CACS by Multi-Row Spiral Computed Tomography (MSCT) has been recognized as useful strategy to initiate or intensify treatment of atherosclerosis. Besides the risk of CV disease, CACS has been demonstrated to be associated with the risk of complication during PCI, including arterial perforation, dissection and resultant stent thrombosis [2]. The non-invasive test such as CACS used for CV disease evaluation in CKD patients has the purpose of identifying Coronary Artery Disease (CAD) and evaluating the risk of CV events and death. CACS identifies calcified plaques using scattered X-rays; it is a marker of atherosclerosis that may improve current risk assessment when added to traditional risk factors [8,9]. The aim of the study concerning Peritoneal Dialysis (PD) patients was to evaluate the association of CACS with long-term (6 years) total and CV mortality in relation to traditional CV risk factors, inflammatory markers and vascular calcification parameters.

## Patients and Methods

The study group consisted of 53 asymptomatic patients (25 women, 28 men) with a mean age of  $52 \pm 12$  years, treated with PD for a median period of 24 months (range 4 to 100 months). Patients were included according to the following criteria: age above 18 years, continuous methods of PD (CADO, CCDO), stable clinical dialysis course for at least 2 months before inclusion into the study, negative history for cardiovascular diseases and neoplasms and no active viral infection (HIV, hepatitis type B or C). PD patients were qualified during routine hospital visits and on this same day CACS was performed, as well as collection of blood samples for biochemical tests. The concentrations of albumin, fibrinogen, total cholesterol, LDL-cholesterol, HDL-cholesterol, Triglycerides (TG), glucose, Osteoprotegerin (OPG), Fibroblast Growth Factor 23 (FGF23), Osteopontin (OPN), Osteocalcin (OC), intact Parathyroid Hormone (iPTH), total calcium (Ca) and Phosphates (Pi) and peripheral blood counts were measured. Peritoneal dialysis dose was assessed using Weekly Creatinine Clearance (WCrCl). An echocardiography was performed in each patient within 1 month from inclusion.

Routine biochemical tests were carried out on automatic biochemical analyzers: Hitachi 917 and Modular P (Roche Diagnostics, Mannheim, Germany). Hematology parameters were measured using Sysmex XE 2100 Hematological Analyzer (Sysmex Corp. Japan). Concentrations of hsCRP were measured using the immunonephelometric method on Nephelometer BN II (Siemens Healthcare Diagnostics, Germany). Bone disease markers were determined using ELISA immunoassay. We used the following sets of reagents: OPG (Biomedica, Wien), FGF 23 (Immutopics, USA) OC (METRA, Germany), OPN (Quantikine Human Osteopontin Elisa kit, R&D Systems). All measurements using ELISA micro-plates were performed on the Automatic Micro ELISA Reader ELX808 (BIO-TEK® Instruments, Inc., Vermont, USA). Body mass index (BMI) was calculated using the Quetelet formula. The assessment of calcifications in coronary arteries was performed by MSCT (Somatom Plus 4 Volume Zoom), using a calcium scoring program (Siemens Company, Nürnberg, Germany). The Agatston scale was employed to interpret the results, using CACS expressed in Hounsfield units (HU). Transthoracic echocardiography was

performed with the Simpson's biplane method, using Vivide 7 GE Healthcare machine.

Mean Arterial Pressure (MAP) was calculated from the formula:  $MAP = (\text{systolic blood pressure} + 2 \times \text{diastolic blood pressure})/3$ . Ten-year risk of coronary artery disease (CAD) was calculated by the Framingham Risk Score (FRS) in accordance with published guidelines [10].

Data on mortality were collected during the 6 year (72 months) period. All deaths occurred in the hospital and causes of death were determined using disease history documentation.

The study was approved by the Bioethics Committee of the Jagiellonian University and all patients signed an informed consent for their participation.

## Statistical analysis

Number of patients (percentage of the group) was reported for categorical variables and mean  $\pm$  standard deviation or median (lower-upper quartile) for continuous variables with normal or non-normal distributions, as appropriate. The Shapiro-Wilk test was used to assess normality. Simple correlations were studied using Spearman coefficient. Multiple linear regression models were constructed using predictors significant in simple analysis, after log-transformation of the right-skewed variables. Survival curves were computed using the Kaplan-Meier method and compared with log-rank test. Patients who underwent renal transplantation during the study period were considered as censored observations. Unadjusted and adjusted Hazard Ratios (HR) for all-cause and cardiovascular mortality were estimated using Cox proportional regression and were reported with 95% confidence intervals (95% CI). HR per one unit increase was reported unless otherwise stated. Multiple Cox models were adjusted for predefined set of confounders, listed in the Results section. Nested Cox models were compared with log-likelihood statistic. Results were considered significant at  $p \leq 0.05$ . Statistical 10 package (StatSoft, Inc., Tulsa, USA) was used for computations.

## Results

Clinical characteristics of the studied group and the concentrations of selected bone markers together with the reference ranges are presented in Table 1.

CACS correlated with age of patients, FRS as well as with OPG and FGF23 levels. Other bone markers (OC, OPN) did not correlate with CACS, nor did Ca or Pi levels, Ca x Pi product and iPTH concentration (Table 2). Also, CACS did not correlate with the parameters of dialysis adequacy. In a multiple model, including age, FRS, log(OPG) and log (FGF23) as the independent variables, age and log(FGF23) were shown to be independent predictors of log (CACS) ( $\beta=0.51$ ,  $p=0.001$  and  $\beta=0.45$ ,  $p=0.003$ , respectively). The model explained 41% of log (CACS) variance ( $p=0.001$  for the model).

During the six years follow-up, 16 patients (30%) experienced non-fatal CV events, including acute myocardial infarction in 13 patients and ischemic stroke in 3. Twenty four patients (45% of the group) died during the study period, including 19 patients (79%) due to CV causes (Table 1), i.e. sudden cardiac death (7 patients), myocardial infarction (5 patients), cerebral stroke (3 patients), chronic heart failure and peripheral vascular disease (2 patients each). Other causes of death in these patients included: encapsulating peritoneal sclerosis (EPS) (3 patients) and infections (2 patients). The studied group included 19 patients (36%) who were transferred to hemodialysis during the study

Peritoneal dialysis patients (N=53)	Average values*	Minimum-maximum	Reference values
Age, years	52 ± 12	19-75	-
Gender: men/women	28 (53%)/25 (47%)		-
Dialysis treatment duration, months	24 (15-51)	4-100	-
Observation period, months	60 (9-72)	1-72	-
All-cause mortality	24 (45%)	-	-
Cardiovascular mortality	19 (36%)	-	-
Active smoking	11 (21%)	-	-
Diabetes	12 (23%)	-	-
Hypertension	46 (87%)	-	-
Left ventricular ejection fraction, %	64 (60-66)	45-74	55-70
Left ventricular mass, g	244 ± 78	102-423	F: 67-162 M: 88-224
Left ventricular mass index, g/m <sup>2</sup>	138 ± 43	55-246	F: maximum to 110 M: maximum to 125
FRS, points	8 (5-10)	8-16	-
FRS, ten-year risk, %	10 (6-16)	1-37	-
BMI, kg/m <sup>2</sup>	25.2 ± 4.2	17.2-34.2	20-25
Systolic blood pressure, mmHg	149 ± 18	105-180	< 130
Diastolic blood pressure, mmHg	90 ± 12	60-115	< 80
Mean arterial pressure, mmHg	110 ± 11	87-133	75-100
Hemoglobin, g/dL	11.9 ± 1.7	7.7-15.3	12-17
Fibrinogen, g/L	6.0 ± 1.3	2.9-8.6	1.8-3.5
WBC, x10 <sup>3</sup> /μL	7.56 ± 2.44	2.77-12.36	4-10
hsCRP, mg/L	4.18 (1.29-11.40)	0.16-35.9	<3.17
Albumin, g/L	38 ± 5	20-47	35-50
Fasting glucose, mmol/L	4.7 (4.4-5.4)	3.4-15.4	3.3-5.6
Total cholesterol, mmol/L	5.54 ± 1.15	3.35-9.02	3.2-5.2
LDL-cholesterol, mmol/L	3.25 ± 0.93	1.45-6.35	0.2-3.4
HDL-cholesterol, mmol/L	1.41 ± 0.33	0.84-2.24	0.9-3.0
Triglycerides, mmol/L	1.95 ± 0.81	0.59-3.66	0.2-2.3
Ca, mmol/L	2.30 ± 0.22	1.59-2.67	2.1-2.4
Pi, mmol/L	1.78 ± 0.48	0.79-2.59	1.1-1.8
Ca x Pi, mmol <sup>2</sup> /L <sup>2</sup>	4.11 ± 1.27	1.81-5.99	< 4.4
iPTH, pg/mL	437 (198-836)	3-2474	12-72
FGF23, RU/mL	3013 (854-12015)	14.9-38798	no data
OPG, pmol/L	9.69 (8.44-13.18)	3.87-27.48	2.5-12.8**
OC, ng/mL	65.2 (38.9-70.3)	10.6-72.5	F: 3.7-10.0 M: 3.4-9.1**
OPN, ng/mL	1475 (1038-1870)	559-3092	49.2-175.0**
CACS, Agatston units	92 (0-761)	0-4555	0-100
WCrcI, L/week/1.73 m <sup>2</sup>	66.7 (58.8-85.7)	43.2-213.8	> 45.0

\* Number of patients (percent) is given for categorical variables; mean ± standard deviation or median (lower-upper quartile) for continuous variables with normal or non-normal distribution, respectively.

\*\* Reference ranges established by manufacturer.

**Table 1:** Characteristics of the study group at the beginning of the study and data on mortality during follow-up period.

period (3 of them died due to CV causes during the follow-up). Eleven patients (21%) underwent successful renal transplantation and were treated as censored observations in survival analysis. Median of overall

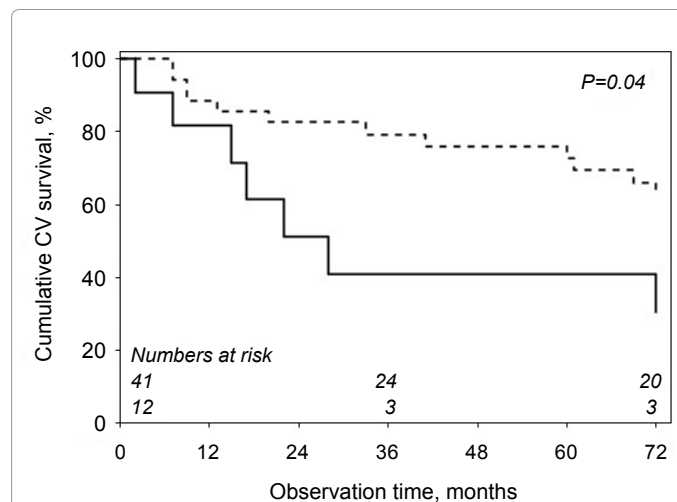
survival in the whole studied group was 72 months (lower quartile: 17 months).

Both all-cause and CV deaths were associated with higher CACS values. Especially, patients who died due to CV causes had much higher CACS comparing to the rest of the group: 778 (73-2476) versus 62 (0-515), p=0.03. CACS value of 800 Agatston units significantly differentiated the group into those with higher and lower risk for CV death (p=0.04). Figure 1 shows CV survival curves of patients with CACS over 800 Agatston units versus those with lower values.

CACS significantly correlated with total and CV mortality in PD patients in simple Cox regression. The hazard ratios per 100 Agatston units' increase in CACS were as following: HR=1.03 (1.01-1.07), p=0.02 for all-cause mortality and HR=1.05 (1.02-1.08), p=0.003 for CV mortality. Of the bone markers studied, only OPG significantly correlated with survival in simple analysis [HR=1.09 (1.004-1.19), p=0.04 for overall survival]. Also, CRP [HR=1.04 (1.01-1.07), p=0.003 and HR=1.04 (1.01-1.07), p=0.006] and FRS [points: HR=1.13 (1.001-1.30), p=0.049 and HR=1.21 (1.03-1.42), p=0.02; ten-year risk: HR=1.04 (1.001-1.08), p=0.04 and HR=1.05 (1.01-1.10), p=0.02] appeared to be significant predictors of all-cause and CV mortality in simple Cox regression. FRS was significantly higher in patients who died from CV

Independent variable	Spearman correlation coefficient	P
Age	0.41	0.002
Dialysis therapy duration	0.17	0.2
FRS, points	0.37	0.007
FRS, ten-year risk	0.28	0.04
Ca	0.22	0.1
Pi	0.08	0.6
Ca x Pi	0.12	0.4
hsCRP	0.27	0.053
iPTH	-0.03	0.8
FGF23	0.43	0.002
OPG	0.39	0.004
OC	-0.14	0.3
OPN	-0.02	0.9

**Table 2:** Simple correlations of selected variables with CACS.



**Figure 1:** Kaplan-Meier survival curves for cardiovascular mortality in patients with CACS above 800 Agatston units (solid line) versus patients with lower CACS values (dashed line). Total numbers at risk at baseline, after 3 and 6 years are shown at the bottom of the graph.

causes [FRS, points: 10 (8-11) versus 7 (3-9);  $p=0.001$ ; FRS, ten-year risk: 13 (10-25) versus 8 (4-13);  $p=0.002$ ].

In multiple models, CACS was shown to predict all-cause and CV mortality independently of age of patients, dialysis therapy duration, weekly creatinine clearance, Ca x Pi, iPTH, CRP and OPG concentrations as well as FRS (Table 3).

Finally, we compared three Cox models to predict CV mortality. The basic model included FRS (points) as the independent variable; the  $R^2$  for this model was 0.29. Adding hsCRP to the model increased the  $R^2$  value to 0.45 ( $p=0.02$  in log-likelihood test). Adding CACS to the model as the third independent variable resulted in further improvement in CV mortality prediction ( $R^2=0.60$ ;  $p=0.02$  in log-likelihood test).

## Discussion

Our study presents comprehensive comparison of biochemical and clinical data with calcification status (CACS) assessed by MSCT. In CKD patients, the prevalence of CAD and the incidence of major adverse CV events are very high. In our study both all cause and CV deaths were associated with higher CACS values. At the threshold of 800 Agatstone units, CACS identified a subgroup with a high risk of CV mortality. The importance of CACS in determining the risk of CV mortality is also confirmed by other researchers [9,11-14]. In the study of Budoff et al., CACS values over 400 and especially over 1000 Agatston units were associated with high risk for all-cause mortality (relative risk 5.78 and 9.36, respectively) [15]. The study group consisted of 25,253 asymptomatic individuals referred by their primary physician for Coronary Artery Calcium (CAC) scanning in order to assess CV risk. Similarly, the 1-year incidence of hard CV events (defined as myocardial infarction or coronary death) demonstrated by Wayhs et al. in patients with CACS above 1000 was 25% [16]. Lee et al. demonstrated high cardiac events rates in CKD patients with both coronary artery stenosis and high CACS at the start of dialysis [17]. In the other study, Roe et al. evaluated 112 asymptomatic renal transplant recipients with no prior history of coronary artery revascularization or myocardial infarction and assessed coronary calcifications early post-transplant and 18 months later [18]. Higher baseline CACS was associated with CV events and mortality, in particular patients with CACS below 100 Agatston units had better survival rates. A quarter (25.9%) of recipients had CAC progression. Coronary calcification progression also predicted CV events and mortality after adjustment for diabetes, age, dialysis vintage and presence of CAC at the time of transplantation. The St. Francis Heart Study included over 4,900 patients who were followed for 4.3 years [19]. CACS above 384 Agatston units was associated with a 30-fold increased risk for myocardial infarction or CV death, independently of FRS and hsCRP. Also, in the Prospective Army Coronary Calcium Project, in which 2000 younger participants were evaluated with electron beam tomography and followed prospectively for a mean period of 3 years, CACS was associated with a 12-fold increased risk for hard CV events even after controlling for the FRS [20].

Consistently, in our study, participants with high CACS had higher CV risk and the association was independent of the age of patients, dialysis duration, weekly creatinine clearance, CRP, Ca x Pi product, iPTH and OPG concentration as well as FRS. Moreover, the addition of CACS to FRS and hsCRP significantly improved CV risk assessment in our group of PD patients. In addition, our study revealed a significant association of baseline hsCRP and FRS with total and CV mortality in dialysis patients. Association of inflammation with mortality in dialysis patients is well known [21-23]. The mechanisms responsible for vascular calcification include inflammation as well as bone and mineral disturbances. We did not find a correlation between CACS and hsCRP (borderline significant), as well as markers of bone turnover, except for FGF23 and OPG. Only FGF23 was shown to be an independent predictor of CACS in a multiple model. Our results are in accordance with the study of Morena et al., demonstrating the relationship between FGF23, OPG and CAC in CKD patients [24]. The univariate analysis showed that high OPG was significantly associated with moderate CAC. Severe CAC was only associated with high phosphate fractional excretion and high FGF23. In another study, Khan et al. enrolled 99 CKD patients initiating hemodialysis in which MSCT was measured at baseline and in 67 study participants after 1 year of hemodialysis treatment. FGF23 was not associated with baseline CAC, but significantly correlated with CAC progression [25]. This association persisted after adjustment for hsCRP, 25-OH vitamin D levels and the use of phosphorus binders. In the study of Masai et al., serum FGF23 levels were associated with coronary calcification independently of classical risk factors, adipocytokines and inflammatory markers in patients without CKD and diabetes mellitus [26]. Among calcium/phosphate metabolism markers, as in our study, FGF23 showed significant correlation with Agatston score and in multivariate linear regression analysis, only age and FGF23 were independently associated with the Agatston score. Authors postulated that FGF23 may also have a direct effect on progression of CAC. On the other hand, several studies reported that FGF23 is independently associated with aortic calcification in HD patients [27,28]. Therefore, extraordinary accumulation of FGF23 in serum may enable inhibition of the calcification process at vessel walls. Osteoblastic transformation and production of several bone proteins were demonstrated in the intima and media of calcified blood vessels obtained from dialysis patients [29]. Another hypothesis is that FGF23, which is also a bone-associated protein, may be a marker of the volume of the tissue producing it (i.e. the proliferating vascular osteoblasts and osteocytes). This may provide an explanation for the repeatedly demonstrated reproducible correlation of 'single' FGF23 measurements with the severity of vascular calcification as well as atherosclerosis [30,31]. Similar results were obtained in our study.

In our study OPG was associated with CAC score only in simple analysis. However, of bone turnover markers, only the OPG significantly correlated with mortality in simple analysis. OPG is known to regulate bone mineral metabolism but it is also associated with inflammation, CV disease and mortality. In the study of Koo et al., OPG levels were positively correlated with inflammatory markers and

Independent variable	All-cause mortality		Cardiovascular mortality	
	HR (95% CI)	p	HR (95% CI)	P
CACS*, 100 Agatston units	1.04 (1.01-1.08)	0.02	1.05 (1.01-1.10)	0.01
hsCRP, mg/L	1.05 (1.02-1.09)	0.002	1.05 (1.01-1.09)	0.01
FRS, points	1.23 (1.05-1.44)	0.01	1.33 (1.10-1.61)	0.004

\*In case of CACS, HR per 100 Agatston units' increase is given.

**Table 3:** Significant predictors of all-cause and cardiovascular mortality in multiple Cox regression. The models additionally included age of patients, dialysis therapy duration, weekly creatinine clearance, Ca x Pi, iPTH and OPG as independent variables.

negatively correlated with nutritional status [32]. CV events occurred in 51 of the 176 patients on peritoneal dialysis recruited to the study during a 5 year observation period. Newly developed CV events were significantly more common in patients with higher OPG levels. Cox regression analysis revealed that higher OPG level was a significant risk factor for CV events even after adjustments for demographic and biochemical parameters. Increased serum concentration of OPG can serve as a surrogate marker of progression of atherosclerosis and severity of vascular calcification in CKD patients [33-36]. Our results are in accordance with the study of Kurnatowska et al. demonstrating the relationship between serum OPG and CAC, as well as common carotid artery intima-media (CCA-IMT) [37]. At baseline, 70% of the HD patients presented detectable CAC. The patients without calcification at baseline remained calcification free at 30 months and presented lower serum OPG and FGF23 than those with CAC. A 64.4% progression of CAC was observed in all patients with CAC at baseline. Additionally, both increased CAC as well as CCA-IMT correlated positively with baseline and follow-up serum OPG. The patients who died had significantly higher baseline CAC and serum OPG. Increased levels of OPG can represent a response to a mineral and bone disorders in CKD patients, it may constitute a compensatory mechanism or perform protective functions [38,39].

Summarizing, although limited by the low number of participants, our study provides further evidence that CACS examination may improve CV risk assessment in CKD patients in addition to hsCRP and traditional CV risk factors represented by FRS. Better identification of high-risk patients exerts the possibility of early prevention of these diseases and may lead to reduced mortality from CV disease in the population of dialysis patients. FGF23, a regulator of phosphorus metabolism, is strongly associated with CACS and may be a simple candidate biomarker of vascular calcification among dialysis patients.

## Conclusion

Coronary calcium imaging is a non-invasive method of CV risk stratification that can accurately identify high-risk asymptomatic dialysis patients. The challenge now is to incorporate these tests into clinical practice in a manner that will improve clinical outcomes. Combination assessment of CACS, inflammatory markers as well as conventional CV risk factors as summarized by FRS at the start of dialysis treatment may contribute to early diagnosis, prevention and reduction of deaths from CV disease in this population.

## Acknowledgments

The manuscript was not published elsewhere except a part of it was presented in abstract form as a poster during ERA-EDTA Congress. These Studies were funded by Grants K/ZDS/000597 and K/ZDS/001453.

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**Citation:** Janda K, Krzanowski M, Dumnicka P, Kapusta M, Klimeczek P, et al. (2014) Risk Stratification in Dialysis Patients: Coronary Artery Calcification Score Combined with High Sensitive C-Reactive Protein and Framingham Score for Cardiovascular Risk Prediction in Asymptomatic Subjects. *J Clin Exp Cardiol* 5: 296. doi:[10.4172/2155-9880.1000296](https://doi.org/10.4172/2155-9880.1000296)

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