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ARTERIAL STIFFNESS AND OTHER BIOMARKERS AS VASCULAR REMODELING AND CARDIOVASCULAR RISK PREDICTORS IN PATIENTS ON RENAL REPLACEMENT THERAPY

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ARTERIJŲ STANDUMO IR KITŲ BIOŽYMENŲ PROGNOSTINĖ REIKŠMĖ VERTINANT KRAUJAGYSLIŲ REMODELIACIJĄ IR KARDIOVASKULINĘ RIZIKĄ TARP PAKAITINE INKSTŲ TERAPIJA GYDOMŲ PACIENTŲ

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ABBREVIATIONS

AoAC – Aortic Arch Calcification
AUC – Area under the curve
BP – Blood pressure
BSA – Body surface area
cfPWV – Carotid–femoral pulse wave velocity
CI – Confidence interval
CKD – Chronic kidney disease
CMV – Cytomegalovirus
crPWV – Carotid–radial pulse wave velocity
CV – Cardiovascular
eGFR – Estimated glomerular filtration rate
ESC – European Society of Cardiology
ESH – European Society of Hypertension
ESRD – End–stage renal disease
HD – hemodialysis
HR – Hazzards ratio
PTH – Parathormone
MACE – Major adverse cardiovascular events
NICE – The National Institute for Health and Care Excellence
OR – Odds ratio
PAD – Peripheral artery disease
PD – Peritoneal dialysis
PWV – Pulse wave velocity
PWV ratio – Pulse wave velocity ratio
RAAS – Rennin–aldosteron–angiotensin system
ROC – Receiver operating characteristic
SD – Standard deviation
VSMCs – Vascular smooth muscle cells

CONTENTS

1. INTRODUCTION

Chronic kidney disease (CKD) is a health care burden affecting 10.6–13.4% of the global population (1) and resulting in health degeneration secondary to CKD-related chronic disability. Together with alcohol and other substance abuse, liver cirrhosis, asthma, Alzheimer's and other dementias, sickle cell disease and gout, CKD has been attributed to neglected "non-communicable diseases" (2). The total mortality rates of CKD from year 2005 to 2015 have increased by 31.7%. According to the ranking of causes of global years of life lost, CKD shifted from the 25th place to the 21st and further to the 17th in the years 1990, 2005 and 2015, respectively (3).

The health of the heart is closely related to kidney health. With a decrease in kidney function, the cardiovascular disease risk increases (4), and it is referred to as a chronic renocardiac syndrome or cardiorenal syndrome type 4 (5). CKD stage 5D (patients on maintenance dialysis) is associated with 50-fold higher cardiovascular disease mortality rates (6, 7). Kidney transplantation is the best renal replacement therapy for end stage renal disease (ESRD). However, even if the kidney transplantation is successful, the cardiovascular disease risk remains increased (8). High CV event rates are mainly influenced by the donor's gender, immunosuppressive drugs, inflammation, kidney graft function, homocystein levels, posttransplant anemia and nutritional status (9, 10). Therefore, a thorough cardiovascular evaluation is crucial for managing the morbidity and mortality rates in patients with ESRD.

The pathogenetic interactions between the cardiovascular system and kidneys are very complex (5). Traditional cardiovascular risk factors, such as age, race, sex, hypertension, diabetes mellitus, dyslipidemia, obesity and family history (11) cannot fully explain the high prevalence of cardiovascular disease in the CKD population. Thus, the exposure of CKD patients to non-traditional CKD-related factors, including inflammation, endothelial dysfunction, oxidative stress, volume overload, impaired bone-mineral metabolism, renning-aldosteron-angiotensin system (RAAS) disturbances, anemia, sympathetic nerve activity etc. (12–14) can better explain the high cardiovascular (CV) risk.

Moreover, vascular remodeling in kidney failure encompasses arterial lesions from atherosclerosis to arteriosclerosis and to calcification (13–16), and leads to arterial stiffening in the long term. The previously mentioned vascular changes are often described in literature as "accelerated arterial aging"(17, 18).

Arterial stiffening alters the arterial cushioning function (19), which inflicts elevation in systolic BP and pulse pressure. These changes in blood pressure (BP) further lead to left ventricular hypertrophy, impaired blood flow in coronary arteries and damage to microvasculature, especially in high blood flow organs such as the kidneys and the brain (18, 20). These alterations translate into an increased CV (18, 21, 22), cerebrovascular event risk (23) and peripheral artery disease (PAD) (24).

Since 1990, when London et al. (23) described increased aortic pulse wave velocity (PWV) as a parameter of arterial stiffness in the CKD stage 5D, comparing it to healthy controls, there has been a growing awareness within the scientific society of the importance of measuring PWV in CKD populations. Although the carotid-femoral PWV (cfPWV) has been considered to be the gold standard for arterial stiffness evaluation in the general population (26, 27), the data on CKD, end-stage renal disease (ESRD) and after-kidney transplants are very controversial. Some reports suggest that the peripheral muscular arterial stiffening is also important. One of the techniques for the measurement of peripheral PWV is carotid-radial PWV (crPWV). Recently, PWV ratio (PWV ratio = cfPWV/crPWV) was proposed as a new and important variable for measuring arterial stiffness (28). Based on previously mentioned debates, several hypotheses have been put forward as a part of this doctoral thesis:

1. Arterial stiffness and related biomarkers can predict the extent of vascular calcification and two-year cardiovascular risk in patients on renal replacement therapy;
2. Both hemodialysis and kidney transplantation are associated with changes of arterial stiffness in 2-year follow-ups.

Goal:

1. To evaluate the change of elastic and muscular arterial stiffness and other biomarkers and to assess their ability of predicting vascular calcification

and cardiovascular risk in patients on renal replacement theraphy in 2-year follow-ups.

Objectives:

1. To assess the predictive value of the elastic and muscular arterial stiffness and other biomarkers in the context of aortic arch calcification and two-year cardiovascular risk in renal replacement theraphy;
2. To evaluate the changes of elastic and muscular arterial stiffness and the biochemical markers affecting it within 2-years follow-up in hemodialysis patients;
3. To evaluate changes in elastic and muscular arterial stiffness and aortic arch calcification after a successful kidney transplantation.

Statements of the thesis:

1. Vascular remodeling and calcification are the underlying pathogenetic mechanisms of arterial stiffening in renal replacement therapy and are associated with increased cardiovascular risk;
2. Kidney transplantation is a treatment of choice in end-stage renal disease and provides the benefit of an improved large artery function.

2. NOVELTY

This is the first study that analyzes the relationship of a missmatch between elastic and muscular arterial stiffness (the so-called PWV ratio) and the extent of aortic arch calcification. In this study, several arterial stiffness measurement techniques are combined and compared. This research is one of the few that show the improvement of elastic arterial stiffness but no change in muscular arterial stiffness in patients after a successful kidney transplantation. Additionally, it provides an insight into the risk of cardiovascular events in the "healthier" patients on renal replacement therapy without any previous cardiovascular, cerebrovascular events or clinically evident peripheral artery diseases.

3. LITERATURE REVIEW

3.1. THE ARTERIAL STIFFNESS OF ELASTIC AND MUSCULAR ARTERIES

The structure of the arterial wall is very complex and can be altered under specific conditions, such as atherogenesis, direct injury or chronic hemodynamic changes (29). Arterial remodeling encompasses the activation, proliferation and migration of vascular smooth muscle cells (VSMCs), endothelium dysfunction and extracellular matrix changes (13, 22, 30). Furthermore, the stiffness of VSMCs per se contributes to vascular stiffening (30). Understanding different patterns of elastic and muscular arteries is crucial in further analyzing all available data about arterial stiffness in kidney failure (Figure 1).

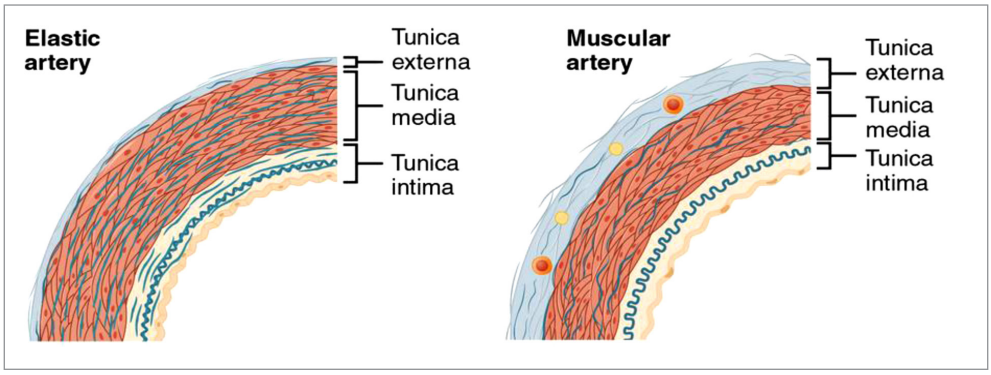

Fig. 1. The structure of elastic and muscular arteries.

The structure of the elastic and muscular arteries walls. The elastic artery has more elastic fibers in tunica intima and less smooth muscle cells in tunica media comparing to muscular artery. Reproduced with permission: © 1999–2017, Rice University. Except where otherwise noted, content created on this site is licensed under a Creative Commons Attribution 4.0 License. https://cnx.org/contents/WNsszrPZ@4/Structure-and-Function-of-Bloo#fig-ch21_01_03

Elastic arteries, or the so-called large arteries (the aorta and its branches), are rich in elastin; thus, it can stretch and compensate pressure waves from the left ventricle (31). Muscular arteries (or distributory arteries) contain more VSMCs in tunica media, have less elastic fibers in tunica intima and distribute blood to small resistant vessels (31, 32). Elastic and muscular arteries have dif-

ferent active and passive contraction characteristics (32) and probably different voltage-gated Ca^{2+}-channels alleviating the dialtezem effect on elastic arteries. Additionally, VSMCs in muscular arteries are longer and narrower and have better contractility abilities comparing to elastic arteries (33).

With advancing age, pronounced changes in the structure of the elastic arteries appear, encompassing collagen deposition in all layers of the arterial wall, a decreased amount of elastic fibers and an increased amount of VSMCs (34). As a result, large arteries become stiffer and more susceptible to blood volume fluctuations from the left ventricle. These transformations are less evident in muscular arteries. The discrepancy between aortic and peripheral stiffness, especially if aortic stiffness is higher than peripheral stiffness, might eventually result in the damage of microvasculature (35).

There are plenty of methods for assessing either local or regional arterial stiffness (36). The mostly acknowledged regional arterial stiffness measurement technique is the determination of pulse wave velocity by using applanation tonometry. This modality can give insights on the stiffness of both muscular and elastic arteries (Table 1). The cfPWV value represents the stiffness of elastic arteries; crPWV and femoral-ankle PWV – the stiffness of muscular arteries; carotid-distal PWV and the PWV ratio – stiffness of the elastic and muscular arteries. The brachial-ankle PWV measuring technique, widely used in East Asian countries (37), differs from applanation tonometry and encompasses cuffs connected to an oscillometric pressure sensor, wrapped around both arms and ankles. It strongly correlates with cfPWV (38) and represents both muscular and elastic arteries.

Table 1. Applanation tonometry derived pulse wave velocity measurements.

PWV type	Artery type	Distance measured
cfPWV (26)	Elastic	From carotid to femoral artery
crPWV (28)	Muscular	From carotid to radial artery
Carotid-distal PWV (39)	Elastic and muscular	From carotid to tibial or dorsal pedis artery
Femoral–ankle PWV (40)	Muscular	From femoral to tibial or dorsalis pedis artery
PWV ratio (41)	Elastic and muscular	From carotid to femoral artery and from carotid to radial artery

cfPWV – carotid-femoral pulse wave velocity, crPWV – carotid-radial pulse wave velocity, PWV –pulse wave velocity, PWV ratio – pulse wave velocity ratio

Vascular remodeling in CKD and ESRD affects both types of arteries (22). In the 2013 guidelines of the *European Society of Hypertension* (ESH)/*European Society of Cardiology* (ESC) (42) and in the 2015 statement of the *American Heart Association* (27), the cfPWV measurement was proposed as the "gold standard," yet it cannot fully represent the ESRD population. Besides, the importance of the use of cfPWV in different renal replacement therapies is often described as a controversial topic (43). The evaluation of both elastic and muscular arteries is very significant in the CKD population.

3.2. ARTERIAL STIFFNESS AND ESRD

The pathogenesis of arterial stiffness in CKD and ESRD depends on conventional and CKD-related risk factors (Table 2).

Table 2. The risk factors of arterial stiffness in CKD and ESRD.

Conventional	CKD-related
Age	Hypervolemia
Hypertension	Bone-mineral metabolism disorders
Diabetes mellitus	Vascular calcification
Dyslipidemia	RAAS overactivation
Obesity	Endothelial dysfunction
Smoking	Inflammation
	Oxydative stress
	Decrease in Klotho expression

CKD – chronic kidney disease, RAAS – rennin-angiotensin-aldosteron system

Conventional risk factors are similar as in the non-CKD population and are determined as ageing, hypertension, diabetes mellitus, dyslipidemia, obesity and smoking (14). However, they are insufficient in explaining the pathogenesis of arterial stiffness in ESRD. The growing evidence about non-conventional specific CKD-related factors (13, 14), such as volume overload, impaired bone-mineral metabolism, vascular calcification, the over-activation of RAAS, endothelial dysfunction, oxidative stress and inflammation and Klotho deficiency, give us

a more complex picture of arterial stiffening in this specific population. For example, volume overload, easily measured by using a bioelectrical impedance analysis, may determine a BP dependent (44) or independent (45) increase in arterial stiffness (46–50).

In 1987, Yuzawa Y et al. (51) described the clinical use of aortic PWV in hemodialysis population. Unfortunately, the article is available only in Japanese. Later researchers from France (52) published data on the relationship between dialysate calcium concentration and aortic and brachial PWV in 26 hemodialysis patients. They observed an increase in aortic and brachial PWV after higher calcium concentration (i.e., 1.75 mmol/l) dialysis, suggesting that hypercalcemia, secondary to the dialysis procedure, reduces arterial distensibility. In 1990, London et al. (25) compared aortic stiffness parameters between hemodialysis patients and controls and confirmed, for the first time, the higher PWV values in the dialysis population as compared to healthy controls. Besides, they also observed that in a cohort with vascular calcification, there was higher aortic PWV but not brachial PWV. Similarly, researchers from Japan observed an increased cfPWV in the dialysis population as compared to controls. Surprisingly, they also showed a higher cfPWV in the predialysis population comparing to dialysis subjects. These results should be considered very carefully, as the cfPWV measurements were performed 1–2 hours after dialysis. There is evidence that an hour after dialysis, the procedure there is significant in reducing PWV, and that it strongly correlates with the ultrafiltration rate (47, 53). On the contrary, immediately after a hemodialysis session, PWV values higher than predialysis ones might be observed (49, 53).

Regarding peritoneal dialysis, there are data (54) that patients on peritoneal dialysis have stiffer arteries comparing to hemodialysis patients as well as to healthy controls (55), although a study by Strozecki et al. has been used to prove otherwise (56). They observed similar cfPWV in both peritoneal and hemodialysis patients. Whether arterial stiffness is affected by dialysis modality remains unclear. The results of the multiple studies are inconsistent, claiming that peritoneal dialysis patients have equal (56–59), increased (54) or decreased (60, 61) PWV values comparing to hemodialysis patients.

There is no doubt that the effect of different dialysis techniques on the CV system is different, but in the long term, the result is the same. For example,

different oxidative stress characteristics in both dialysis modalities lead to the same result – an accelerated arterial stiffening (57).

3.3. VASCULAR REMODELING AND CALCIFICATION IN ESRD

The origin of vascular remodeling in CKD is multifactorial and often described as "accelerated arterial aging" (14) affecting mostly large arteries and less peripheral muscular arteries (62). The pathways linking CKD to accelerated arterial aging may involve genetic predisposition: polymorphism in a gene for type IV collagen (COL4A1) has been associated with a higher cfPWV value (63, 64) as well as with CKD (65). Similarly, metabolic alteration and elevated blood pressure can accelerate both arterial aging (66–68) and CKD (69).

Vascular calcification, a prevalent feature of CKD and ESRD, has been previously considered as a passive process, but more recent studies have proved otherwise (70, 71). It has been confirmed that under specific conditions, VSMCs are able to differentiate to osteoblasts, chondrocytes and adipocytes, leading to ectopic vascular calcification similar to physiologic bone ossification (70). These changes are regulated by the balance that promoters have between circulating inhibitors and the locally acting inhibitors (72) of vascular calcification. In addition to traditional calcification promoters, the uremic milieu per se incorporates a large amount of calcification-inducing factors (70). For example, calcium-phosphate hydroxyapatite crystal deposition, hyperphosphatemia (73, 74), elevated leptin levels, dialysis duration, chronic inflammation and an elevated parathyroid hormone level (70). There are also quite a number of identified inhibitors of vascular calcification: fetuin A, bone morphogenetic protein-7, parathyroid hormone-related peptide, high density lipoprotein cholesterol, magnesium, Matrix Gla protein, α-klotho, osteopontin, pyrophosphate and osteoprotegerin (70, 75, 76). Some of them have been studied in the context of vascular calcification treatment.

Vascular calcification in CKD affects both intimal and medial layers (15), promoting a premature aging of the arteries (Table 3).

Table 3. A comparison of intimal and medial calcification.

	Intimal calcification	Medial calcification
Localization	Atherosclerotic plaque calcification	Medial calcific arteriosclerosis
Calcification extent	Focal	Diffuse
Primary process of ossification	Endochondral bone formation	Intramembranous bone formation
Artery type and name	Elastic and coronary: Aorta and its arch branches, pulmonary artery, coronary arteries	Muscular: branches of external carotid artery, femoral, ulnar, radial etc.
Factors	Inflammatory macrophages, VSMCs, lipid	Elastin, VSMCs
Consequences	Stenosis, occlusion	Stiffening (no occlusion)

VSMCs – vascular smooth muscle cells.

Intimal calcification mainly affects large vessels (elastic) and coronary arteries and is associated with inflammation and atherosclerotic changes (70, 71, 77). It also mimics the characteristics of endochondral bone formation (78). On the contrary, medial sclerosis is more diffuse in calcium deposition within tunica media of the arterial wall and is independent from atherosclerosis. Medial calcification only very rarely results in the arterial lumen narrowing and involves mostly muscular arteries (femoral, radial, ulnar etc.) (70). In addition, it primarily evolves as an intramembranous ossification process (78). Without exception for CKD, medial sclerosis has been previously attributed to normal aging, diabetes mellitus (79) and obstructive sleep apnoe (80).

Some patients with CKD are resistant to vascular calcification, which suggests the role of genetic predisposition. For example, the ENPP1 K121Q genotype has been linked to a more pronounced coronary calcification and an increase of aortic stiffness in ESRD (81) and particularly in diabetic kidney disease (82).

Several studies provided direct clinical evidence that increased PWV is linked to coronary calcification in CKD (18, 83–85) as well as in healthy men (86, 87) or postmenopausal, overweight women (88). The aortic arch calcification score (89), the abdominal aortic arch calcification score (90) and the simple

vascular calcification score (91) have also been shown to be associated with arterial stiffness in CKD (83, 85, 92).

There is no evidence so far about the relationship between the PWV ratio and any localization of vascular calcification.

3.4. THE PULSE WAVE VELOCITY RATIO AND END-STAGE RENAL DISEASE

An arterial stiffness gradient has been suggested to be superior over cfPWV (28) for assessing arterial stiffness, especially in patients with ESRD. An arterial stiffness gradient can be simply calculated as the PWV ratio by dividing cfPWV by crPWV (41) or vice versa (93).

In 1983, Avolio et al. described that in healthy Chinese subjects, PWV in legs and arms is higher than in the aorta at the younger age (94). A later report on healthy subjects from the Framingham Heart Study also observed a strong, nonlinear increase in cfPWV with age, which was less obvious in the carotid-brachial PWV (95). Other research with 198 patients from the ambulatory cardiovascular department (96) detected that pulse wave reflection in elastic and muscular arteries have different characteristics. They observed unchanged arterial stiffness in muscular arteries with advancing age. The authors have suggested that due to a mismatch between the elastic and muscular arteries, there is a decrease in pulse wave reflection, resulting in more damage to microcirculation. It explains the pathogenic pathways for end-organ damage in hypertensive and diabetic patients.

An arterial stiffness gradient, calculated as the PWV ratio, was for the first time described by Fortier et al. in 2015 (41). They revealed the importance of the PWV ratio in predicting an all-cause mortality in 310 chronic dialysis patients within a median of 29 months follow-up. The superiority of the PWV ratio over cfPWV, central pulse pressure and pulse pressure amplification was also demonstrated. Similarly, another study with non-diabetic dialysis patients (93) confirmed the predictive value of cfPWV together with the PWV ratio and aortic geometry in an all-cause and CV mortality. Interestingly, by comparing healthy subjects with hemodialysis patients (48), higher PWV values in an

ESRD dependant on renal failure etiology and hydration status were found. Furthermore, in this study, the PWV ratio had blood pressure-independent characteristics. In 2017, Fortier et al. (97) published the results of another study revealing that the PWV ratio is a blood pressure-independent measure of vascular aging in CKD. To date, there are no more studies analyzing the PWV ratio in the background of ESRD.

3.5. THE PWV RATIO AND VASCULAR CALCIFICATION

To my knowledge, there are no studies so far analyzing the PWV ratio in the context of vascular calcification.

3.6. ARTERIAL STIFFNESS AND CARDIOVASCULAR RISK

There are plenty of evidence that increased cfPWV can predict the risk of cardiovascular disease beyond traditional risk factors and is associated with CV mortality in ESRD (Supplemental Table S1). All studies listed in Supplemental Table S1 prove that cfPWV is a valuable parameter in predicting CV mortality, but its value in assessing the CV event risk is questionable. For example, data from 47 European dialysis centers (98) showed that an increased cfPWV, especially combined with a high grade of abdominal aortic arch calcification, can predict death and non-fatal CV events. Another study (99) revealed the borderline predictive value of cfPWV for a new onset of CV events. Besides, it has been confirmed that aortic PWV can better predict all-cause and CV mortality than age or time on dialysis (100, 101). An interesting study from French researchers (102) presents a calculated difference between measured cfPWV and theoretically determined PWV, and it finds that the PWV index has superior predictive value in predicting mortality over other risk factors.

Regarding the Brachial-ankle PWV, representing elastic and muscular arteries, the results are inconsistent (Supplemental Table S2). Some studies (103) claim that the Brachial–ankle PWV is a good predictor of CV events,

while other studies (38, 104) show opposite results. This discrepancy could be explained by the inclusion or exclusion of fatal CV events. An ambulatory PWV measurement technique is very promising (105), revealing a strong association with CV events and CV mortality, and may simplify further risk stratification in ESRD patients.

There are at least two studies analyzing the PWV ratio in the context of CV risk (93, 106). One of them (106) included a healthy cohort (n=2114) from the Framingham Heart Study without any prevalent cardiovascular disease and could not confirm the superiority of the PWV ratio over cfPWV in this population. Others (107) have studied non-diabetic ESRD patients and showed that the PWV ratio is important in predicting CV mortality, but the main focus of the study was on arterial geometry and not the PWV ratio.

3.7. THE PROGRESSION OF ARTERIAL STIFFNESS

A working group of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) has drawn attention to the importance of the progression of arterial stiffness (108). Studies dedicated to this issue are listed in Supplemental material (Supplemental Table S3). Utescu et al. (109) studied 109 patients on chronic hemodialysis and observed that diabetes mellitus, age, the presence of cardiovascular disease and time on dialysis have no influence on aortic arterial stiffness progression within 1.2 years of follow-up. Similarly, the change of brachial arterial stiffness was not influenced by age. Another study (110) compared hemodialysis patients with controls and found out that cfPWV progression is more rapid in dialysis population in 3 years follow-up. Besides, opposite to the previously mentioned study, they showed that age plays an important role in determining the cfPWV change in this population. It should be noted, however, that all measurements of cfPWV in the later study were accomplished after the dialysis procedure to diminish the effect of hypervolemia.

At least two studies analyzed the impact of dialysate calcium on the progression of arterial stiffness in either hemodialysis (111) or peritoneal dialysis (112) patients. The hemodialysis population (111) showed no association

between crPWV progression and higher calcium dialysate when compared to the peritoneal dialysis population (112). Another study with peritoneal dialysis patients (113) identified mean arterial BP and time-averaged triglyceride concentration as triggers for the progression of arterial stiffness. An interesting work related to vitamin K deficiency and warfarin therapy (73) revealed that hemodialysis patients on warfarin suffer worser outcomes and greater arterial stiffening. Similar results were observed in hemodialysis patients on α-calcidol therapy ≥2 μg/week (114). Besides, it has been shown that an increase in cfPWV appears together with the progression of coronary artery calcification (115).

3.8. ARTERIAL STIFFNESS AND VASCULAR CALCIFICATION AFTER A KIDNEY TRANSPLANT

A kidney transplant is the most effective ESRD treatment method, which leads to an improved quality of life and an increased life expectancy in comparison with the patients on chronic dialysis (116, 117). However, even if the kidney graft function is sufficient, patients after a kidney transplant remain with an increased risk for CV events and CV mortality comparing to healthy populations (8). Given that CKD is characterized by accelerated vascular aging (118, 119), kidney recipients have an already different extent of vascular changes, which might progress after a kidney transplant. Kidney transplant-related factors responsible for further vascular remodeling are (120): immunosupressive drugs, inflammation, kidney graft damage with proteinuria, homocysteine, anemia and nutritional status (9, 10).

The implementation of an arterial stiffness measurment in renal transplant patients provides a functional evaluation of vascular stiffness and, indirectly, of athero- and arteriosclerosis.

Similarly to ESRD, several reports confirmed the relationship between vascular calcification and arterial stiffness after a kidney transplant (56, 121, 122) and the importance of both of these measures in CV risk evaluation (122). There are only few reports about the influence of arterials stiffness on other outcomes. Several studies by Bahous et al. (123, 124) checked whether the arterial stiffness of a living donor has any particular influence on the recipient's

graft function. The results were borderline, suggesting that high donor pulse wave velocity is related to the recipient's renal outcome. Dahle et al. confirmed not only the importance of aortic stiffness (125) but also that of the serum calfication propensity score (126) in predicting the overall mortality of kidney transplantant recipients.

The recent study by Davis B et al. (127) analyzed the CT scans of 131 kidney transplant recipients and found out that vascular calcification morphology presented in the iliac artery predicts the complexity of the surgical technique and is associated with delayed graft function. For now, there is only one study from Corea (128) that analyzed pretransplant AoAC on chest X-ray scans by using the AoAC scoring (89) system. The results showed the significant impact that AoAC has on the onset of cardiovascular disease and CV events but no relationship with kidney graft function. A review concerning coronary artery calcification evolution in kidney recipients (129) revealed a slowing down in the progression of calcification process but no significant regression. In concordance with these results, a previously mentioned study (128) confirmed an increase in AoAC within a 5 year follow-up.

Data regarding posttransplant changes in arterial stiffness as well as in vascular calcification are conflicting. There are evidence in no changes (130) or improved brachial-ankle PWV (131–135) within a period of 1 to 2 years after the kidney transplant; no changes (136, 137) or improvement (138, 139) or even progression (140) of cfPWV within a period of 3 months to more than 1 year after a successful kidney transplant.

4. METHODOLOGY

4.1. STUDY POPULATION

A single-center observational longitudinal study from December 2014 to July 2017 was conducted. One part of the study was focused on dialysis patients, the other – on patients before and after kidney transplantation.

4.1.1. CKD STAGE 5D POPULATION

Out of 200 Caucasian-origin chronic ambulatory dialysis patients from the Nephrology Center at Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania, 130 were initially selected for the study. The exclusion criteria were as follows: age <18 years, history of cerebrovascular events (ischemic stroke), cardiovascular events and diseases (myocardial infarction, clinically evident ischemic heart disease), clinically evident peripheral artery disease (ankle-brachial index below 0.9), less than 3 months on peritoneal dialysis or hemodialysis, acute illness (infection, bleeding), atrial fibrillation, complete heart block, patients with not all data available, an absence of written informed consent.

Out of the 130 initially eligible patients, only 101 patients with all requiring data were included in the final analysis (Figure 2). Of them, 20 had received kidney grafts almost immediately after performing measurements. The rest 81 remained on chronic dialysis.

In this study, we also aimed to evaluate the development of arterial stiffness within time. Therefore, we selected only hemodialysis patients (n=60) who had their repeated measurements taken after 6 months, and 46 patients – after 2 years. The exact causes of such a small final sample size are depicted in Figure 2.

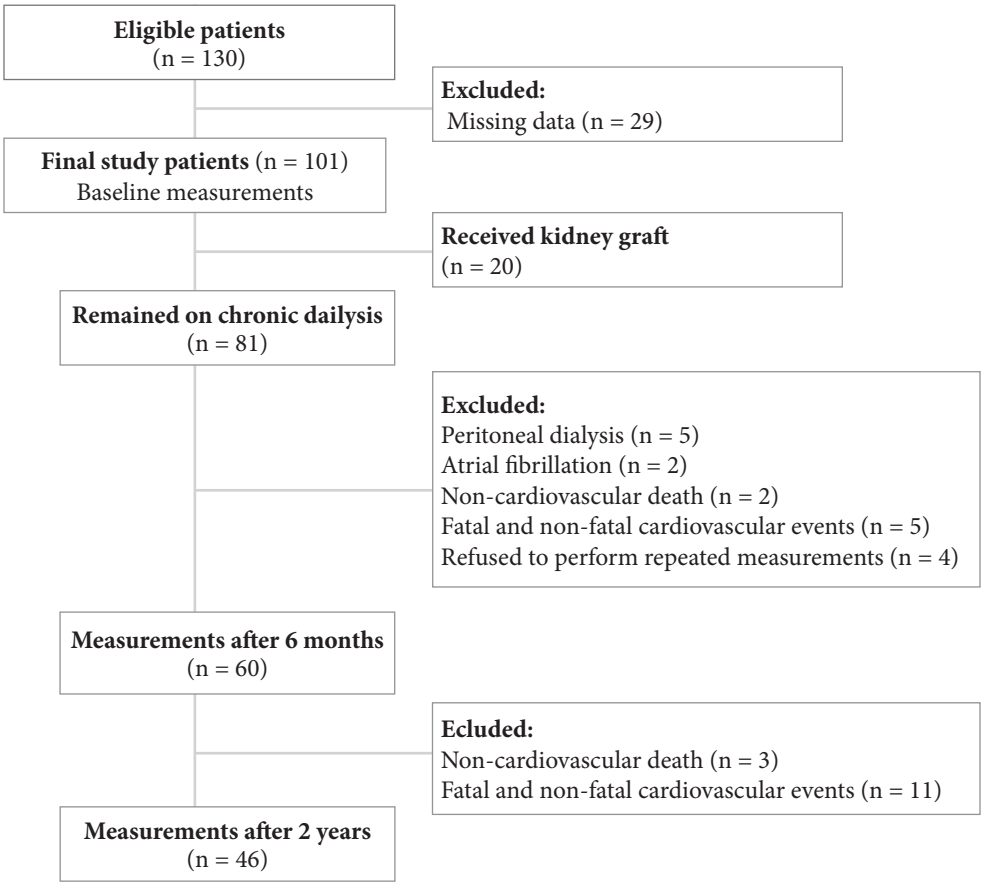

Fig. 2. The chart of the selection and outcome of patients on maintainance dialysis.

The chart represents the selection of study participants and clinical outcomes. Twenty patients received a deceased kidney transplant within a follow-up. Only 46 patients were eligible for repeated measurements after a follow-up of 2 years.

4.1.2. PATIENTS AFTER KIDNEY TRANSPLANTATION

From the 60 deceased donor kidney transplant recipients, only 37 of them (20 males, 17 females) were eligible for further investigation. Each participant had to be older than 18 years, without any previous history of cerebrovascular events (ischemic stroke), cardiovascular events and diseases (myocardial infarction, clinically evident ischemic heart disease), without any clinically evident peripheral artery disease (ankle-brachial index was >0.9), without acute illness (infection, bleeding), atrial fibrillation and complete heart block. All 37

kidney transplant recipients who had met the inclusion criteria were studied before the kidney transplant and after a median 12 and 24 months of follow-up (Figure 3).

Our study did not influence the choice of initial or maintenance immunosuppressive treatment. Induction therapy was considered when necessary according to immunological risk (low, medium or high) and included methylprednisolone, basiliximab or antithymocyte globulin. All patients received standard maintenance triple therapy, which consisted of a calcineurin inhibitor (cyclosporin A or tacrolimus), mycophenolate mofetil and methylprednisolone and had a stable kidney graft function in 6 months after the kidney transplant.

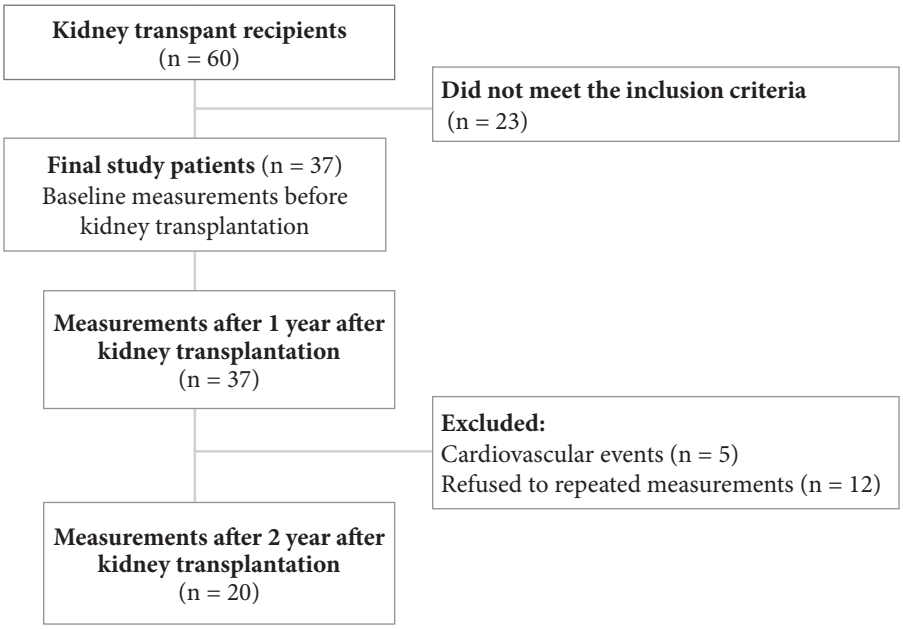

Fig. 3. The chart of the selection and outcome of kidney transplant recipients.

4.1.3. INFORMED CONSENT

This study was conducted with all the subjects' written informed consent and in accordance with the 1975 Helsinki declaration and its later amendments. It was also approved by the Vilnius Regional Biomedical Research Ethics Committee (Permission No. 1582000-14-750-268) (Supplement S4).

4.2. STUDY PROTOCOL

4.2.1. STUDY PROTOCOL FOR PATIENTS ON DIALYSIS

All 101 patients were interviewed, underwent blood tests, chest X-ray and PWV measurements at the beginning of the study. Sixty of them on chronic hemodialysis were eligible for repeated blood tests and PWV measurements after a follow-up of 6 months. Finally, 46 patients underwent blood tests, chest X-ray and PWV measurements after a 2-year observation period.

All blood samples were drawn between 7:00 and 12:00 in the morning. Hemodynamic parameters and chest X-rays were evaluated on the same day. Hemodialysis subjects were examined before a mid-week dialysis session. All of them received standard hemodialysis treatments 3-times a week and had stable dry weight.

Demographic data about age, gender, cause of CKD, smoking status, hypertension, time on dialysis, type of dialysis, medication and the presence of diabetes mellitus were collected from medical records as well as by directly interviewing patients.

The etiology of ESRD was categorized into diabetic nephropathy, nondiabetic glomerulopathy, vascular renal disease, tubulointerstitial nephropathy, hereditary nephropathy and an ESRD of unconfirmed etiology as proposed in a paper of Ghoul et al. (141). ESRD due diabetic nephropathy was considered as an ESRD caused by diabetic nephropathy without evidence of other systemic or renal disease. Vascular renal disease was defined as an ESRD caused by renal artery sclerosis or long-lasting hypertension. Nondiabetic nephropathy was, in all cases, previously proved by biopsy. Tubulointerstitial nephropathy encompassed an ESRD secondary to chronic pyelonephritis, renal stones, refluxnephropathy and other urogenital malformations, analgesic nephropathy and chronic urate nephropathy. Hereditary nephropathy was considered as an ESRD caused by polycystic kidney disease or by other genetically confirmed diseases.

4.2.2. STUDY PROTOCOL FOR KIDNEY TRANSPLANT PATIENTS

All patients (n=37) were interviewed, underwent blood tests and PWV measurements at the beginning of the study (before the kidney transplant) as well as in 1 year (n=37) and 2 years (n=20) after their kidney transplantations. Chest X-rays were performed before the renal transplantations and 2 years after the transplantations.

All blood samples were drawn at the time of admission to the hospital for the kidney transplant and later, after one and two years of follow-ups at 7:00 and 12:00 in the morning. Hemodynamic parameters and chest X-rays were evaluated on the same day.

Demographic and clinical data about age, gender, cause of kidney failure, hypertension, diabetes mellitus, time on dialysis, type of dialysis, donor and recipient cytomegalovirus (CMV) serostatus and the prescribed antihypertensive and maintenance immunosuppressive regimen were collected from medical records and interviews with patients.

4.3. ANTHROPOMETRIC DATA

All participants had their body height and weight measured with calibrated standardized measurement equipment. The body mass index (BMI) was calculated by using the following formula: BMI = weight/height^2 (kg/m^2); the body surface area (BSA) was calculated using the DuBois formula: BSA = (weight^{0,425} × height^{0,725}) × 0,007184 (m^2).

4.4. BLOOD SAMPLE ANALYSIS

The level of serum β2-microglobulin, serum cystatin C, serum creatinine, urea, calcium, ionized calcium, phosphate, albumin, total cholesterol, uric acid, C-reactive protein, ferritin levels were measured in a local laboratory using standard certified assays (the ARCHITECT ci8200 integrated system, US, Abbot). An intact parathormone (PTH) was performed using Advia Centaur XP (Abbott Laboratories, US). The white blood cell count, hemoglobin and platelet

count was measured with a standard, certified hematologic analyzer (SYSMEX XE-5000, Sysmex Corporation, Japan).

During further analysis, plasma calcium levels were adjusted to albumin levels using the formula for Corrected Calcium mmol/L = (0.02 * (Normal Albumin - Patients Albumin)) + Serum calcium (12,142). Calcium phosphate products were calculated in dialysis patients as calcium multiplied by phosphate as suggested by KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, Guideline 6 (12).

4.5. BRACHIAL BLOOD PRESSURE MEASUREMENT

Brachial BP was measured by a trained medical doctor according to the 2011 guidelines of the National Institute for Health and Care Excellence (NICE) (143); the procedure was conducted in a sitting position, after 10–15 min of resting, and it was repeated three times with 2 min intervals. The measurements were done on the dominant arm or the one without an arteriovenous fistula using a calibrated manual blood pressure monitor (Riester precisa® N Sphygmomanometer, Germany).

Pulse pressure was calculated using the following formula: Pulse pressure = systolic BP – diastolic BP (mmHg); mean arterial BP was determined as mean arterial BP = diastolic BP + 1/3 (systolic BP – diastolic BP) (mmHg).

4.6. ARTERIAL STIFFNESS AND CENTRAL HEMODYNAMIC ASSESSMENT

Applanation tonometry (SphygmoCor, AtCor Medical Pty Ltd, Sydney, Australia) was used for the evaluation of central hemodynamic and pulse wave velocity parameters. After resting for 10 min in the supine position, arterial pulse pressure forms on the carotid and femoral, and carotid and radial arteries (on site without an arteriovenous fistula, a central venous catheter or kidney transplant) were measured at least for 30s using a pen-like tonometer. The heart rate was monitored using simple three-lead electrocardiography. The distance between the pulse sites was measured using an anthropometric tape: from the

carotid artery pulse site to the sternal notch and from the sternal notch to the femoral artery pulse site; from the carotid artery pulse site to the sternal notch, from the sternal notch to the shoulder, and from the shoulder to the radial artery pulse site (Figure 4). All distances were measured in millimeters and multiplied by 0.8. Pulse wave velocity was calculated automatically using the equation for pulse wave velocity in software, PWV = (0.8x D)/Δt, where D is the distance between two pulse sites, Δt – the pulse transit time. All measurements, such as central systolic BP, end-systolic BP, central pulse pressure, heart rate, cfPWV and crPWV were made by a trained operator. Results with an operator index greater than 80% were considered eligible for further analysis. The PWV ratio was calculated based on a formula suggested by Fortier et al. in 2015 (41): PWV ratio = cfPWV/crPWV.

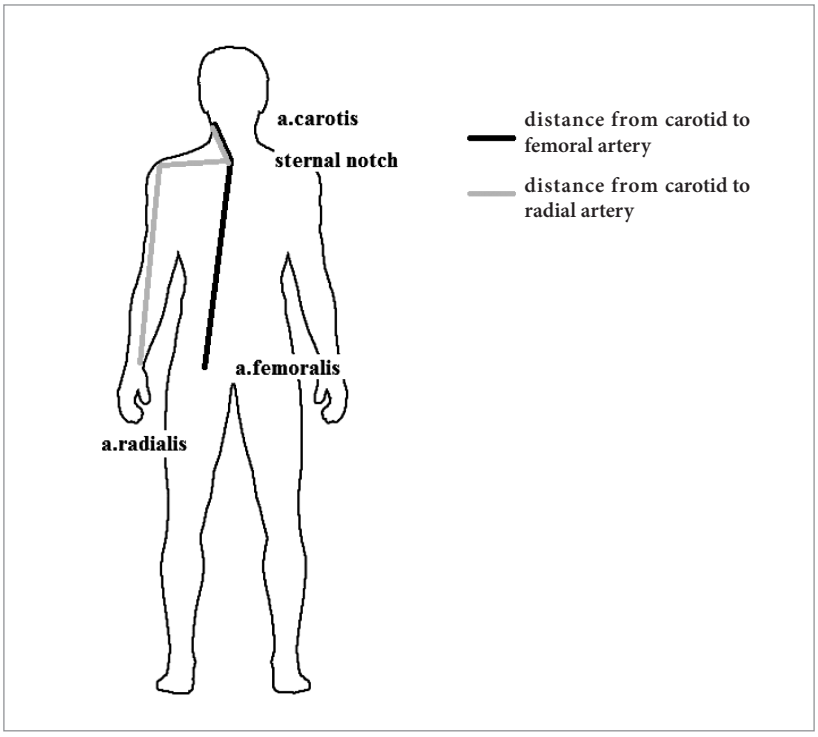

Fig. 4. The distance measurement technique.

4.7. AORTIC ARCH CALCIFICATION VISUALIZATION

In 2009, Ogawa et al. created a unique Aortic Arch Calcification (AoAC) scale that is simple to use by attaching it on a chest X-ray (Figure 5) (89). This scale divides the aortic arch into 16 equivalent sectors, and the calcified sectors are calculated. This calcification evaluation method has been proven to correspond to the AoAC volume evaluated by multi-detector computed tomography (CT) (15, 144). A written permission to use the AoAC scale was received from the authors.

Two experienced radiologists from the Center of Radiology and Nuclear Medicine at Vilnius University Hospital Santaros Klinikos, unknowing of patient medical records, evaluated postero-anterior chest X-ray scans and calculated the calcified sectors (from 0 to 16). The initial Cohen's kappa coefficient between two radiologists was 0.81. Therefore, mismatching chest X-ray scores were repeatedly reviewed, and a consensus was reached.

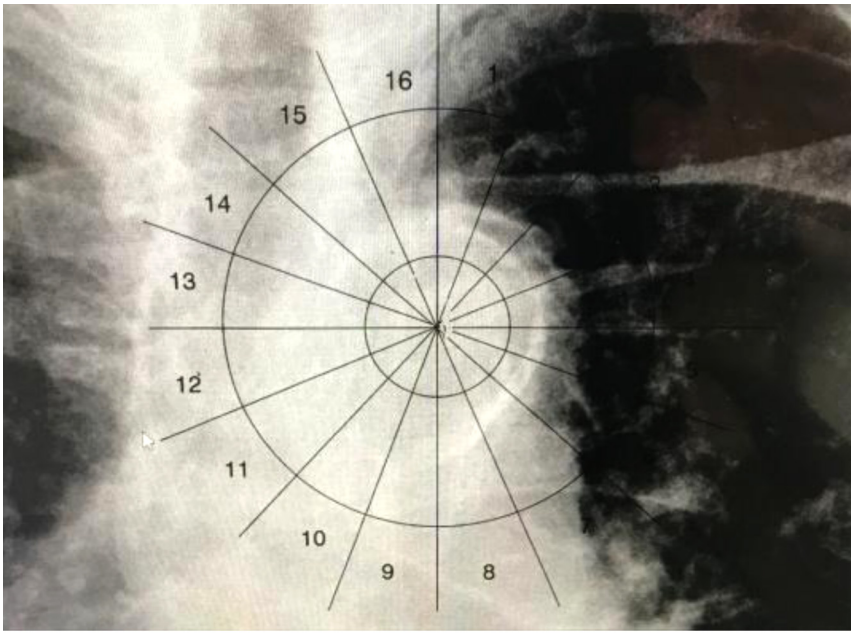

Fig. 5. Aortic arch calcification scale attached to a chest X-ray.
Chest X-ray of a 62-year-old female on chronic hemodialysis.

4.8. CARDIOVASCULAR EVENT-FREE SURVIVAL ANALYSIS IN THE DIALYSIS POPULATION

A prospective analysis of all death records (in hospital and at home) from December 2014 to July 2017 was performed. The death cause was determined by an experienced physician on the basis of all data available from medical records or death certificates. Only deaths secondary to cardiovascular pathology were selected. Major adverse cardiovascular events (MACE) and all CV events were analyzed separately. MACE included cardiovascular death, myocardial infarction and ischemic stroke. Additional to these pathologies were coronary revascularization, lower extremity amputation or revascularization and hospitalization secondary to unstable angina pectoris, and these were attributed to all CV events. Atrial fibrillation and congestive heart failure not requiring hospitalization were not determined as CV events.

4.9. STATISTICAL ANALYSIS

Continuous variables are expressed as mean ±standard deviations (SD), discrete variables as medians with min-max values in parentheses and categorical variables as percentages with numbers in parentheses. Where appropriate, the equality of two populations for normally distributed continuous data were tested by an F-test, and only after this, a Student's t-test was performed. Nonparametric tests, such as a two-sample Wilcoxon test, was performed on not normally distributed data. A Chi-square test was applied to categorical variables. To determine the correlation among normally distributed variables, a Pearson correlation test was performed and among not normally distributed variables, a Spearman's rank test was used. The strength of the relationship was determined as follows: strong ($-1.0 \leq r \leq -0.7$ or $0.7 \leq r \leq 1.0$), moderate ($-0.69 \leq r \leq -0.4$ or $0.4 \leq r < 0.69$), weak ($-0.39 \leq r \leq -0.2$ or $0.2 \leq r < 0.39$), none or very weak (($-0.19 \leq r \leq 0$ or $0 \leq r < 0.19$).

Before applying linear regression, the not normally distributed variables were log-transformed to achieve a Gaussian distribution. Univariable linear regression was used for finding the determinants of the PWV ratio and of the

evolution of arterial stiffnes. To avoid multicollinearity, only variables without any interdependent correlation were included in multivariable linear regression models.

Before logistic regression analysis, the dialysis population was divided in two groups in accordance with the AoAC score: AoAC (no) – no AoAC calcification, score 0; AoAC (yes) – evident AoAC, scores 1 and above. Univariable logistic regression was performed to find the variables that were associated with AoAC as binary response variables. If, in a univariable logistic regression, a selected variable had a significance level of at least <0.15, it was enrolled in multivariable logistic regression. After a stepwise model selection using the Akaike information criterion (AIC), the most significant factors were revealed. For a depiction and comparison of the significant variable/model, the receiver operating characteristic curves were drawn and areas under the ROC were compared using the method of DeLong et al. (145)

A cardiovascular event-free survival comparison was accomplished using a Kaplan-Meier analysis. A Cox proportional hazards regression was used to assess the influence of the PWV ratio and other selected variables on CV events. For predicting MACE, we have performed only a univariable Cox regression analysis, as the event rate was rather low.

To evaluate the progression of arterial stiffness parameters, we used the PWV value at the follow-up as a key independent variable and adjusted it for the PWV value at baseline.

P-values lower than 0.05 were considered as statistically significant. Statistical analysis was performed using R commander (Rcmdr) 3.3.2 version.

5. RESULTS FOR PATIENTS ON DIALYSIS

5.1. PATIENT CHARACTERISTICS

The baseline characteristics of the study population are listed in Table 4. The average age was 55.03 years (±15.65 years); 50.5% of the patients were males, 13.8% were current smokers or had a history of smoking, only 5.9% had no hypertension, 21.7% had diabetes mellitus and 87.1% were on chronic hemodialysis. The most prevalent cause of ESRD was nondiabetic glomerupathy (33.66%). Diabetic nephropathy was identified in 10.89% of the subjects.

Biochemical parameters were as expected in uremic patients on chronic dialysis. The average cfPWV was 11.35 m/s and it was higher than 10 m/s as recommended in the ESH/ESC guidelines (42). The median PWV ratio was 1.06, and the highest AoAC calcification score was 11 points.

Table 4. The baseline characteristics of the study population.

	Total (n=101)
Age (years)	55.03 ± 15.65
Male	50.5% (51)
Height (cm)	167.91 ± 10.67
Weight (kg)	72.69 ± 16.63
Body mass index (kg/m2)	25.87 ± 5.32
Body surface area (m^2)	1.81 ± 0.22
Smoking (yes)	13.8% (14)
Hypertension (yes)	94.1% (95)
Diabetes mellitus (yes)	21.7% (22)
Time on dialysis (days)	1035 (93-6556)
Kidney disease duration (years)	10.0 (1.0-40.5)
Etiology of ESRD	
Diabetic nephropathy	10.89% (11)
Nondiabetic glomerulopathy	33.66% (34)
Vascular renal disease	20.79% (21)
Tubulointerstitial nephropathy	23.76% (24)
Hereditary nephropathy	7.92% (8)
Unknown origin	2.97% (3)

Table 4 (continuation). The baseline characteristics of the study population.

	Total (n=101)
Dialysis modality	
Peritoneal	12.9% (13)
Hemodialysis	87.1% (88)
Blood tests	
White blood cells (10e9/L)	6.80 ± 2.07
Hemoglobin (g/l)	114.80 ± 14.19
Platelets (10e9/L)	218 (80 - 547)
Total protein (g/l)	67.71 ± 8.88
Albumin (g/l)	39.52 ± 4.06
Total cholesterol (mmol/l)	5.24 ± 1.43
Creatinine (μmol/l)	819 (364 - 1768)
Cystatin C (mg/l)	5.97 ± 1.29
Urea (mmol/l)	23.41 ± 7.07
C–reactive protein (mg/l)	4.87 (0.30 - 54.50)
β2-microglobulin (mg/l)	35.25 (14.25 - 100.36)
Ferritin (μg/l)	390 (44 - 1459)
Uric acid (μmol/l)	359.17 ± 87.81
PTH (pmol/l)	51.4 (0.5 - 201.4)
Calcium (mmol/l)	2.23 ± 0.18
Phosphate (mmol/l)	1.88 ± 0.57
Corrected to albumin calcium (mmol/l)	2.24 ± 0.17
Ca x P products ($mmol^2/l^2$)	4.19 ± 1.25
Hemodynamic and cardiovascular parameters	
Systolic BP (mmHg)	146.26 ± 18.76
Diastolic BP (mmHg)	99.90 ± 12.84
Pulse pressure (mmHg)	59.76 ± 17.43
Mean arterial BP (mmHg)	105.80 ± 12.61
Heart rate (beats/min)	72.21 ± 11.00
Central systolic BP (mmHg)	124.98 ± 15.67
cfPWV (m/s)	11.35 ± 3.54
crPWV (m/s)	10.21 ± 1.79
PWV ratio	1.06 (0.59 - 3.40)
AoAC score (0-16)	2 (0 - 11)

ESRD-end-stage renal disease, PTH-parathormone, Ca x P products-calcium phosphate products, BP- blood pressure, cfPWV-carotid-femoral pulse wave velocity, crPWV-carotid-radial pulse wave velocity, PWV ratio-pulse wave velocity ratio, AoAC-aortic arch calcification.

Significant correlations between age and cfPWV (r=0.525, p<0.001), the PWV ratio (r=0.556, p<0.001) and the AoAC score (r=0.597, p<0.001) were observed. No significant correlation was found between age and crPWV (r=-0.141, p=0.181) (Figure 6).

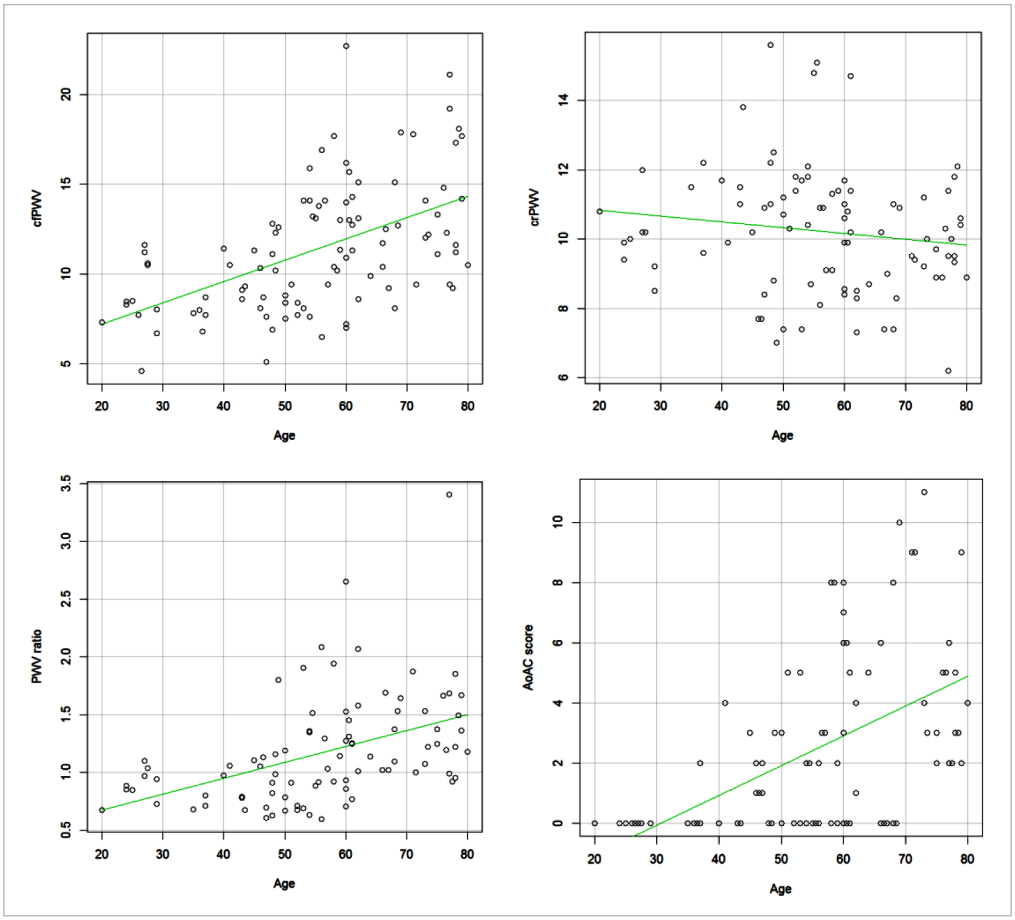

Fig. 6. The correlation between age and different vascular remodeling representing variables.

cfPWV – carotid-femoral pulse wave velocity, crPWV – carotid-radial pulse wave velocity, PWV ratio – pulse wave velocity ratio, AoAC – aortic arch calcification.

5.2. MEDICATION

In our study population, there was only one case of statin use and no cases of warfarin use. Four patients with hypertension admitted to nonadherence to prescribed medications. Other patients with hypertension received at least 1 blood pressure lowering medication: 52.47% (53) ACE-inhibitors or ARB, 60.39% (61) calcium channel blockers, 64.35% (65) vasodilating or non-vasodilating beta-blockers, 27.72% (28) alfa-blockers, 41.58% (42) centrally acting antihypertensive medication and 15.84% (16) diuretics.

5.3. SEX-BASED PATIENT CHARACTERISTICS

A comparison of genders (Supplemental Table S5) yielded the following results: almost all smokers were men, there was a significant difference in anthropometric parameters (height, weight, BSA), the total cholesterol level (higher in females), creatinine concentration (higher in males), the β2M level (higher in males), the corrected to albumin calcium level (higher in females) and pulse pressure (higher in females).

5.4. DETERMINANTS OF THE PWV RATIO

To achieve a normal distribution of β2-microglobulin, ferritin, C-reactive protein and the AoAC score points, these variables were log10 transformed and then included in a univariable and mulativariable linear regression. The PWV ratio significantly positively correlated with age, the presence of diabetes mellitus, time on chronic dialysis, inflammatory markers (β2-microglobulin, ferritin, C-reactive protein) and with the AoAC score; it significantly negatively correlated with total cholesterol levels (Table 5). The association with PTH in a univariable analysis was not significant (p=0.095), but it became significant after an adjustment for confounding variables (age, diabetes mellitus, AoAC score).

Variables with significance level below 0.15 were included in a stepwise multivariable linear regression. The most accurate Model 1 for PWV description included age, diabetes mellitus, time on dialysis and AoAC score (R^2=0.459, p<0.001).

Table 5. The clinical, biochemical and vascular determinants of the PWV ratio: univariable and multivariable linear regression.

Univariable linear regression	Std Coeficient	P-value	R^2
Age (years)	0.005	<0.001	0.248
Diabetes mellitus (yes)	0.115	0.004	0.086
Time on dialysis†(days)	0.140	<0.001	0.193
β2-microglobulin†(mg/l)	0.240	0.005	0.103
Cystatin C (mg/l)	0.044	<0.001	0.173
Ferritin†(μg/l)	0.129	0.011	0.082
C-reactive protein†(mg/l)	0.116	<0.001	0.147
PTH (pmol/l)	0.059	0.095	0.030
Total cholesterol (mmol/l)	-0.032	0.002	0.097
AoAC score†	0.225	<0.001	0.292
Multivariable linear regression			
Model 1: p <0.001			
Age (years)	0.002	0.019	0.459
Diabetes mellitus (yes)	0.093	0.004	
Dialysis duration†(days)	0.080	0.004	
AoAC score†	0.123	0.006	
Model 2: p <0.001			
Age (years)	0.002	0.009	0.439
Diabetes mellitus (yes)	0.097	0.003	
PTH† (pmol/l)	0.064	0.026	
AoAC score†	0.150	<0.001	
Model 3: p <0.001			
Age (years)	0.002	0.023	0.431
Diabetes mellitus (yes)	0.076	0.023	
Total cholesterol† (mmol/l)	-0.235	0.034	
AoAC score†	0.154	<0.001	

Univariable and multivariable linear regression.
PTH – parathormone, AoAC aortic arch calcification.
†log10 transformed values.

We also compared cfPWV, crPWV and the PWV ratio based on the etiology of ESRD (Figure 7). There was no significant difference in crPWV in different ESRD etiologies. Diabetic nephropathy was related to higher cfPWV values comparing to unknown-origin ESRD (p=0.038) and nonsignificantly to vascular renal disease (p=0.092). Diabetic nephropathy was also associated with a

higher PWV ratio when compared to vascular renal disease (p=0.039), hereditary nephropathy (p=0.0134) and nonsignificantly to nondiabetic glomerulopathy (p=0.0819).

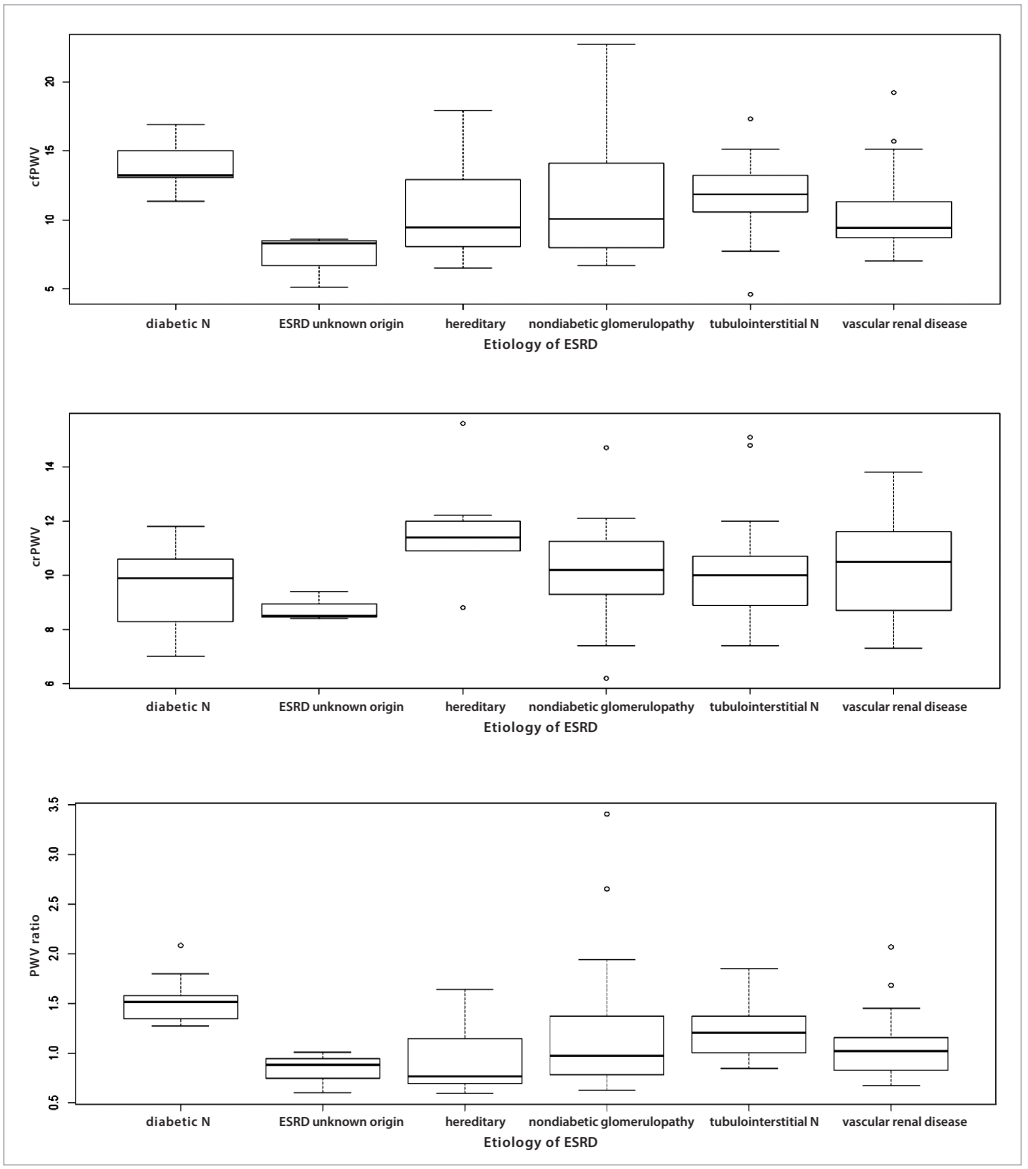

Fig. 7. A comparison of arterial stiffness representing the variables in accordance with ESRD etiology.

N – Nephropathy, ESRD – end-stage renal disease, hereditary – hereditary nephropathy, cfPWV – carotid-femoral pulse wave velocity, crPWV – carotid-radial pulse wave velocity, PWV ratio – pulse wave velocity ratio.

5.5. PWV RATIO AS A RISK FACTOR FOR AORTIC ARCH CALCIFICATION

Before further analysis of factors associated with AoAC, all study participants were divided in two groups: AoAC (no) – no evident calcification, AoAC score 0; AoAC (yes) – evident calcification, AoAC score ≥1. 43. Of all participants, 56% (n=44) had no calcification; the rest of the study patients were considered as with aortic arch calcification. Both group patient characteristics are available in Supplemental material (Supplemental Table S6).

Patients with aortic arch calcification were older, had shorter body height, a higher body mass index and a longer history of chronic dialysis. They also had higher levels of inflammatory markers such as C-reactive protein, β2-microglobulin, ferritin. Their diastolic BP, mean arterial BP, central systolic BP, end-systolic BP and crPWV were lower, but their cfPWV was higher; therefore, the calculated PWV ratio was also higher (Figure 8). No association between antihypertensive treatment and vascular calcification was found. Significant correlation in both sexes between PWV ratio and AoAC score was confirmed. (Figure 9).

A univariable and multivariable logistic regression (Supplemental Table S7) uncovered factors associated with the presence of AoAC in study population. Older age, higher body mass index, longer time on dialysis, higher C-reactive protein and ferritin levels, a higher cfPWV and PWV ratio were significantly related to an increased risk of AoAC. On the other hand, higher body height, higher crPWV, elevated diastolic BP, mean arterial BP, central systolic BP and end-systolic BP were associated with a decreased risk of AoAC. An increased β2-microglobulin concentration was also nonsignificantly related to AoAC (Figure 10).

Variables that had no interrelationship were included in multivariable logistic regression. Stepwise model selection revealed the most significant variables (Table 6). A PWV ratio adjusted for age and mean arterial BP (Model 4) were associated with an risk of increased vascular calcification.

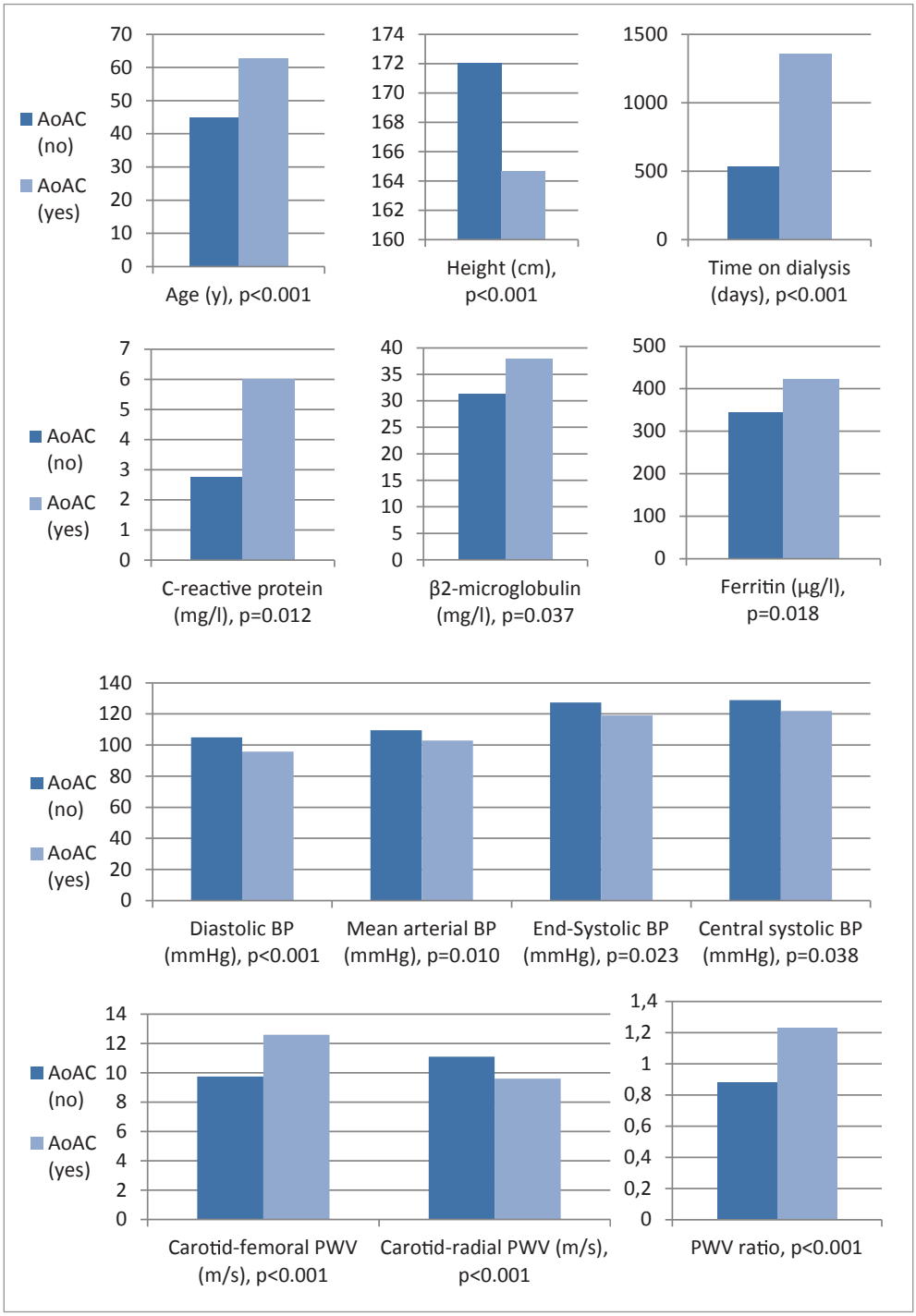

Fig. 8. A comparison of baseline characteristics in aortic arch calcification groups.

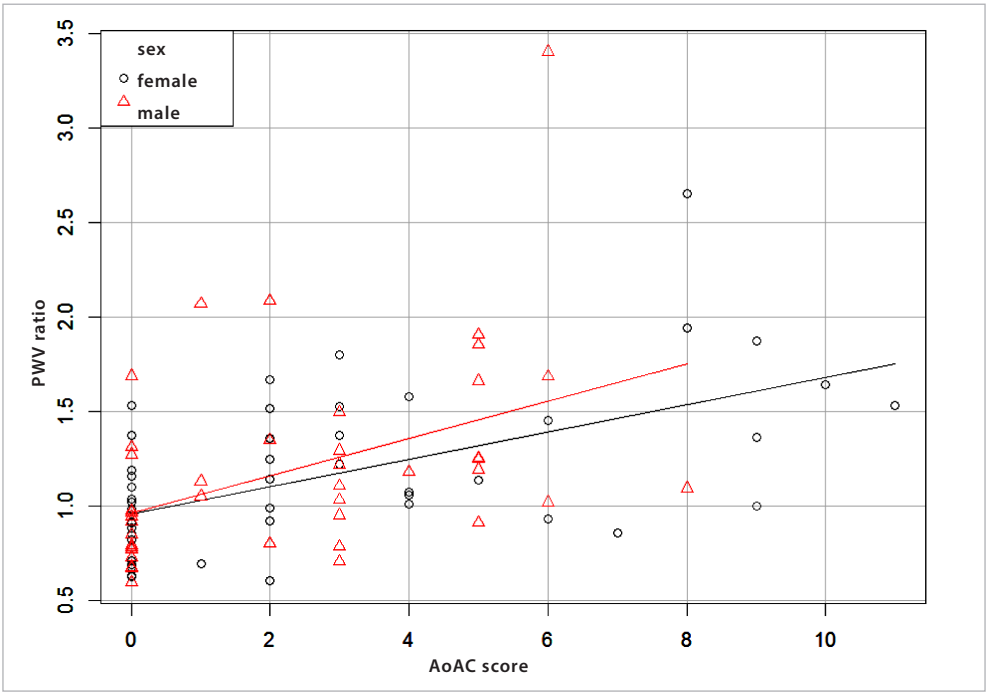

Fig. 9. The correlation between the aortic arch calcification score and the pulse wave velocity ratio in sexes.

Spearman rank correlations between aortic arch score and pulse wave velocity ratio in sexes. Correlation coefficients in females r=0.498, p<0.001; in males r= 0.572, p<0.001. PWV ratio – pulse wave velocity ratio, AoAC –aortic arch calcification.

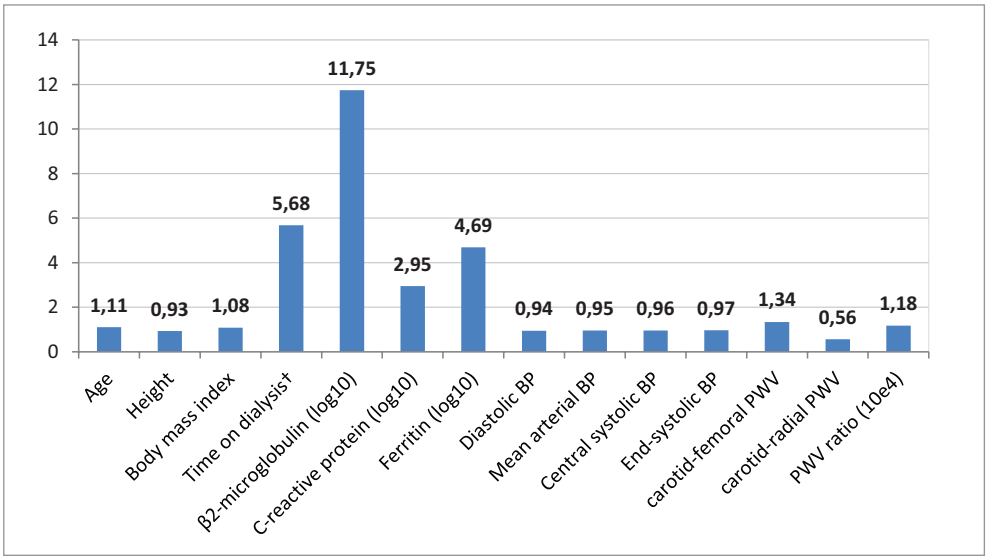

Fig.10. Aortic arch calcification influencing factors

Table 6. Factors associated with aortic arch calcification: multivariable logistic regression.

Model 4	estimate	SE	OR	95% CI	P-value
Age	0.087	0.027	1.09	1.04, 1.16	0.001
Mean arterial BP	-0.080	0.028	0.92	0.86, 0.97	0.005
PWV ratio†	6.423	2.444	6.15e+02	7.31, 1.17e+05	0.008

PWV ratio – pulse wave velocity ratio.
†log10 transformed values.

The receiver operating characteristic (ROC) curves of all statistically significant risk factors were drawn (Supplemental Table S8) and areas under the curve (AUC) were compared (Table 7). Age, height, cfPWV, the PWV ratio and Model 4 had the highest AUC (Figure 11). The specificity (82%) of Model 4 was the highest comparing to other variables, but the sensitivity (77%) was lower than age (Table 12).

Table 7. The comparison, sensitivity and specificity of the ROC curves analysis on aortic arch calcification.

Variables	AUC	95%CI (DeLong)	Sensitivity (%)	Specificity (%)
Age	0.833	0.757-0.910	79	71
Height	0.744	0.646-0.842	68	60
Body mass index	0.592	0.480-0.709	81	61
Dialysis duration†	0.695	0.586-0.805	74	65
β2-microglobulin†	0.634	0.512-0.757	57	58
C-reactive protein†	0.645	0.536-0.755	70	58
Ferritin†	0.675	0.560-0.789	57	56
Diastolic BP	0.647	0.539-0.755	66	56
Mean arterial BP	0.642	0.532-0.752	68	50
Central systolic BP	0.616	0.496-0.737	57	62
End-systolic BP	0.655	0.538-0.771	81	61
cfPWV	0.747	0.653-0.842	66	65
crPWV	0.676	0.558-0.793	74	67
PWV ratio†	0.792	0.697-0.887	74	73
Model4	0.893	0.826-0.960	77	82

BP – blood pressure, cfPWV – carotid-femoral pulse wave velocity, crPWV – carotid-radial pulse wave velocity, PWV ratio – pulse wave velocity ratio, 95%CI – 95% confidence interval.
Model 4: age + mean arterial pressure +pulse wave velocity ratio
†log10 transformed values

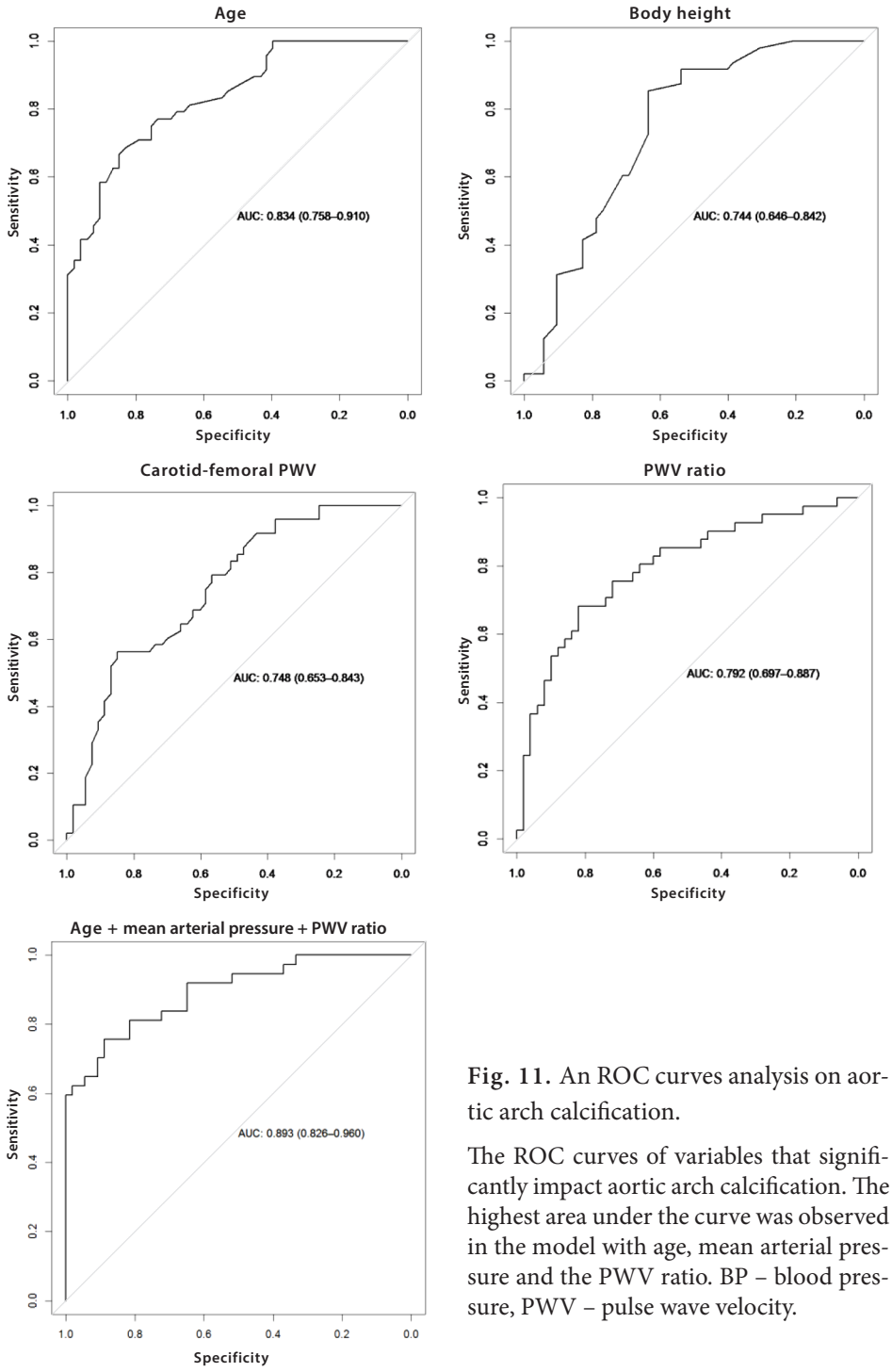

Fig. 11. An ROC curves analysis on aortic arch calcification.

The ROC curves of variables that significantly impact aortic arch calcification. The highest area under the curve was observed in the model with age, mean arterial pressure and the PWV ratio. BP – blood pressure, PWV – pulse wave velocity.

5.6. THE EFFECT OF THE PWV RATIO AND OTHER RISK FACTORS ON THE CARDIOVASCULAR OUTCOME

During mean 683±149 days follow-up, 20 (19.8%) of the patients experienced CV events. We analyzed the CV event risk factors for the whole population (n=101), including 20 patients who were transplanted during the follow-up, and for the patients who remained on chronic dialysis (n=81) separately.

In the dialysis population, PWV above median 1.17 was not significantly associated with cardiovascular event-free survival (p=0.120) (Figure 12).

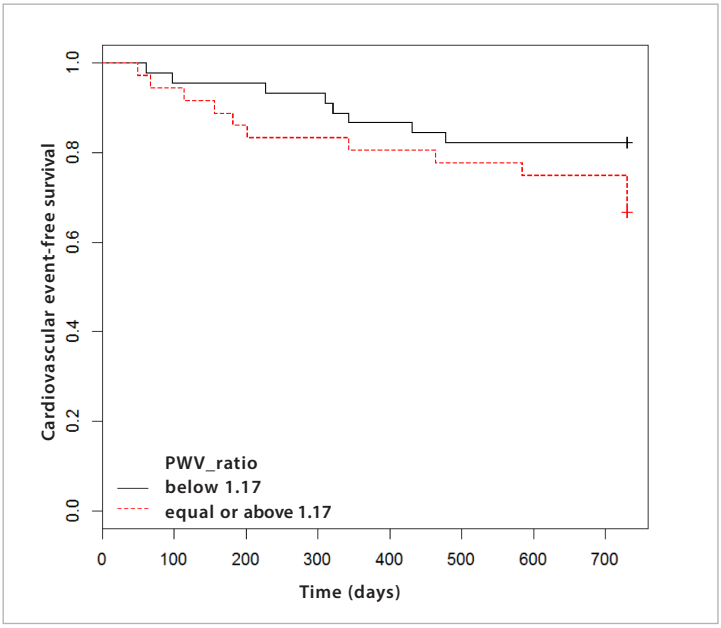

Fig. 12. Cardiovascular event-free survival in accordance with the PWV ratio median value.

Cardiovascular event-free survival in accordance with the median PWV ratio value 1.17. PWV ratio – pulse wave velocity ratio.

A univariable Cox regression analysis with all CV events (Supplemental Table S9) revealed that in the whole study population, older age, shorter body height, β2-microglobulin value above median 35.25 mg/l, higher C-reactive protein level, higher total cholesterol and parathormone level, lower phosphate levels and AoAC score above 1 were associated with an increased cardiovascular

event risk. None of the hemodynamic or vascular parameters were important in predicting the cardiovascular outcome. When analyzing the dialysis population separately, the same risk factors, except β2-microglobulin, were identified (Figure 13).

The PWV ratio's significance in predicting CV events was uncovered after adjusting for different confounding variables (age, AoAC score, sex). Models that included diabetes mellitus were not significant. In the dialysis population, the PWV ratio had a significant predictive value after adjusting for age, AoAC score and sex. On the contrary, in the whole population, these adjustments had no significant value; cfPWV remained insignificant even after the adjustment for selected variables.

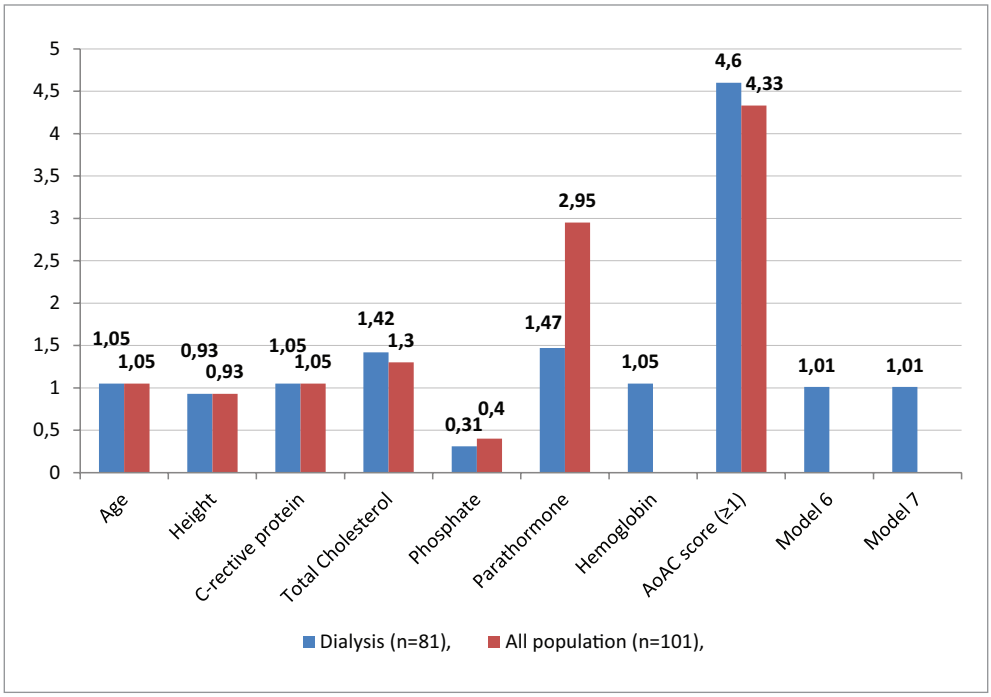

Fig. 13. The hazard ratios of significant cardiovascular risk predictors. Model 6: the PWV ratio adjusted for age, AoAC score; Model 7: the PWV ratio adjusted for age, AoAC score, sex.

We have also analyzed MACE in the dialysis population separately. Due to the quite low event rate of 8.6% (n=7), only a univariable Cox regression analysis was performed. Figure 14 represents the significant risk factors for MACE in the dialysis population. Lower body height, higher C-reactive protein, total cholesterol, parathormone and Hgb levels, higher central systolic BP and end-systolic BP could predict MACE. Age (p=0.102), cfPWV (p=0.763) and the PWV ratio (p=0.796) had no significant impact.

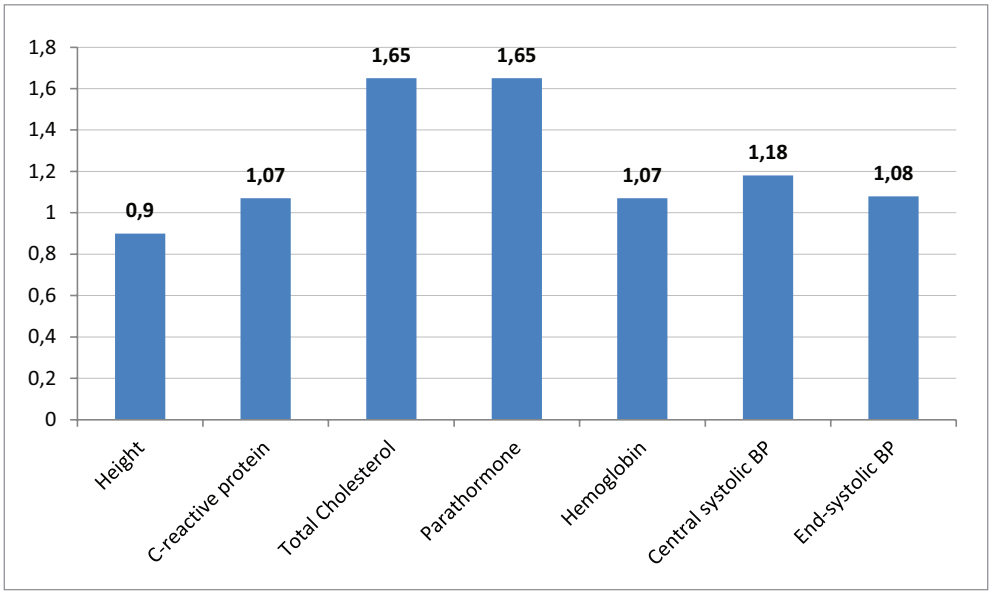

Fig. 14. Factors associated with major cardiovascular event risk.

5.7. THE PROGRESSION OF ARTERIAL STIFFNESS IN ESRD

Out of 101 patients studied, only 60 patients (mean age 57.61 ±13.01 years) had their measurements after 6 months available. Of them, 50% were males, 15.58% were current or former smokers, 30.77% were diabetic, 96.15% had hypertension and all had received treatment with chronic hemodialysis. After 2 years, only 46 of them consented to repeated measurements.

We have observed a statistically significant increase in the total protein level and a decrease in diastolic BP and mean arterial BP after a 6-month observation period (Figure 15, Supplemental Table S10). Other variables did not change

significantly. After 2 years, there was a significant decrease in weight, platelet count, uric acid, corrected calcium level, pulse pressure and crPWV; there was a significant increase in cystatin C concentration, PTH level, cfPWV and the PWV ratio value. A decrease in systolic BP and central systolic BP was also observed; however, it was not significant.

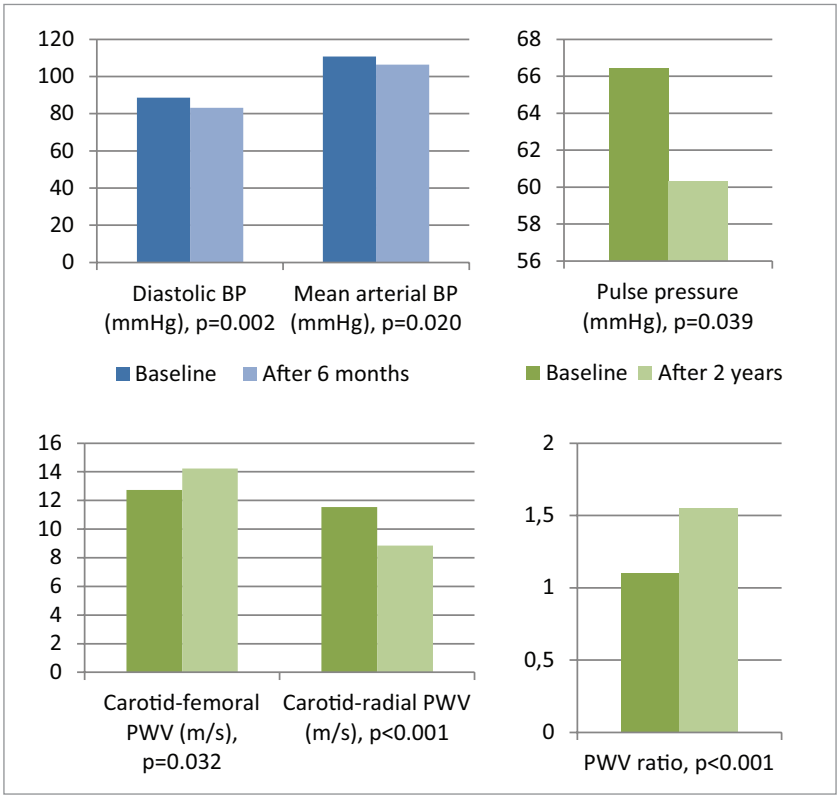

Fig. 15. Significant hemodynamic changes reflecting variables in patients on hemodialysis in different time periods.

Age had no relationship with arterial stiffness change for 6 months but was significantly associated with an increase in cfPWV (p=0.037) and borderline significantly with crPWV (p=0.050) during 2 years of follow-up (Table 8). The change in the PWV ratio was not related to aging. We found the relationship of a C-reactive protein increase with the progression of both cfPWV and crPWV, and of a β2-microglobulin increase with the progression of cfPWV within 2 years. The baseline vascular calcification scores were strongly associated with

Table 8. The determinants of change in arterial stiffness: linear regression analysis.

	Adjusted $cfPWV_{6mo}$			Adjusted $crPWV_{6mo}$			Adjusted PWV $ratio_{6mo}$		
	β	**P-value**	**R^2**	**β**	**P-value**	**R^2**	**β**	**P-value**	**R^2**
Age †	0.064	0.059	0.158	-0.005	0.883	0.071	0.004	0.240	0.331
Dialysis duration (log)	-0.214	0.829	0.016	0.281	0.784	0.073	-0.022	0.841	0.281
β2-microglobulin †	-0.014	0.688	0.023	-0.045	0.238	0.137	-0.001	0.700	0.286
Δβ2-$microglobulin_{6mo}$	-0.005	0.931	0.014	-0.011	0.871	0.071	0.001	0.860	0.281
C-reactive protein (log) †	0.748	0.489	0.034	-0.731	0.541	0.088	0.125	0.335	0.315
ΔC-$reactive\ protein_{6mo}$	-0.010	0.870	0.015	-0.0063	0.323	0.117	0.004	0.511	0.296
Mean arterial BP †	0.079	0.075	0.147	0.114	0.004*	0.402	-0.002	0.651	0.268
ΔMean $arterial\ BP_{6mo}$	0.081	0.031*	0.245	0.066	0.05*	0.242	0.003	0.342	0.400
AoAC†	0.080	0.646	0.023	-0.297	0.751	0.075	0.014	0.488	0.298
	Model 8: **R2 0.325, p=0.037**			***Model 9:*** **R2 0.402, p=0.029**					
Age †	0.071	0.028*		-0.001	0.959		-	-	-
Mean arterial BP †	0.087	0.035*		0.114	0.006*		-	-	-
	Adjusted $cfPWV_{2y}$			**Adjusted $crPWV_{2y}$**			**Adjusted PWV $ratio_{2y}$**		
	β	**P-value**	**R^2**	**β**	**P-value**	**R^2**	**β**	**P-value**	**R^2**
Age †	0.136	0.037*	0.550	-0.036	0.050*	0.441	0.006	0.438	0.571
Dialysis duration (log)	7.149	0.300	0.502	1.46	0.399	0.136	0.581	0.374	0.625
β2-microglobulin †	0.040	0.675	0.334	0.005	0.799	0.021	-0.001	0.899	0.531
Δβ2-$microglobulin_{2y}$	0.219	0.022*	0.568	0.039	0.335	0.142	0.009	0.542	0.556
C-reactive protein (log)†	3.977	0.186	0.476	0.528	0.478	0.084	0.346	0.200	0.634
ΔC-$reactive\ protein_{2y}$	0.331	0.031*	0.599	0.097	0.022*	0.554	0.0247	0.135	0.666
Mean arterial BP†	-0.063	0.613	0.342	-0.007	0.779	0.0232	-0.006	0.558	0.554
ΔMean $arterial\ BP_{2y}$	-0.085	0.471	0.368	-0.002	0.914	0.013	-0.002	0.800	0.573
AoAC †	0.753	0.034*	0.553	0.103	0.384	0.119	0.0717	0.035*	0.710

Adjusted values: PWV at follow-up as key independent variable adjusted for PWV value at baseline
Δ - difference from baseline value within follow-up, 2y – two years, 6mo – 6 months.
BP – blood pressure, AoAC aortic arch calcification.
†baseline measurements; *p value ≤0.05, β – linear regression beta coefficient

the progression of aortic stiffness and the PWV ratio. A baseline mean arterial BP was strongly associated with crPWV progression during the 6 months of follow-up. An increase in mean arterial BP resulted in both an increased aortic and peripheral arterial stiffness. In a multivariable linear regression adjusted for age, several significant models were established (Model 8, Model 9). Change in both aortic and brachial arterial stiffness for 6 months was still significantly dependent on baseline mean arterial BP.

There was no significant association between arterial stiffness evolution and dialysis duration.

6. RESULTS FOR PATIENTS AFTER RENAL TRANSPLANTATION

Table 9 represents the baseline characteristics of patients who were admitted to the Nephrology Center for renal transplantation. The mean age was 46.95 ± 11.96 years, 54.1% were males, 5.4% had pretransplant diabetes mellitus and 86.5% had hypertension. Recipients received kidneys from cadaveric donors aged 46.33 ± 11.26 years.

Table 9. The baseline characteristics of kidney transplant recipients.

Variables	Mean ± SD
Demographics and comorbid conditions	
Recipient age (y)	46.95 ± 11.96
Recipient sex (men)	20 (54.1%)
Body mass index (kg/m2)	24.04 ± 4.57
Hypertension	32 (86.5%)
Diabetes mellitus	2 (5.4%)
Kidney disease duration (y)	14.49 ± 11.51
Donor age (y)	46.33 ± 11.26
Donor sex (male)	22 (59.4%)
Hemodynamic and vascular parameters	
Systolic BP (mm Hg)	143.78 ± 16.87
Diastolic BP (mm Hg)	86.43 ± 12.38
Mean arterial BP	105.59 ± 12.09
Pulse pressure (mm Hg)	57.38 ± 11.23
Heart rate (beats/min)	72.12 ± 11.47
Central systolic BP (mm Hg)	125.93 ± 15.73
cfPWV(m/s)	8.91 ± 2.11
crPWV(m/s)	10.13 ± 1.24
PWV ratio	0,88 ± 0,27
Biological markers	
C-reactive protein (mg/L)	2.49 ± 2.66
Total cholesterol (mmol/L)	5.90 ± 1.21
Albumin (g/L)	44.34 ± 3.48
Calcium (mmol/L)	2.39 ± 0.15

Table 9 (continuation). The baseline characteristics of kidney transplant recipients.

Variables	Mean ± SD
Ionized calcium (mmol/L)	1.14 ± 0.11
Phosphate (mmol/L)	1.67 ± 0.50
PTH (pmol/L)	71.27 ± 57.54
Creatinine (μmol/l)	830.38 ± 215.31
Urea (mmol/l)	19.16 ± 7.53
Uric acid (mkmol/l)	292.74 ± 86.22
White blood cells ($x10^9$/L)	6.73 ± 2.00
Hemoglobin (g/L)	120.79 ± 12.56
Platelets ($x10^9$/L)	219.35 ± 53.52
Type of dialysis	
Hemodialysis	30 (81.1%)
Peritoneal dialysis	7 (18.9%)
Citomegalovirus serology	
CMV donor positive	33 (89.2%)
CMV recipient positive	30 (81.1%)
Drug therapy	
Beta-blockers	24 (70.6%)
Calcium chanel blockers	21 (61.8%)
Centrally acting antihypertensive drugs	21 (61.8%)
Doxazosin	13 (38.2%)
Diuretics	4 (11.8%)
Angiotensin II receptor blockers	3 (8.8%)
Tacrolimus	27 (73.0%)
Cyclosporine	10 (27.0%)

BP: Blood pressure; CMV: Cytomegalovirus infection; PTH: Parathyroid hormone; cf-PWV: Carotid-femoral pulse wave velocity; cr-PWV: Carotid-radial pulse wave velocity; PWV ratio: Pulse wave velocity ratio

In two years, 4 patients experienced acute kidney graft rejection episodes (3 patients – acute antibody mediated rejection; 1 patients – acute cell rejection). There were other complications as well: renal artery stenosis – 2 cases; CMV infection – 2 cases; transplant hematoma – 4 cases; deep vein thrombosis – 1 case and transplant hydronephrosis – 1 case; urinary tract infection – 16 cases.

Blood test results and vascular parameters before the kidney transplant and after 12 and 24 months of follow-up are available in supplementary material (Supplemental Table S11).

When comparing blood test results, as expected, there was a significant improvement in hemoglobin level, a reduction in phosphate, parathormon and uremic toxin levels. Regarding hemodynamic parameters, reduced systolic BP, pulse pressure and central systolic BP were established. But there was no significant change in diastolic BP and mean arterial BP. The elastic artery stiffness reduced significantly after 1-year follow-up but not after 2 years. Muscular artery stiffness, the PWV ratio and vascular calcification changes were not significant (Figure 16).

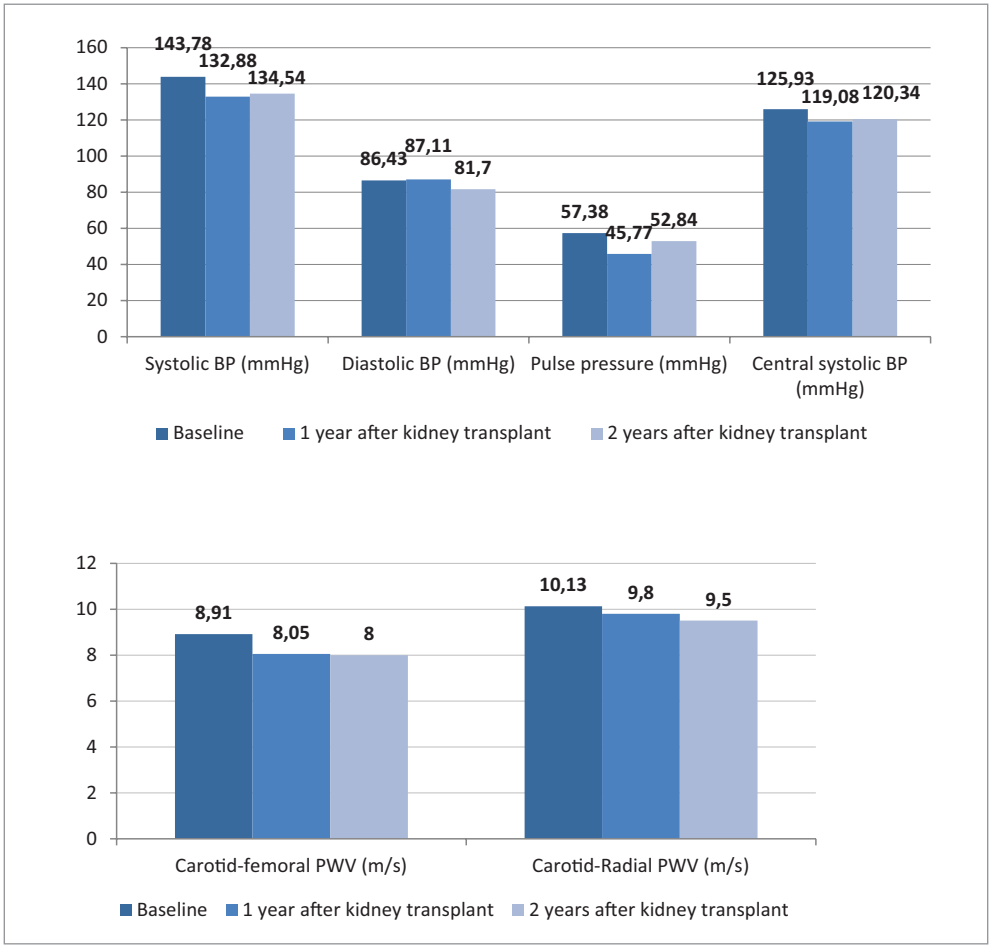

Fig. 16. Hemodynamic changes after a successful kidney transplant.

The slowly detiorating graft function was observed when comparing the eGFR in one year and two years after the renal transplant (71.92 ±25.15 vs 64.39 ±18.03 ml/min/1.73m^2, p=0.2435).

Of the study participants, 27 (72.29%) showed no change in AoAC evaluated on chest X-rays. Only in 6 (16.21%) of the patients the extent of AoAC had decreased, and in 4 (10.81%) – increased (Figure 17).

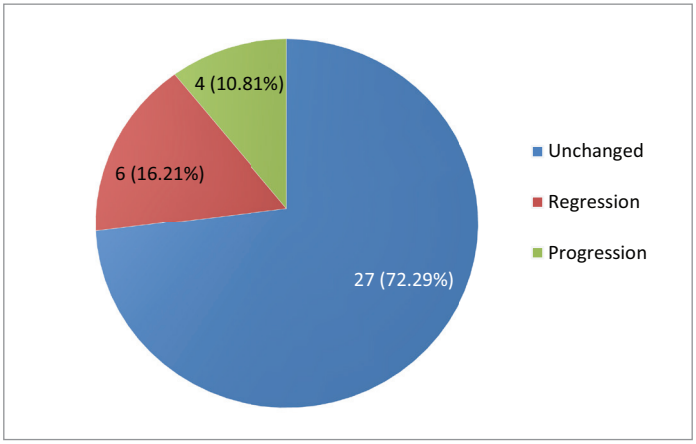

Fig. 17. The evolution of aortic arch calcification in 2 years after a kidney transplant

In our study, we also collected data about CV events in posttransplant period. During the 2-year follow-up, 5 (13.51%) participants experienced CV events: 3 myocardial infarctions, 1 pulmonary artery embolism and 1 stroke. These patients had a higher level of pretransplant C-reactive protein (1,00 *vs* 5,25 mg/l, p=0,012), AoAC present on a chest X-ray (X^2=4,36, p=0,036) and their kidney graft was from an older donor (p=0,045); however, PWV did not differ from those patients without posttransplant CV events (0,80 vs. 1,02, p=0,352). We did not perform a Cox-regression analysis due to the small sample size and quite low event rate.

Additionally, we observed that patients without a pretransplant AoAC had a better kidney graft function when comparing creatinine (122,18 *vs* 96,00 mkmol/l, p=0,042) and calculated eGFR values (61,15 *vs* 47,79 ml/min/1,73 m^2, p<0,001). Furthermore, in patients with an unchanged AoAC after the kidney transplant, significantlly lower ionized calcium levels were observed (p=0,026).

7. DISCUSSION

Our study represents dialysis and kidney transplant recipient populations without previous CV events, cerebrovascular events and PAD. It provides valuable information about the importance of the PWV ratio and the other factors in predicting the extent of vascular calcification, CV events and posttransplant outcomes. Additionally, it gives an insight on arterial stiffness progression in 2-year follow-ups in two different populations: in patients on chronic dialysis and after successful kidney transplants.

7.1. DIALYSIS POPULATION

7.1.1. SEX DIFFERENCES

Sex differences in the study population were as expected. The creatinine level in the dialysis population is an indicator of protein-energy intake status and represents skeletal muscle mass (146); therefore, it was lower in females. Elevated corrected calcium levels in women may be a consequence of different sex-specific patterns of a CKD-mineral and bone disorder (147), but only bone histology could prove the exact underlying bone pathology. Lower cholesterol levels have been previously shown to be associated with inflammation and nutrition statuses (148). Similarly, very high β2-microglobulin levels are more prevalent in malnutrition, inflammation and an atherosclerosis (MIA) syndrome in the CKD population (149). Thus, we could suggest that males from our study population were more affected by the abovementioned changes. Finally, an observed higher pulse pressure in women is recognized as one of the characteristics of vascular aging (150) with a steeper increase with advancing age as compared to men. In fact, women on dialysis have higher rates of premature menopause and other sex hormone disturbances (151), which only increases the risk for cardiovascular disease.

7.1.2. THE DETERMINANTS OF ARTERIAL STIFFNESS

The first evidence about age influence on different localization of PWV appeared in 1983 (94). Later, multiple studies have confirmed this relationship (93, 95, 152, 153). In our cross-sectional analysis, we have also observed a significant correlation between age and cfPWV or the PWV ratio, and no correlation between age and crPWV. This confirms different aging related patterns in elastic and muscular arteries, also characteristic of and prevalent in the community setting (154).

Since 2014 (153), the aortic-brachial stiffness gradient has been an issue for debate within scientific community. It is well-known that elastic arteries become stiffer with advancing age. These changes are less evident in periphery (109). Barry et al. (155) analyzed the histology of coronary, radial and left internal thoracic artery grafts. They reported a thickening of tunica intima, a myocite migration from tunica media and its hypertrophy and fibrosis in muscular (coronary, radial) arteries. In contrast, aging in elastic arteries (internal thoracic artery) had manifested by more evident intimal thickening and a loss of elastin in tunica media, leading to arterial stiffening. These histologic findings might explain the different crPWV and cfPWV values in ESRD. Besides, the CKD and ESRD populations are suffering from a phenomenon called "accelerate aging" (119); therefore, vascular remodeling is more pronounced.

In study by Fortier et al. (153), the determinants of the PWV ratio in dialysis patients such as age, diabetes mellitus, time on dialysis, C-reactive protein level and PTH were similar to our study. In concordance with a Framingham substudy (106), the association of the PWV ratio with cholesterol was observed. The relationship of aortic brachial stiffness gradient and cystatin C, ferritin and the AoAC score has not been previously described. Some researchers showed the association between cystatin C and pulse wave velocity in coronary artery disease in patients with no or mild CKD (156–158),and the significance of these markers in identifying patients with an increased CV risk (159). However, the importance of cystatin C measurement in the dialysis population is less clear. A small sample size study with cystatin C at the initiation of dialysis suggested that it could be an independent CV event risk marker (160). Unfortunately, we

did not measure the residual renal function; thus, the relationship with cystatin C cannot be fully explained.

In comparison to other PWV ratio-analyzing studies in patients with ESRD (48, 97, 109, 153), together with London et al. (93), we observed lower cfPWV values and higher crPWV values (Supplemental Table S12). A possible explanation for such a discrepancy of the measurements might be the younger age of participants, the exclusion of patients with diabetes (93) and cardiovascular history (i.e., the exclusion of patients with cardiovascular/cerebrovascular history and PAD in our study; also, the CV outcomes within 6 months – in the study by London et al. (93) study).

Previous studies (141, 161) have also focused on the influence of ESRD etiology on pulse wave velocity values. We could not confirm (141) a higher cfPWV in vascular renal disease. Similarly to our study, Bia et al. (161) observed the highest cfPWV and PWV ratio values in diabetic nephropathy. Of course, the role of diabetes mellitus in vascular damage is unquestionable. It encompasses hyperglycemia, insulin resistance and the production of advanced glycolysation end products (AGE) and it promotes vascular aging (118). Diabetes mellitus also results in microvascular changes (162). Further studies focusing on the relationship of arterial stiffness with primary kidney disease in non-dialysis population are necessary.

The relationship between fluid status and arterial stiffness in the dialysis population have already been described (46, 47, 161, 163). Aortic PWV, but not peripheral PWV, has been shown to be dependent on volume status but not on blood pressure (46,161). However, it is still not clear whether hypervolemia leads to a BP dependent (44) or independent (45) pulse wave velocity increase and whether these potential effects are similar in elastic and muscular arteries. Our data did not include the volume status measurement of patients, but all of them had a stable dry weight.

7.1.3. ARTERIAL STIFFNESS GRADIENT AND VASCULAR CALCIFICATION

This is the first study describing the association of aortic-brachial stiffness gradient and aortic arch calcification. Aortic arch calcification detection (164)

on a plain chest X-ray is one of the simple methods for evaluating the extent of calcification and, at the same time, for predicting the outcome (103, 165, 166). A chest X-ray is performed annually for every dialysis patient as a routine test. Although multi-detector CT is the best method so far for the identification of vascular calcification, it is quite expensive and not available in all centers. Besides, Nitta et al. have succeeded in confirming the strong relationship between the AoAC extent evaluated on a chest X-ray and on multi-detector CT (165).

We found significant positive correlation between AoAC scores and the PWV ratio. Multivariable linear regression models, which included age, diabetes mellitus and an AoAC score, had a descriptive value of more than 0.43. Recently, the relationship between the coronary calcification score on CT and the brachial-ankle PWV in hypertensive patients has been described (167). A couple of studies with hemodialysis populations have also observed the correlation between PWV and the AoAC score (103, 168), but the PWV measuring techniques had varied. Our results were surprising; patients with vascular calcification had higher cfPWV, but lower crPWV; therefore, an increased PWV ratio. This difference remained significant even after adjusting for age.

CKD patients are prone to both intimal and medial calcification. Medial calcification is more diffuse, affecting mainly muscular arteries and resulting in apoptosis of VSMCs and leading to ectopic vascular calcification (71, 119, 169). Remembering that muscular arteries, when compared to elastic arteries, have less elastic fibers and are rich in VSMCs, these abovementioned processes affect the contractile ability of the arteries. Thus, the peripheral resistance diminishes and the lower crPWV values are recorded. On the other hand, inflammation and atherosclerosis caused intimal calcification, which focally affects large arteries, results in an increased cfPWV and a greater pulse wave reaching microvasculature. It is the main mechanism for end-organ damage, well-described in type 2 diabetes mellitus (162).

The patients of our study without AoAC had lower inflammatory markers, including β2-microglobulin, C-reactive protein and ferritin. However, we did not collect data on intravenous iron supplementation as one of the possible causes of the increased ferritin level. Therefore, we cannot deny the direct effect of iron on the vascular wall. *In vitro* studies revealed that intravenous iron

supplements might trigger oxidative stress, due to a transformation to labile iron, and promote vascular calcification (170). The revelation of iron accumulation-caused aortic valve calcifications might also support the possible pathogenetic links between iron supplementation and vascular calcification in ESRD (171).

Also, the role of β2-microglobulin in vascular calcification has been previously studied (172, 173). Murine models revealed that β2-microglobulin has osteoclastogenetic characteristics (174), and it might be one of the factors inducing the osteoblastic differentiation in VSMCs. Besides, β2-microglobulin might alter the arterial structure by amyloid formation (175) and can per se promote atherosclerosis (176), resulting in increased arterial stiffness.

We observed that patients without signs of AoAC were higher in body height, and lower body height was associated with an increased AoAC risk. This result may be influenced by the older age in patients with AoAC and more pronounced CKD-related mineral-bone disorders. Furthermore, patients with AoAC had a higher body mass index. Obesity and/or an increase in abdominal fat are the risk factors of metabolic syndrome and metabolic syndrome per se is associated with calcified atherosclerosis (177–179).

Though some researchers (180, 181) found that elevated diastolic BP, systolic BP and mean arterial BP in non-CKD populations are associated with a different localization of vascular calcification, we failed to confirm these results. In concordance with other studies with dialysis populations (103, 168), we observed lower diastolic BP and mean arterial BP in patients with AoAC. Noting that mean arterial BP is dependent from cardiac output, central venous pressure and systemic vascular resistance (182) and is relative stable in the whole arterial system (183), the decreased mean arterial BP may suggest decreased vascular resistance in vascular calcification. Therefore, on peripheral vascular resistance, a dependent PWV ratio adjusted for age and mean arterial BP might be the best tool for evaluating the presence of AoAC. Additionally, we have confirmed that lower central systolic BP (184) does not translate into lower AoAC risk in ESRD. Unfortunately, we were able to evaluate only clinically evident vascular calcification; therefore, the role of subclinical microcalcifications that could affect central blood pressure cannot be excluded.

7.1.4. ARTERIAL STIFFNESS AND CARDIOVASCULAR RISK

In our study, the established risk factors for CV events, such as age, elevated total cholesterol and elevated C-reactive protein, did not differ from those published in the "Systematic Evidence Review from the Risk Assessment Work Group" (185). However, we failed to identify sex, diabetes mellitus and smoking as variables associated with an increased CV event risk. Regarding smoking, not all participants were honest about their smoking status; thus, the results are inaccurate.

The role of body height in predicting CV and an all-cause mortality is very controversial. The meta-analysis showed that shorter height is an independent risk factor for all-cause and cardiovascular mortality (186). A study with ESRD revealed opposite results, especially in the Caucasian race, suggesting that taller patients have a higher all-cause mortality risk at the initiation of dialysis (187). We found that shorter body height was associated with an increased CV event and MACE rates. Further epidemiological research projects are needed to test the link between body height adjusted for age, sex and, for example, for vascular calcification as a risk marker for cardiovascular morbidity and mortality.

Although β2-microglobulin has been identified as a significant cardiovascular risk predictor in different CKD stages (149, 173, 188, 189) and a marker for PAD (176), our study could not fully confirm this relationship. We can only suggest that the importance of β 2M in the cardiac and vascular damage is more evident in patients with a longer history of chronic dialysis or in patients with previous cardiovascular events.

At least 2 large trials (190, 191) showed that high phosphate and high PTH levels are associated not only with cardiovascular morbidity and mortality but also with all-cause mortality. Besides, there are significant evidences that phosphate plays more important role in vascular calcification than calcium (192). In contrast, the Dialysis Outcomes and Practice Patterns Study (DOPPS) (193) revealed that phosphate concentration below 0.8mmol/l is associated with an increased all-cause mortality. Block el al. (190) found a J-shaped, unadjusted relationship between phosphate and an all-cause mortality. Surprisingly, in our patients, a lower phosphate level was associated with CV events. Unfortunately, we have no data about other factors that may influence phosphate blood levels,

such as the concentration of vitamin D, nutritional status and phosphate binder intake (194). The difference in calcium concentration or in the number of calcium-phosphate products was also absent.

None of the randomized studies succeeded in proving the relationship between a higher level of hemoglobin and mortality (195). The association between higher hemoglobin concentration with CV events and MACE in our research should be considered in the context of erythropoesis stimulating agents and iron supplementation. Previously, the relationship between higher erythropoesis stimulating agent dose and death has been confirmed (196), though an interventional trial with a fixed erythropoiesis-stimulating agent dose failed to show the beneficial influence on CV events and all-cause mortality.

An AoAC score ≥1 presented the highest hazard risk values comparing to other significant variables. The influence of calcification on CV events was similar to other published papers (103, 165, 168, 197). Besides, the PWV ratio gained significance in predicting CV events only after the adjustment for age and AoAC.

The attempt to confirm the importance of cfPWV as a CV event predictor in our study was unsuccessful. Since 1990, when London et al. (198) described the increased aortic PWV in dialysis patients comparing to controls, a lot of inconsistent studies followed. For example, a study by Shinohara et al. (199) found higher cfPWV values in dialysis patients (n=144) when comparing to predialysis patients (n=144). A study with 109 hemodialysis patients from Canada (109) observed an increase in cfPWV and a decrease in crPWV within a 1.2-year follow-up, but the impact of this change on cardiovascular events has not been discussed. The same trends have been observed in a peritoneal dialysis population (200) with an increasing cfPWV after 2 years of treatment with this dialysis modality. There are undeniable evidence from a meta-analysis, which included 17 635 non-CKD participants (201), that an aortic PWV improves cardiovascular risk prediction in models with a traditional risk factor. A cfPWV measurement has been included in several guidelines (42, 202) as an independent risk factor for CV morbidity and mortality.

Regarding an ESRD population, some reports (93, 203) could not confirm cfPWV's importance in predicting CV events or an all-cause mortality after

adjusting for age and other confounding variables. Contrarily, the Calcification Outcome in Renal Disease cohort study (n= 1084) (98) showed that cfPWV, together with an abdominal arch calcification score, can predict a CV event risk very accurately. Regarding peritoneal dialysis, the data are very limited. One report showed that a higher cfPWV (>9 m/s) predicts CV risk in peritoneal dialysis (204), while others claim that a cfPWV higher than 10 m/s was associated with death rates but lost its significance after adjusting for confounding variables. Studies combining hemodialysis and peritoneal dialysis (153) showed that higher cfPWV and lower crPWV, and thereof a higher PWV ratio were associated with mortality in unadjusted models. Unfortunately, only the PWV ratio had remained the significant variable after adjusting for age in the previously mentioned analysis. These results lead us to the debate regarding the superiority of the aortic-stiffness gradient over cfPWV in predicting the clinical outcomes.

In a community setting (106), the PWV ratio did not provide superior value over cfPWV in predicting CV events. There are at least 2 studies so far analyzing the influence of the PWV ratio on the clinical outcome in a dialysis population (93, 153), and the results are inconsistent. In our study, the PWV ratio became significant in CV event prediction only after adjusting for age, sex and the AoAC score, although when analyzing MACE separately, it had no predictive value at all. London et al. (93) showed that both cfPWV and the PWV ratio are important in non-diabetic ESRD. One of the inclusion criteria for the study were absent cardiovascular complications within 6 months before analysis. In contrast, we have selected patients without previous CV events and PAD at all, though diabetic patients were also included. The mismatching results might be also influenced by the different descriptions of clinical outcomes and different follow-up periods (Supplemental Table S13).

We did not consider heart failure not requiring hospitalization as an endpoint in our analysis as it has multifactorial etiology in ESRD encompassing hypervolemia, pressure overload and CKD-related factors (205). And based on the New York Heart Association (NYHA) Functional Classification (206) alone, it is challenging to identify the exact cause of heart failure. In 2014, a new classification for heart failure in ESRD from a Acute Dialysis Quality Initiative

XI working group (205) was proposed. Implementing this classification could improve the differential diagnosis in heart failure in ESRD and in considering it as an endpoint.

7.1.5. THE PROGRESSION OF ARTERIAL STIFFENING

There is at least one published study that measured PWV in a 6 months period repeatedly (111). The progression of arterial stiffness was evaluated in the context of dialysate calcium. Patients randomized to dialysate calcium 1.37 mmol/l showed progression in cfPWV and no change in crPWV. We did not collect data about dialysis prescription parameters; therefore, dialysate calcium impact has not been included. However, in Vilnius University Hospital Santaros Klinikos, the use of dialysate with calcium 1.25mmol/ is a routine prescription. Only patients prone to hypocalcemia receive treatment with dialysate calcium 1.5mmol/l. We can only suggest that our observed absence in the significant cfPWV change in 6 months might be also influenced by dialysis prescription. Overall, in our study population, the progression of cfPWV was determined by an increase in mean arterial BP. It only confirms the fact that with an increase in elastic arteries stiffness, there is a decrease in systemic vascular resistance and a particular increase in mean arterial BP. However, this causal relationship was absent after 2 years of follow-up, suggesting that arterial stiffness is more likely a mean arterial BP independent variable.

Other studies (73, 109, 110, 115, 207) have focused on a longer observational period ranging from 12 to 36 months for evaluating the progression of arterial stiffness. Iorio et al. (115) could not confirm an increase in aortic stiffness in patients without a parallel progression of coronary artery calcification. We also found that a baseline aortic calcification score influenced the progression of aortic stiffness and the PWV ratio in a 2-year period. Similarly to Utescu et al. (109), we found the relationship between change in inflammatory status and arterial stiffness. And particularly, for the first time, we showed that an increase in β2-microglobulin concentration within a 2-year period results in an increase of aortic arterial stiffness, emphasizing the β2-microglobulin's role not only in peripheral (18) but also in large artery remodeling. Previous murine models revealed that β2-microglobulin has osteoclastogenetic characteristics (19),

and that it might be one of the factors inducing the osteoblastic differentiation of VSMCs. Besides, β2-microglobulin might alter the arterial structure by amyloid formation (20) and can per se promote atherosclerosis (18), resulting in increased arterial stiffness.

Two studies (73, 110) did not provide p-values for aortic stiffness change during the follow-up period. We calculated them from mean values and standard deviations provided in papers. Both studies did not show a significant increase in cfPWV in a follow-up period of 29–36 months. The results about stiffness progression are very controversial (Supplemental Table S14). Some studies observed progression in aortic stiffness (109, 115, 207) as well as our study, while the others did not give away the details about it (73, 110). We have also observed a significant aortic stiffening during a 2-year follow-up and a significant decrease in brachial arterial stiffness. Unfortunately, we did not screen repeatedly for peripheral arterial disease (PAD) in our population. Tests for PAD diagnosing were performed only if the patient had complaints. Additionally, we confirmed a dramatic PWV ratio increase in our study population after a 2-year observation. It would be interesting to analyze the microvascular changes of our study population, because the decreased peripheral stiffness/resistance and increased aortic pulse wave velocity eventually cause end-organ damage.

The decrease in diastolic BP and mean arterial BP after 6 months might be influenced by a patient's participation in this study. Every patient was informed about their measurement results and possible causes, such as hypertension, were pointed out. It supposedly resulted in a more responsible intake of antihypertensive medication (drug compliance) in the short term. The increased total protein level might be accidental, as the albumin level did not change significantly after 6 months.

Although we have observed a decrease in uric acid levels in a 2-year follow-up, it had no influence on the progression of cfPWV or the regression of crPWV. The relationship of uric acid with arterial stiffness was also absent in cross-sectional analysis. Data from a Framingham Heart Study (208) showed that uric acid concentration significantly correlated with cfPWV and crPWV in a healthy younger population. The report from the Baltimore Longitudinal Study of Aging showed that high levels of uric acid resulted in a higher increase in arterial

stiffness in men but not in women. The information about uric acid association with stiffness parameters in dialysis population is very limited. Caliskan (209) analyzed 37 patients on peritoneal dialysis and found no correlation between cfPWV and uric acid in blood.

7.2. KIDNEY TRANSPLANT POPULATION

This is the first study in Lithuania that analyzes the importance of the PWV ratio and aortic arch calcification in kidney transplanted patients without previous CV events and PAD. Overall, this is one of the few studies worldwide focusing on the prognostic value of AoAC in predicting the kidney graft function in a 2-year follow-up.

Of our kidney transplant patients, 54.05% had significant pretransplant AoAC on chest X-rays. The number of patients with AoAC increased and reached 67.75% in a 2-year posttransplant period. These results correspond with other studies (128, 210–212), which provided the prevalence of pretransplant vascular calcification ranging from 20% to 80%. Besides, the data confirm the stabilization (213) or, in most cases, the progression of vascular calcification after kidney transplantation (128, 129, 214).

A recently published paper (127) evaluated pretransplant abdominal CT scans for calcification (n=131). They used specific iliac artery calcification scoring and found out that the complexity of transplant surgery and the development of delayed graft function is closely related to a particular calcification morphology in iliac arteries. The other work from Corea (164) (n=258) used similar scale as in our study for an evaluation of AoAC on chest X-rays. The association of age, dialysis duration, diabetes mellitus and the presence of AoAC with an increased CV risk and worse prognosis was established. In our study, dialysis duration had no influence on the development of AoAC. The authors did not report any relationship between AoAC and the kidney graft function. It should be mentioned that in this research, patients with previous CV events (19%) were enrolled. Moreover, recipients with AoAC spent 67.9±49.2 months, and without calcification – 34.2±44.0 months on the kidney transplant waiting list. Our recipients waited for an average of 32.6±27.5 months regardless of their AoAC status.

Interestingly, the absence of any pretransplant AoACs in our study participants was related to a better kidney graft function after 2 years. This finding could be explained in several ways. First, a pretransplant AoAC on a chest X-ray might mirror the extent of vascular calcification in the whole body. Unfortunately, we did not perform pretransplant tests for detecting iliac artery calcification and had no data about any intraoperatively observed changes of recipient vasculature. Second, in patients with a progressive AoAC, higher ionized calcium levels were measured. These findings correspond with a study of Park et al. (128). An increased calcium concentration might alter the kidney graft function in several ways (215): by causing vasoconstriction and calcium deposition in tubulointerstitial space (216, 217). Besides, the posttransplant plasma calcium level reflects the remaining secondary hiperparatiroidism (218). Previous data suggest that about 25–66% (215, 218) of patients after having their kidney transplants end up with increased plasma calcium levels.

We have also observed a significant decrease in cfPWV after 1 year of having the kidney transplant but no improvement after 2 years. These conflicting results are in concordance with other studies. All studies reported a different evolution of postransplant pulse wave velocity: no change in cfPWV (136–138) in one year after kidney transplant; a decrease (135, 139) in the average posttransplant period of 3 months to 1 year; a brachial-ankle PWV decrease (131–133, 199) ranging from 6 months to 2 years after the kidney transplant.

It should be noted that the mean pretransplant cfPWV values in patients studied did not exceed the <10 m/s value, which is recommended in the guidelines (42). This could explain the absence of a further decrease in elastic arterial stiffness after 2 years and clarify why the observed decrease in postransplant BP did not translate in a significant improvement of arterial stiffness. Besides, in the posttransplant period, crPWV did not change significantlly in our population and the calculated PWV ratio was mainly below 1.0 (aortic PWV lower than peripheral PWV). These patophysiological changes are beneficial for a kidney transplant patient, because they are related to the microvasculature's protection from further damage (35). It also supports the idea that kidney transplantation should be the treatment of choice for patients with ESRD.

Several studies revealed the importance of cfPWV in predicting composite recipient outcomes (123, 125, 219). Interesting data were reported by Bahous et al. (124), providing new information about living donor arterial stiffness and its impact on posttransplant graft function in the kidney recipient. Claes et al. (122) found that incident renal transplant patients with posttransplant CV events, in addition to traditional risk factors, had a higher lumbal AoAC score and higher cfPWV values. Similarly, an increased brachial-ankle PWV might predict posttransplant CV events (133). We have failed to confirm the advantage of the arterial stiffness measurement in predicting posttransplant outcomes in our study population. These results might be influenced by the small sample size and only 5 CV events during the 2-year follow-up.

The weaknesses of this research are the following: a small sample size secondary to the low kidney transplant rate in our center in the years of 2015–2016 and patient responsiveness to a secondary measurement of PWV. The main strenghts of our study lie in the longitudinal design and thoroughly selected recipient population (without previous CV events, PAD). We also showed that the significance of a simple chest X-ray scan is often underestimated, and that the aortic arch calcification is ignored.

We did not compare our kidney transplant and dialysis cohorts because of the age mismatch (younger kidney transplant recipients), significantly lower PWV measurement results at the start point and different factors affecting arterial stiffness and vascular calcification in these two cohorts.

8. CLINICAL IMPLICATIONS

Measurements of aortic and brachial arterial stiffness should be incorporated into the routine clinical evaluations of chronic dialysis patients and kidney transplant recipients. It is a simple, noninvasive method that provides not only information about CV outcomes but is beneficial in weighing the long-term CV risk. This research shows that cfPWV is inferior to the calculation of the PWV ratio for identifying patients with vascular calcification as well as for predicting cardiovascular risk in the dialysis population. For every dialysis patient and kidney transplant recipient, the cfPWV and crPWV should be measured at least once per year.

β2-microglobulin is a valuable biomarker, not routinely tested in patients on renal replacement therapy, which is associated with the progression of elastic arterial stiffness. Treatment modalities that lower the concentration of β2-microglobulin in blood and preserve residual renal function should be prioritized for patients with end-stage renal disease.

Usually, clinicians underestimate the information yielded by a simple chest scan and ignore the importance of evaluating of aortic arch calcification in patients with ESRD. This study shows that in every patient with ESRD, the AoAC score should be calculated and evaluated annually.

9. CONCLUSIONS

1. Arterial stiffness and other biomarkers predict aortic arch calcification and two-year cardiovascular risk in patients on maintenance dialysis:
   1.1. The PWV ratio, which reflects the mismatch between elastic and muscular arterial stiffness, C-reactive protein and ferritin, predicts the presence of aortic arch calcification in patients on dialysis;
      1.1.1. The PWV ratio, adjusted for age and mean arterial blood pressure, predicts aortic arch calcification with 77% sensitivity and 82% specificity;
   1.2. An increased C-reactive protein, an elevated total cholesterol level, hypophosphatemia, an elevated parathormone level, an increased hemoglobin level and the presence of aortic arch calcification are associated with an increased cardiovascular event risk in patients on dialysis;
   1.3. Increased PWV ratio adjusted for age, aortic arch calcification and sex is not associated with cardiovascular risk;
   1.4. Carotid-femoral PWV has no cardiovascular predictive value in the analyzed population;

2. Two years of hemodialysis maintenance result in an increased elastic arterial stiffness and decreased muscular arterial stiffness:
   2.1. An increase in mean arterial blood pressure results in an increased elastic and muscular arterial stiffnessess within 6 months of maintenance hemodialysis;
   2.2. A C-reactive protein increase is related to the progression of both elastic and muscular arterial stiffness within 2 years of maintenance hemodialysis;
   2.3. An increased level of β2-microglobulin results in the progression of elastic but not muscular arterial stiffness within 2 years of maintenance hemodialysis.

3. Kidney transplantation results in a decrease of elastic but not muscular arterial stiffness, and it has only one particular effect on aortic arch calcification:
    3.1. Of the kidney recipients, 72.29% had a similar aort arch calcification status in 2 years after undergoing kidney transplantation.

10. PUBLICATIONS, ORAL AND POSTER PRESENTATIONS

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12. SUPPLEMENTS

S1. Studies analyzing cfPWV as a predictor of cardiovascular risk in ESRD.

Study	Year	Participants, age (years)	Follow-up	PWV measurement technique	Outcome	Association
Blacher J et al. (100)	1999	241 HD patients, age 51.5±16.3	72 ±41 months	Transcutaneus Doppler flow recording	CV mortality	PWV >12.0 vs <9.4 m/s OR 5.9 (95% CI, 2.3-15.5)
Blacher J et al. (103)	2001	110 HD patients, age 54±16	53 ±21 months	Transcutaneus Doppler flow recording	CV mortality	Not available
Blacher J et al. (102)	2003	242 HD patients vs. 469 controls, age 52 ±16	78 ±46 months	Transcutaneus Doppler flow recording	CV mortality	Not available
Speer G et al. (104)	2008	98 HD patients, age 63.4 ±14.4	Median 24 months	Applanation tonometry	CV mortality	HR 1.31 (95% CI 1.14-1.50)
Shin SJ et al. (105)	2009	72 HD patients, age 50.4 ±13.0	46 ±33 months	Applanation tonometry	CVE and CV mortality	HR 2.07 (95% CI 1.59-2.79)
Nemeth ZK et al. (106)	2011	98 HD patients, age 63.4 ±4.4	30 (1–51) months	Applanation tonometry	CV mortality	HR 1.16 (95% CI 1.01–1.33)
Verbeke F et al. (98)	2011	1076 HD and PD patients, age 59.2 (no events); 68.1 (events)	Median 2 years	Applanation tonometry	Nonfatal CVE	HR 1.154 (95% CI 1.085-1.228)
Yu WC et al. (107)	2012	145 HD patients, age 55.0 ±15.0	72.6 ±28.5 months.	Applanation tonometry	CV mortality	HR 1.19 (95% CI 1.09-1.29)
Lee JE et al. (99)	2013	97 HD patients, age 56.5 ±12.2	40 (14-42) months	Applanation tonometry	CVE	HR 1.001 (95% CI 1.000-1.002)
Avramovski P et al. (108)	2013	80 HD patients, age 59.3 ±11.8	3 years	Transcutaneus Doppler flow recording	CV mortality	HR 1.4289 (95% CI 1.1696-1.7457)
Xu T et al. (109)	2015	59 PD patients, age 50.82 ±13.23	91 ±21 weeks	Applanation tonometry	Cardio-cerebro-vascular mortality	HR 1.482 (95% CI 1.01–2.176)
London GM et al. (93)	2016	156 HD patients vs. 73 controls, age 54 ±1.25	60 (6-132) months	Applanation tonometry	CV mortality	cfPWV RR 1.36 (95% CI 1.23-1.49); crPWV 1.22 (95% CI 0.99-1.50)
Ferreira JP et al. (110)	2017	278 HD patients, age 53 ±16	74 (41–115) months	Applanation tonometry	CV mortality	Patients <60 years old HR 14.382 (95% CI 7.120-29.047)

HD – hemodialysis, PD – peritoneal dialysis, PWV – pulse wave velocity, cfPWV – carotid-femoral pulse wave velocity, crPWV – carotid-radial pulse wave velocity, CV – cardiovascular, CVE – cardiovascular event, OR – odds ratio, HR – hazard ratio, CI – confidence interval

S2. Studies analyzing brachial–ankle PWV or ambulatory PWV as a predictor of cardiovascular risk in ESRD.

Study	Year	Participants, age (years)	Follow-up	Type of PWV	PWV measurement technique	Outcome	Association
Kitahara T et al. (114)	2005	785 HD patients, age 60.2 ±12.5	33.8 ±10.8 months	baPWV	Ankle-brachial index-form device (oscilliometric method)	CV mortality	baPWV >23.8m/s HR 7.03 (95% CI 1.49-33.08)
Morimoto S et al. (112)	2009	199 HD patients, age 61 ±13	43.2 ±10.2 months	baPWV	Ankle-brachial index-form device (oscilliometric method)	CVE and CV mortality	HR 1.001 (95% CI 0.999–1.003)
Tanaka M et al. (38)	2011	445 HD patients, age 63 ±11	43 ±17 months	baPWV	Ankle-brachial index-form device (oscilliometric method)	CVE and CV mortality	CVE HR 1.07 (95% CI 0.69–1.66); CV mortality HR 2.15(95% CI 0.88–5.19)
Inoue T et al. (111)	2011	197 HD patients, age 66.3 ± 12.0	69 ±45 months	baPWV	Ankle-brachial index-form device (oscilliometric method)	CVE	HR 1.046 (95% CI 1.006–1.086)
Kato A et al. (115)	2012	135 HD patients, age 60 ± 11	63 ± 4 (55-70) months	baPWV	Ankle-brachial index-form device (oscilliometric method)	CV mortality	baPWV ≥16.6 m/s HR 16.9 (95% CI 1.1-251.8)
Wei SY et al. (116)	2016	205 HD patients, age 59.3 ±13.1	4.4 ±1.5 years	baPWV	Ankle-brachial index-form device (oscilliometric method)	CV mortality	baPWV ≥88 cm/s HR 1.006 (95% CI 1.000-1.013)
Sarafidis PA et al. (113)	2017	170 HD patients, age 63.76 ±14.32	28.1 ±11.2 months	48 hour ambulatory PWV	48 hours monitoring with Mobil-O-Graph-NG	CVE and CV morality	HR 1.579 (95% CI 1.187-2.102)

HD – hemodialysis, PWV – pulse wave velocity, baPWV – brachial-ankle pulse wave velocity, CV – cardiovascular, CVE – cardiovascular event, , HR – hazard ratio, CI – confidence interval

S3. Studies analyzing the progression of arterial stiffness in ESRD.

Study	Year	Participants, age (years)	Follow-up	PWV measurement type	Purpose/Hypothesis	Determinants
Demirci MS et al. (122)	2009	49 PD patients, age 51 ±11	6 months	crPWV	To evaluate the relationship between dialysate calcium concentration (1.75 mmol/l vs. 1.5 mmol/l) and arterial stiffness progression.	crPWV progression: in a group with calcium dialysate 1.75 mmol/l
Jung JY et al. (123)	2010	67 PD patients, age 50 ±14	1 year	cfPWV	Fetuin A is associated with vascular calcification and arterial stiffness progression.	cfPWV change: change in mean arterial BP, time-averaged triglyceride concentration.
Matsumae T et al. (126)	2010	148 HD patients, age 62.4 ±1.0	3 years	cfPWV	To determine factors associated with the worsening of arterial stiffness.	cfPWV progression: hepatitis C infection, LDL-C/HDL-C ratio, ankle-brachial blood pressure index.
Iorio BD et al. (125)	2011	132 HD patients, age 65.3 ±16.6	12 months	cfPWV	To evaluate the impact of coronary artery calcification on the progression of arterial stiffness.	PWV increased in patients with a progression of coronary artery calcification from 8.8 ±1.7 to 11.0 ±2.7 m/s, p <0.05.
LeBoeuf A et al. (121)	2011	27 HD patients, age 66 ±13	5.8 ±3.6 months	cfPWV, crPWV	To determine the effect of calcium dialysate (1.37 mmol/l vs. 1.12 mmol/l) on arterial stiffness.	cfPWV progression observed in a group with dialysate Ca 1.37 mmol/l comparing to 1.12 mmol/l. crPWV did not change significantly in groups.
Utescu MS et al. (120)	2013	109 HD patients, age 66 ±19	1.2 ±0.4 years	cfPWV, crPWV	To evaluate progression of cfPWV and crPWV and to evaluate the impact of selected variables on the progression of arterial stiffness.	cfPWV progression: higher plasma pentosidine (P=0.001) crPWV regression: higher CRP, higher baseline cfPWV.

S3 (continuation). Studies analyzing the progression of arterial stiffness in ESRD.

Study	Year	Participants, age (years)	Follow-up	PWV measurement type	Purpose/Hypothesis	Determinants
Avramovski P et al. (108)	2013	80 HD patients, age 59.3 ±11.8 vs. 60 controls (eGFR >60ml/min/1.73m^2), age 57.5 ± 10.9	36 months	cfPWV after dialysis	The comparison of arterial stiffness progression between hemodialysis and controls.	Arterial aging is more pronounced in dialysis patients. cfPWV progression: traditional risk factors, hemoglobin albumin, CRP.
Mac-Way F et al. (73)	2014	18 HD patients on warfarin, age 67 ±15 vs. 54 HD patients without warfarin, age 67 ±15	29 months	cfPWV	Vitamin K deficiency and warfarin use may result in the progression of arterial stiffness.	cfPWV progression: patients on warfarin.
Fortier C et al. (124)	2014	85 HD patients, α-Calcidol <2 μg/wk (n=70) age 65 ±16; α-Calcidol ≥2μg/wk (n=15) age 58 ± 21.	1.2 ± 0.4 years	cfPWV	Active vitamin D therapy results in the progression of aortic stiffness.	α-calcidol ≥2 μg/ week promotes the progression of aortic arterial stiffness.

HD – hemodialysis, PD – peritoneal dialysis, PWV – pulse wave velocity, cfPWV – carotid-femoral pulse wave velocity, crPWV – carotid-radial pulse wave velocity, LDL-C – low density cholesterol, HDL-C – high density cholesterol level, CRP – C reactive protein

S4. Vilnius Regional Biomedical Research Ethics Committee Permission No. 1582000-14-750-268.

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LEIDIMAS
ATLIKTI BIOMEDICININĮ TYRIMĄ

2014-11-11 Nr.158200-14-750-268

Tyrimo pavadinimas:

Arterijų standėjimo svarba širdies kraujagyslių sistemai pacientams sergantiems lėtine inkstų liga: kohortinė perspektyvinė dviejų grupių (1. sergantys lėtine inkstų liga, kai glomerulų filtracijos greitis <90 ml/min; 2. pacientai po inkstų transplantacijos) studija.

Protokolo Nr.:	N18 ArtStand
Versija:	2.2
Data:	2014-10-29
Asmens informavimo ir informuoto asmens sutikimo forma:	Pacientams po inkstų transplantacijos
Versija:	2.2
Data:	2014-10-29
Asmens informavimo ir informuoto asmens sutikimo forma:	Pacientams, sergantiems lėtine inkstų liga, kai glomerulų filtracijos greitis <90 ml/min
Versija:	2.1
Data:	2014-10-29
Duomenų surinkimo anketa:	
Versija:	1.0
Data:	2014-09-25
Protinės būklės mini tyrimas:	lietuviška versija
Versija:	1.0
Data:	2014-09-25
Monrealio pažintinio įvertinimo anketa:	
Versija:	1.0
Data:	2014-09-25
Depresijos ir nerimo sutrikimų vertinimo skalė:	
Versija:	1.0
Data:	2014-09-25
Pagrindiniai tyrėjai:	**Marius Miglinas**
Įstaigos pavadinimas:	Vilniaus Universiteto Ligoninės Santariškių Klinikos
Adresas:	Santariškių g. 2, LT-08661 Vilnius
Leidimas galioja iki:	2018-09-30

Leidimas išduotas Vilniaus regioninio biomedicininių tyrimų etikos komiteto posėdžio (protokolas Nr. 158200-2014/11), vykusio 2014 m. lapkričio mėn. 11 d., sprendimu.

Nr.	Vilniaus regioninio biomedicininių tyrimų etikos komiteto ekspertų grupės vardas, pavardė	veiklos sritis	narių dalyvavo posėdyje
1	doc. dr. Laimutė Jakavonytė	filosofija	ne
2	prof.dr. Jolanta Dadonienė	epidemiologija, medicina	ne
3	doc.dr. Jaunius Gumbis	teisė	ne
4	Genovaitė Bulzgytė	slauga	taip
5	Laura Linkevičienė	odontologija	taip
6	prof.dr. Augustina Jankauskienė	medicina	taip
7	dr. Laura Malinauskienė	medicina	taip
8	Eglė Zubienė	psichologija	taip
9	Ugnė Šakūnienė	pacientų teisės	taip

Pirmininkė Laura Malinauskienė

VILNIAUS UNIVERSITETAS Vilniaus regioninis biomedicininių tyrimų etikos komitetas MEDICINOS FAKULTETAS

LR Asmens duomenų teisinės apsaugos įstatymo 10 str. 3 punktas numato, jog asmens duomenys apie asmens sveikatą automatiniu būdu, taip pat mokslinio **medicininio tyrimo tikslais** gali būti tvarkomi tik pranešus Valstybinei duomenų apsaugos inspekcijai. Šiuo atveju Valstybinė duomenų apsaugos inspekcija privalo atlikti išankstinę patikrą.

Pasibaigus tyrimui, tyrėjas ar tyrimo užsakovas privalo informuoti VRBTEK raštu apie tyrimo pabaigą bei pateikti tyrimo ataskaitos santrauką.

Reikalavimas pateikti pranešimą apie tyrimo pabaigą bei ataskaitos santrauką įsigaliojo nuo 2010 m. gegužės 6 d. Šį reikalavimą rasite Lietuvos Respublikos sveikatos apsaugos ministro įsakymo "Dėl leidimų atlikti biomedicininį tyrimą išdavimo tvarkos aprašo patvirtinimo" (Žin., 2008, Nr. 6-225; 2010, Nr. 55-2706; 2011, Nr. 233-1570; Nr. 67-3184) 18^1 punkte *„Leidimas atlikti biomedicininį tyrimą galioja iki biomedicininio tyrimo paraiškoje nurodytos tyrimo pabaigos datos. Biomedicininių tyrimų užsakovas, jo įgaliotas atstovas ir (ar) pagrindinis tyrėjas per 30 kalendorinių dienų privalo raštu pranešti leidimą atlikti biomedicininį tyrimą išdavusiai institucijai (Lietuvos bioetikos komitetui ar regioniniam biomedicininių tyrimų etikos komitetui) apie tyrimo pabaigą ir per 90 kalendorinių dienų pateikti tyrimo vykdymo ataskaitos santrauką“*.

Įsakymo nuostata taikoma visiems biomedicininiams tyrimams.

S5. The comparison of baseline characteristics in sexes.

	Female (n=50)	Male (n=51)	P-value
Age (years)	56.51 ±15.00	53.59 ±16.29	0.352
Height (cm)	160.44 ±7.27	175.38 ±7.95	<0.001
Weight (kg)	67.82 ±13.16	77.56 ±18.35	0.003
Body mass index (kg/m2)	26.57 ±5.09	25.17 ±5.50	0.191
BSA (m^2)	1.70 ±0.17	1.92 ±0.22	<0.001
Smoking (yes)	2% (1)	25.5%(13)	<0.001
Hypertension (yes)	90% (45)	98% (50)	0.112
Diabetes mellitus (yes)	18.0% (9)	25.5% (13)	0.470
Time on dialysis (days)	1106 (93-6556)	878 (93-5114)	0.935
Kidney disease duration (years)	11 (1.5-40.5)	10 (1.0-30.0)	0.517
Dialysis modality			
Peritoneal	18.0% (9)	7.8% (4)	0.148
Hemodialysis	82.0% (41)	92.2% (47)	
Blood tests			
White blood cells (10e9/L)	6.72 ±2.01	6.87 ±2.14	0.723
Hemoglobin (g/l)	114.92 ±12.15	114.68 ±16.06	0.934
Platelets (10e9/L)	225.46 ±58.00	225.11 ±87.41	0.461
Total protein (g/l)	67.74 ±6.17	67.79 ±10.97	0.570
Albumin (g/l)	38.96 ±3.65	40.07 ±4.41	0.169
Total cholesterol (mmol/l)	5.70 ±1.49	4.77 ±1.21	<0.001
Creatinine (μmol/l)	765.5 (364-1137)	928 (607-1768)	<0.001
Cystatin C (mg/l)	5.67 ±1.44	6.27 ±1.04	0.086
Urea (mmol/l)	22.53 ±6.76	24.26 ±7.33	0.224
C-reactive protein (mg/l)	5.10 (0.30-54.50)	3.81 (0.50-45.10)	0.749
β2-microglobulin (mg/l)	27.68 (14.12-100.36)	35.72 (15.19-85.18)	0.013
Ferritin (μg/l)	420.05(44.00-1459.00)	380.50(49.90-1040.40)	0.802
Uric acid (μmol/l)	356.16 ±78.88	362.11 ±96.48	0.734
PTH (pmol/l)	62.3 (2.1-201.4)	49.2 (0.5-201.4)	0.230
Calcium (mmol/l)	2.68 ±0.19	2.19±0.17	0.058
Phosphate (mmol/l)	1.80 ±0.49	1.96 ±0.64	0.148
Corrected to albumin calcium (mmol/l)	2.28 ±0.17	2.19 ±0.14	0.004
Ca x P products ($mmol^2/l^2$)	4.10 ±1.21	4.28 ±1.30	0.476

S5 (continuation). The comparison of baseline characteristics in sexes.

	Female (n=50)	Male (n=51)	P-value
Hemodynamic and cardiovascular parameters			
Systolic BP (mmHg)	147.92 ±18.66	144.60 ±18.91	0.379
Diastolic BP (mmHg)	97.76 ±12.02	102.04 ±13.42	0.123
Pulse pressure (mmHg)	63.28 ±18.77	56.31 ±15.43	0.044
Mean arterial BP (mmHg)	104.83 ±12.26	106.76 ±13.00	0.446
Heart rate (beats/min)	72.32 ±11.34	72.10 ±10.77	0.920
Central systolic BP (mmHg)	124.55 ±15.63	125.42 ±15.88	0.800
crPWV (m/s)	10.32 ±1.80	10.09 ±1.80	0.538
cfPWV (m/s)	11.57 ±3.54	11.14 ±3.56	0.536
PWV ratio	1.06 (0.60-2.65)	1.07 (0.59-3.40)	0.958
AoAC score (0-16)	2 (0-11)	1 (0-8)	0.419

BSA – body surface are, PTH-parathormone, Ca x P products-calcium phosphate products, BP – blood pressure, cfPWV-carotid-femoral pulse wave velocity, crPWV-carotid-radial pulse wave velocity, PWV ratio-pulse wave velocity ratio, AoAC-aortic arch calcification.

S6. An aortic arch calcification based on a baseline characteristic.

	AoAC (no, n=44)	AoAC (yes, n=57)	P-value
Age (years)	44.98 ±14.43	62.79 ±11.71	<0.001
Male	52.3% (23)	49.1% (28)	0.753
Height (cm)	172.04 ±8.29	164.66 ±11.26	<0.001
Weight (kg)	73.13 ±17.43	72.33 ±16.12	0.815
Body mass index (kg/m2)	24.65 ±5.47	26.84 ±5.03	0.042
BSA (m^2)	1.84 ±0.22	1.78 ±0.22	0.173
Smoking (yes)	15.9% (7)	12.3% (7)	0.600
Hypertension (yes)	95.5% (42)	93.0% (53)	0.694
Diabetes mellitus (yes)	20.5% (9)	22.8% (13)	0.776
Time on dialysis (days)	533 (93 – 5114)	1354 (93 – 6556)	<0.001
Kidney disease duration (years)	9.75 (1 – 31)	10 (2 – 40.5)	0.467
Dialysis modality			
Peritoneal	15.9% (7)	10.5% (6)	0.423
Hemodialysis	84.1% (37)	89.5% (51)	
Blood tests			
White blood cells (10e9/L)	7.07 ±2.21	6.59 ±1.94	0.263
Hemoglobin (g/l)	115.88 ±15.36	113.96 ±13.29	0.510
Platelets (10e9/L)	220.47 ±88.66	229.00 ±60.81	0.430
Total protein (g/l)	67.85 ±6.78	67.61 ±10.27	0.847
Albumin (g/l)	39.47 ±4.55	39.56 ±3.69	0.916
Total cholesterol (mmol/l)	5.44 ±1.51	5.09 ±1.37	0.241
Cystatin C (mg/l)	5.66 ±1.23	6.19 ±1.30	0.069
Urea (mmol/l)	22.80 ±7.93	23.89 ±6.33	0.459
C-reactive protein (mg/l)	2.74 (0.3 – 28.6)	6.00 (0.5 – 54.5)	0.012
β2-microglobulin (mg/l)	31.25 (14.25 – 85.18)	37.99 (15.19 – 100.36)	0.037
Ferritin (μg/l)	344.3 (44.0 – 1024.8)	421.8 (55.1 – 1459.0)	0.018
Uric acid (μmol/l)	363.70 ±91.00	355.66 ±85.92	0.653
PTH (pmol/l)	48.7 (0.5 – 201.4)	54.9 (2.1 – 201.4)	0.768
Calcium (mmol/l)	2.24 ±0.17	2.23 ±0.19	0.686
Phosphate (mmol/l)	1.96 ±0.62	1.82 ±0.54	0.239
Corrected to albumin calcium (mmol/l)	2.23 ±0.16	2.24 ±0.17	0.691
Ca x P products ($mmol^2/l^2$)	4.34 ±1.29	4.07 ±1.22	0.287

S6 (continuation). An aortic arch calcification based on a baseline characteristic.

	AoAC (no, n=44)	AoAC (yes, n=57)	P-value
Hemodynamic and cardiovascular parameters			
Systolic BP (mmHg)	149.88 ±17.73	143.52 ±19.21	0.090
Diastolic BP (mmHg)	105.02 ±12.94	95.85 ±11.33	<0.001
Pulse pressure (mmHg)	59.09 ±15.52	60.28 ±18.90	0.729
Mean arterial BP (mmHg)	109.55 ±12.74	102.97 ±12.85	0.010
Heart rate (beats/min)	70.00 ±10.24	73.94 ±11.35	0.074
Central systolic BP (mmHg)	128.89 ±15.29	121.89 ±15.42	0.038
End-systolic BP	127.40 ±16.17	119.02 ±17.50	0.023
cfPWV (m/s)	9.75 ±2.40	12.59 ±3.79	<0.001
crPWV (m/s)	11.10 ±1.96	9.61 ±1.37	<0.001
PWV ratio	0.88 (0.59-1.68)	1.23 (0.61-3.40)	<0.001

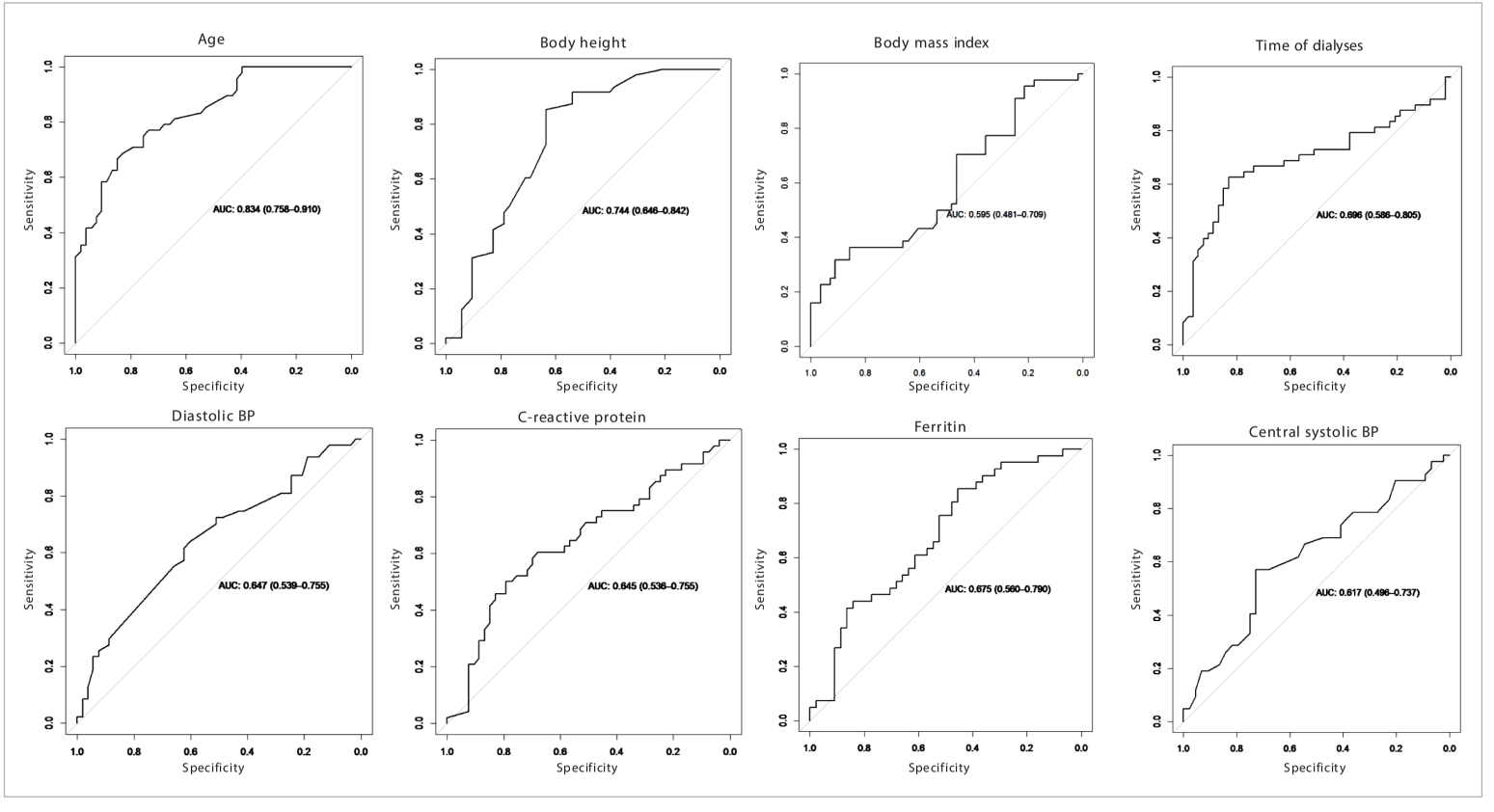
BSA – body surface are, PTH-parathormone, Ca x P products-calcium phosphate products, BP-blood pressure, cfPWV-carotid-femoral pulse wave velocity, crPWV-carotid-radial pulse wave velocity, PWV ratio-pulse wave velocity ratio, AoAC-aortic arch calcification.

S7. The related factors of aortic arch calcification: a univariable logistic regression.

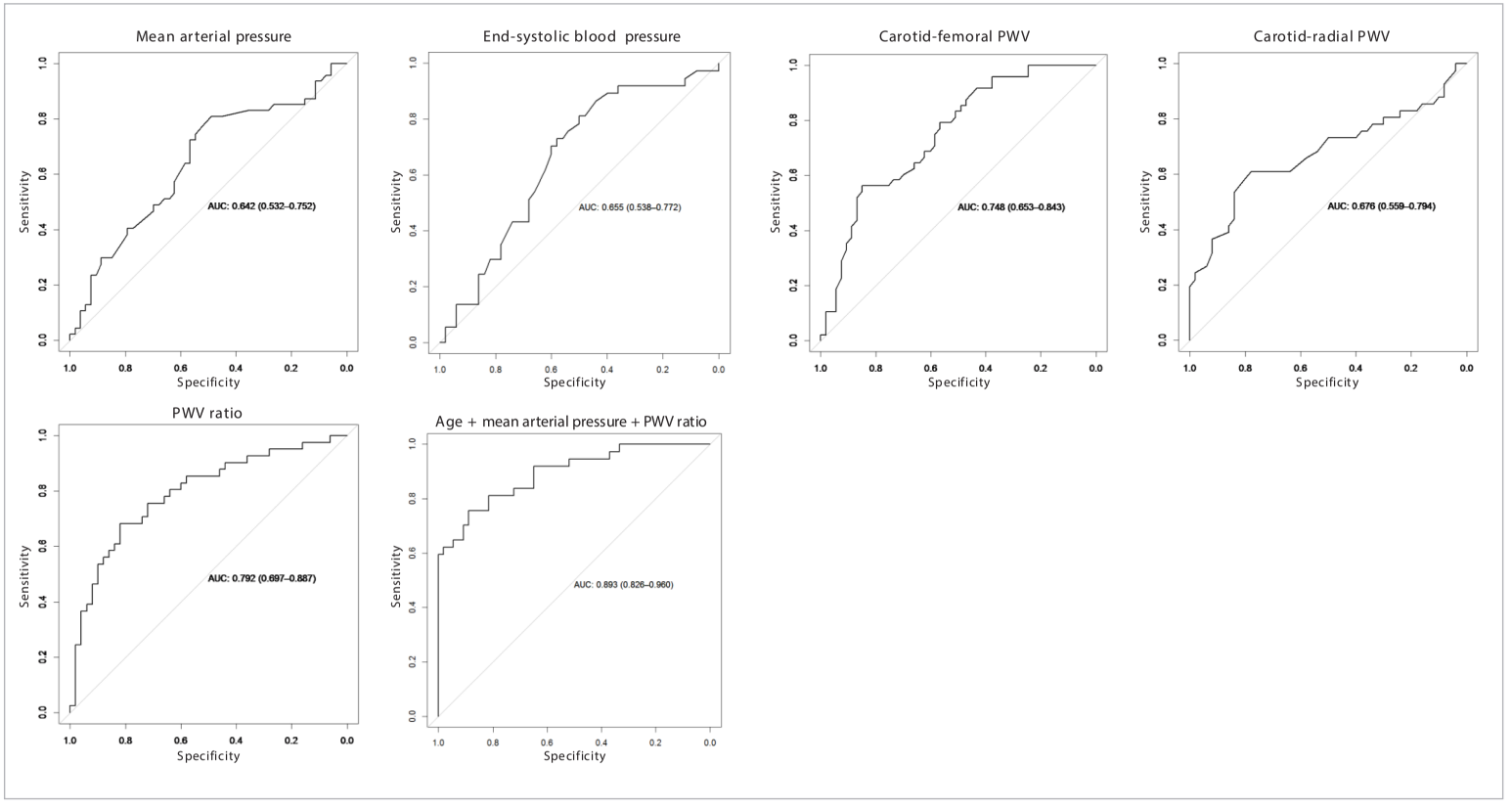
	estimate	SE	OR	95% CI	P-value
Age	0.101	0.021	1.11	1.06, 1.16	<0.001
Height	-0.072	0.022	0.93	0.88, 0.96	<0.001
Body mass index	0.081	0.040	1.08	1.004, 1.17	0.043
Time on dialysis†	1.738	0.501	5.68	2.23, 16.27	<0.001
β2-microglobulin†	2.464	1.273	11.75	1.03, 1.59e+03	0.052
C-reactive protein†	1.084	0.435	2.95	1.29, 7.22	0.012
Ferritin†	1.546	0.711	4.69	1.22, 2.05e+01	0.029
Diastolic BP	-0.066	0.021	0.94	0.89, 0.97	0.002
Mean arterial BP	-0.045	0.018	0.95	0.91, 0.98	0.012
Central systolic BP	-0.030	0.015	0.96	0.94, 0.99	0.043
End-systolic BP	-0.029	0.013	0.97	0.94, 0.99	0.029
cfPWV	0.289	0.078	1.34	1.16, 1.57	<0.001
crPWV	-0.575	0.164	0.56	0.39, 0.75	<0.001
PWV ratio†	9.377	2.203	1.18e+04	2.25e+02, 1.38e+06	<0.001

BP – blood pressure, cfPWV – carotid-femoral pulse wave velocity, crPWV – carotid-radial pulse wave velocity, PWV ratio – pulse wave velocity ratio.
†log10 transformed values.

S8. The ROC curves analysis on aortic arch calcification.



S8 (continuation). The ROC curves analysis on aortic arch calcification.



ROC curves of the variables that have significant impact on aortic arch calcification. The highest area under the curve was observed in model with age, mean arterial pressure and the PWV ratio. BP – blood pressure, PWV – pulse wave velocity.

S9. Cardiovascular event risk association with selected variables in not transplanted patients and in the whole population: univariable and multivariable Cox regression analyses.

		Dialysis (n=81), events n=16			All population (n=101), events n=20	
Unadjusted	**HR**	**95%CI**	**P-value**	**HR**	**95%CI**	**P-value**
Age	1.05	1.01-1.09	0.012	1.05	1.01-1.08	0.006
Sex (male)	0.56	0.20-1.56	0.271	0.79	0.32-1.91	0.604
Diabetes	0.17	0.02-1.30	0.088	0.17	0.02-1.27	0.084
Smoking	0.30	0.04-2.30	0.250	0.31	0.04-2.34	0.26
Height	0.93	0.88-0.98	0.013	0.93	0.89-0.98	0.009
Body mass index	0.99	0.91-1.08	0.980	1.02	0.94-1.11	0.569
BSA	0.10	0.01-1.18	0.068	0.16	0.02-1.50	0.11
Time on dialysis	1.95	0.64-5.94	0.237	1.80	0.67-4.87	0.245
Albumin	0.95	0.81-1.12	0.549	0.98	0.87-1.10	0.769
β2-microglobulin	1.02	0.99-1.05	0.136	1.02	0.99-1.05	0.084
C-reactive protein	1.05	1.01-1.09	0.005	1.05	1.02-1.09	0.001
Ferritin	1.002	0.99-1.003	0.059	1.001	0.99-1.003	0.076
Total cholesterol	1.42	1.11-1.83	0.005	1.30	1.01-1.67	0.039
Corrected calcium	11.81	0.42-3.25e+02	0.114	6.61	0.35-124	0.207
Phosphate	0.31	0.12-0.81	0.017	0.40	0.17-0.94	0.036
PTH	1.47	1.14-2.75	<0.001	2.95	1.65-9.77	0.047
Hemoglobin	1.05	1.01-1.09	0.016	1.03	0.99-1.06	0.082
AoAC score (≥1)	4.60	1.30-16.17	0.017	4.33	1.44-12.98	0.008
Systolic BP	1.008	0.98-1.03	0.58	1.01	0.98-1.03	0.427
Diastolic BP	0.98	0.94-1.03	0.539	0.98	0.94-1.02	0.430
Pulse pressure	1.01	0.98-1.04	0.28	1.01	0.98-1.04	0.242
Mean arterial BP	0.99	0.95-1.04	0.922	1.01	0.97-1.04	0.756
Central systolic BP	1.005	0.97-1.04	0.808	1.01	0.97-1.04	0.615
End-systolic BP	1.013	0.98-1.04	0.435	1.01	0.98-1.04	0.413
cfPWV	1.04	0.91-1.19	0.581	1.04	0.93-1.17	0.442
crPWV	1.16	0.91-1.47	0.229	1.14	0.90-1.45	0.429
PWV ratio	0.69	0.21-2.25	0.543	0.90	0.33-2.41	0.945
		Multivariable/PWV ratio				
Model 5	1.02	1.0001-18.11	0.062	1.07	1.001-73.79	0.100
Model 6	1.01	1.009-12.30	0.038	1.05	1.0009-20.23	0.067
Model 7	1.01	1.008-9.52	0.049	1.07	1.001-47.42	0.081

BSA – body surface area, AoAC – aortic arch calcification, BP – blood pressure, cfPWV – carotid-femoral pulse wave velocity, crPWV – carotid-radial pulse wave velocity, PWV ratio – pulse wave velocity ratio.

Hazard ratio and 95% confidence interval obtained by univariable and multivariable Cox regression analysis are listed. In the whole population older age, beta2-microglobulin concentration above median value, higher C-reactive protein, total cholesterol, hemoglobin levels, PTH level, shorter body height, lower phosphate concentration and AoAC score more than 1 point are associated with increased risk for cardiovascular events.

Model 5: PWV ratio adjusted for age

Model 6: PWV ratio adjusted for age, AoAC score

Model 7: PWV ratio adjusted for age, AoAC score, sex

S10. Major cardiovascular event risk association with selected variables in not transplanted patients: univariable Cox regression analyses.

	Univariable Cox regression		
Unadjusted (events n=7)	**HR**	**95%CI**	**P-value**
Height	0.90	0.82-0.99	0.037
C-reactive protein	1.07	1.02-1.12	0.001
Total cholesterol	1.65	1.17-2.31	0.003
PTH	1.65	1.12-9.33	0.046
Hemoglobin	1.07	1.01-1.14	0.035
Central systolic BP	1.18	1.02-1.38	0.025
End-systolic BP	1.08	1.01-1.15	0.016

PTH – parathormone, BP – blood pressure.
Hazard ratio and 95% confidence interval obtained by univariable Cox regression analysis.

S11. The comparison of antropomethric, laboratory and vascular data in the follow-up period.

Variable	Baseline (n=60)	Follow-up 6 months (n=60)	Follow-up 2 years (n=46)	P-value†	P-value‡
Height (cm)	166.88 ±10.92	166.88 ±10.92	164.30 ±12.64	1	0.262
Weight (kg)	74.34 ±20.70	72.64 ±20.09	66.00 ±11.82	0.648	0.016
Body mass index (kg/m^2)	26.53 ±5.92	25.75 ±5.57	24.69 ±5.00	0.458	0.093
White blood cells (10e9/L)	6.65 ±1.70	6.22 ±1.29	6.31 ±1.76	0.123	0.317
Hemoglobin (g/l)	110.50 ±15.87	115.34 ±14.89	112.27 ±12.43	0.087	0.534
Platelets (10e9/L)	232.92 ±75.19	222.03 ±71.50	192.63 ±63	0.417	0.004
Total protein (g/l)	64.49 ±12.79	68.49 ±5.13	66.20 ±3.88	0.026	0.383
Albumin (g/l)	37.78 ±2.84	38.36 ±2.49	38.74 ±3.21	0.236	0.106
Total cholesterol (mmol/l)	4.86 ±1.59	4.78 ±1.15	4.91 ±1.31	0.752	0.863
Cystatin C (mg/l)	5.51 ±1.09	5.77 ±1.09	7.23 ±1.16	0.193	<0.001
Urea (mmol/l)	23.54 ±5.76	24.06 ±6.73	23.07 ±5.78	0.650	0.678
C-reactive protein (mg/l)	6.7 (0.6-28.6)	3.4 (0.6-23.5)	6.15 (1.2-22.70)	0.203	0.853
β2-microglobulin (mg/l)	36.27 ±12.73	37.03 ±13.06	35.06 ±12.86	0.747	0.630
Ferritin (μg/l)	417.55 (49.90-1038.80)	491.03 (63.6-1459)	372 (61.50-986.30)	0.390	0.637
Uric acid (μmol/l)	387.80 ±64.38	379.50 ±66.70	360.90 ±34.97	0.489	0.012
PTH (pmol/l)	44.95 (2.1-201.4)	54.4 (12.5-201.4)	58.6 (8.8-132.2)	0.435	0.013
Phosphate (mmol/l)	1.83 ±0.60	1.91 ±0.50	1.80 ±0.61	0.421	0.800
Corrected to albumin calcium (mmol/l)	2.24 ±0.15	2.18 ±0.20	2.05 ±0.59	0.065	0.018
Ca x P products ($mmol^2/l^2$)	3.98 ±1.30	4.11 ±1.17	3.74 ±1.74	0.565	0.418
Systolic BP (mmHg)	155.00 ±15.93	152.91 ±15.14	149.50 ±14.30	0.462	0.068
Diastolic BP (mmHg)	88.56 ±10.27	83.21 ±8.85	89.20 ±5.41	0.002	0.702
Pulse pressure (mmHg)	66.44 ±14.52	69.69 ±13.31	60.30 ±15.72	0.203	0.039
Mean arterial BP (mmHg)	110.70 ±10.40	106.44 ±9.45	109.3 ±5.72	0.020	0.412

S11 (continuation)**.** The comparison of antropomethric, laboratory and vascular data in the follow-up period.

Variable	Baseline (n=60)	Follow-up 6 months (n=60)	Follow-up 2 years (n=46)	P-value†	P-value‡
Central systolic BP (mmHg)	133.15 ±16.42	129.47 ±12.96	128.40 ±10.50	0.175	0.090
cfPWV (m/s)	12.73 ±2.57	12.28 ±2.18	14.24 ±4.52	0.303	0.032
crPWV (m/s)	11.53 ±2.75	10.75 ±2.07	8.85 ±0.90	0.111	<0.001
PWV ratio	1.10 (0.48-2.05)	1.17 (0.67-1.68)	1.55 (0.94-2.65)	0.756	<0.001
AoAC score (0-16)	2 (0-9)	2 (0-9)	1 (0-11)	1	0.203

AoAC – aortic arch calcification, BP – blood pressure, cfPWV – carotid-femoral pulse wave velocity, crPWV – carotid-radial pulse wave velocity, PWV ratio – pulse wave velocity ratio.

S11. The comparison of blood test results and vascular parameters.

	Pretransplant N=37	After 12 months N=37	After 24 months N=37	p†	p‡
White blood cells (10e9/L)	6.73 ± 2.00	6.94 ±2.31	8.24 ±4.50	0.900	0.213
Hemoglobin (g/L)	120.79 ± 12.56	134.23 ±16.21	138.47 ±15.35	0.001	<0.001
Platelet (10^9/L)	219.35 ± 53.52	228.42 ±71.86	238.73 ±86.77	0.593	0.356
C-reactive protein (mg/l)	2.49 ± 2.66	2.83 ±6.43	11.20 ± 2.32	0.804	0.07
Ferritin	314.30 (68.10 – 1024.80)	242.95 (27.4-1198.1)	430.4 (20.60-1040.40)	0.812	0.75
Albumin (g/L)	44.34 ± 3.48	-	42 ±2.05	-	0.795
Calcium(mmol/L)	2.39 ± 0.15	2.43±0.16	2.40 ±0.20	0.305	0.973
Ionized calcium (mmol/L)	1.14 ± 0.11	1.16 ±0.11	1.15 ±0.11	0.781	0.619
Phosphate (mmol/L)	1.67 ± 0.50	1.03 ±0.24	1.05 ±0.25	<0.001	<0.001
Parathormone (pmol/L)	71.27 ± 57.54	13.33 ±11.05	12.13 ±8.44	<0.001	0.002
Uric acid (mkmol/L)	292.74 ± 86.22	409.52 ±88.69	365.46 ±71.78	<0.001	0.013
Total cholesterol (mmol/L)	5.90 ± 1.21	5.91 ±0.88	6.42 ±1.20	0.535	0.780
Urea (mmol/L)	19.16 ± 7.53	7.65 ±2.36	7.87 ±2.95	<0.001	<0.001
Creatinine (μmol/L)	830.38 ± 215.31	105.38 ±31.30	108.52 ±30.23	<0.001	<0.001
Vascular parameters					
	N=37	**N=37**	**N=37**		
AoAC score	1 (0-7)	0(1-7)	0 (1-7)	0.110	0.116
	N=37	**N=37**	**N=20**		
Systolic BP (mmHg)	143.78 ± 16.87	132.88 ±17.10	134.54±15.76	0.016	0.029
Diastolic BP (mmHg)	86.43 ± 12.38	87.11±9.87	81.7 ±11.10	0.428	0.028
Mean arterial BP (mmHg)	105.59 ± 12.09	102.36±11.12	99.31±12.10	0.055	0.066
Pulse pressure (mmHg)	57.38 ± 11.23	45.77±10.24	52.84 ±10.76	0.035	0.042
Central systolic BP (mmHg)	125.93 ± 15.73	119.08±12.37	120.34 ±13.62	0.019	0.038
cfPWV	8.91 ± 2.11	8.05±2.00	8.00±1.90	0.020	0.113
crPWV	10.13 ± 1.24	9.80±1.37	9.5±1.80	0.680	0.125
PWV ratio	0,88 ± 0,27	0.82±0.28	0.84±0.29	0.354	0.605

BP – blood pressure; cfPWV – carotid – femoral pulse wave velocity; crPWV – carotid-radial pulse wave velocity; PWV ratio – pulse wave velocity ratio; AoAC – Aortic arch calcification
†p value for pretransplant versus 1-year posttransplant tests results; ‡p value for pretransplanta versus 2-year posttransplant tests results

S12. The comparison of pulse wave velocity values in patients with ESRD.

Study	Patient (n), age (y)	Dialysis modality	crPWV (m/s)	cfPWV† (m/s)	PWV ratio
Utescu MS et al. 2013, France (120)	n=109 age 66 ±19	HD	8.80 ±1.86	12.39 ±4.10	not available
Fortier C et al. 2015, France (164)	n=310 age 67 (56-76)	PD+HD	8.76 ±1.68	12.73 ±4.41	1.59 ±0.52
London GM et al. 2015, France (93)	n=156 (n=74 control) age 54±1.25	HD (without diabetes, no CVE within 6 months)	11.4 ±0.2	11.1 ±0.2	0.97 ±0.01‡
Bia D et al. 2017, Argentina (48)	n=151 (n=283 control) age 58.7 ± 13.5	HD vs. control group	9.66 ±2.92	12.15 ±3.59	1.31 ±0.37
Fortier C et al. 2017, France (97)	n=304 (n=114 control) age 65 (57–77)	PD+HD vs control group (eGFR>45ml/min/1.73m^2)	8.67 ±1.64	12.79 ±4.40	1.61 ±0.51
Our study, 2017, Lithuania	n=101 age 55.0±15.6	PD+HD	10.21 ±1.79	11.35 ±3.54	1.06 (0.59-3.40)

HD – hemodialysis, PD – peritoneal dialysis, n – number, y – years, cfPWV – carotid-femoral pulse wave velocity, crPWV – carotid-radial pulse wave velocity, PWV ratio – pulse wave velocity ratio, eGFR – estimated glomerular filtration rate, CVE –cardiovascular events.

†standardized values

‡originally in this report the PWV ratio was calculated as crPWV/cfPWV, an the result was 1.03±0.01. We converted this result to cfPWV/crPWV ratio.

S13. The comparison of studies analyzing the PWV ratio in the context of different outcomes.

Study	Participants	Follow-up	PWV is superior over cfPWV	Outcome
Niiranen TJ et al. (117)	Framingham Heart Study participants (n= 2114)	12.6 years	No	Cardiovascular death, fatal and not fatal myocardial infarction, unstable angina, stroke and heart failure
London GM et al. (118)	ESRD (n=156) vs. controls (n=73)	60 months (6 to 132).	Both are important	Cardiovascular mortality, all-cause mortality
Fortier C et al. (164)	ESRD (n=310)	29 months (12 to 51)	Yes	All-cause mortality
Our study	ESRD (n=101)	23 months (2 to 25)	Only in predicting all CVE	Cardiovascular death, myocardial infarction, ischemic stroke, coronary revascularization, lower extremity amputation or revascularization, unstable angina

ESRD – end-stage renal disease, CVE – cardiovascular events

S14. The comparison of pulse wave velocity development analyzing studies in ESRD.

Study	Participants, mean age (years)	Follow-up	Baseline PWV (m/s)	Repeated PWV (m/s)	p-value	Increased(↑)/ decreased(↓)
Matsumae T et al. (126)	148 HD patients, age 62.4 ±1.0	3 years	cfPWV 9.57 ±0.17	10.33 ±0.52	0.002	↑
Iorio BD et al. (125)	132 HD patients, age 65.3 ±16.6	12 months	cfPWV CAC progression 8.8 ±1.7	11.0 ±2.7	<0.05	↑
			CAC non-progression 7.5 ±1.9	8.7 ±2.0	NS	Unchanged
Utescu MS et al. (120)	109 HD patients, age 66 ±19	1.2 ±0.4 years	cfPWV 13.17 ±3.79	14.26 ±3.89	<0.001	↑
			crPWV 8.80 ±1.86	8.05 ±1.67	0.31	Unchanged
Avramovski P et al. (108)	80 HD patients, age 59.3 ±11.8 vs. 60 controls (eGFR >60ml/ min/1.73m^2), age 57.5 ± 10.9	36 months	cfPWV after dialysis 11.18 ±2.29	11.82 ±2.34	0.1124†	Unchanged†
Mac-Way F et al. (73)	18 HD patients on warfarin, age 67 ±15 vs. 54 HD patients without warfarin, age 67 ±15	29 months	cfPWV in controls 12.8 ±3.1	13.7 ±3.2	0.1406†	Unchanged†
Our study	60 HD patients, age 57.61 ±13.01	6 and 24 months	cfPWV 12.73 ±2.57	6 months: 12.28 ±2.18	0.303	Unchanged
				2 years: 14.24 ±4.52	0.030	↑
			crPWV 11.53 ±2.75	6 months: 10.75 ±2.07	0.081	Unchanged
				2 years: 8.85 ±0.90	0.026	↓

HD- hemodialysis,eGFR – estimated glomerular filtration rate, PWV – pulse wave velocity, cfPWV – carotid-femoral pulse wave velocity, crPWV – carotid-radial pulse wave velocity, CAC – coronary artery calcification, NS – not significant, p-value – significance level. †calculated by using t-test online (218)

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