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ORIGINAL ARTICLE

Aortic calcifications and arterial stiffness as predictors of cardiovascular events in incident renal transplant recipients

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Summary

Renal transplant recipients have an increased risk of cardiovascular (CV) disease. Arterial stiffness (AS) and aortic calcifications (ACs) are well-known CV risk factors in patients with chronic kidney disease. We aimed to determine the prognostic value of AS and AC in incident renal transplant recipients (RTRs). We conducted a prospective study in 253 single RTR. AC were scored by means of lumbar X-ray. Carotid-femoral pulse wave velocity (PWV) was assessed in a subgroup of 115 patients. AC were present in 61% of patients. After a mean follow-up of 36 months, 32 CV events occurred in the overall group and 13 events in the PWV subgroup. When we accounted for age, gender, and CV history, AC score (HR, hazard ratio 1.09 per 1 unit increase; 95% CI 1.02–1.17) and PWV (HR 1.45 per 1 m/s; 95% CI 1.16–1.8) remained an independent predictor of CV events in Cox-regression analyses. Using receiver operating characteristics, the area under the curve for predicting CV events amounted to 0.80 and 0.72 for sum AC and PWV, respectively. Both AS and AC are strong predictors of future CV events in an incident RTR population. These vascular assessments are readily available and easy to perform, making them ideal tools for further risk stratification.

(ClinicalTrials.gov number: NCT00547040)

Introduction

Renal transplantation (Tx) is the renal replacement therapy of choice to reduce the high cardiovascular (CV) morbidity and mortality in patients with chronic kidney disease (CKD) [1]. Although the incidence of CV events (CVEs) and death after Tx is reduced, it remains high compared to the general population with the highest risk occurring in the first 3 months following Tx [2,3]. Accurate risk stratification of these patients, allowing targeted application of interventions designed to prevent or limit adverse outcome, remains a challenge.

The increased risk after Tx can, in part, be attributed to an overrepresentation of traditional risk factors as well as transplant-specific factors, such as side effects of immunosuppressive drugs [4]. However, vascular damage accumulated prior to Tx probably increases the risk likewise.

The assessment of aortic calcification (AC) and arterial stiffness may help to stratify the CV risk in incident renal transplant recipients (RTRs). Both parameters are well-established and independent predictors of adverse long-term CVEs and mortality in the general population as in patients with CKD [5–9]. Previous studies have shown that the severity of calcification and aortic stiffness also predicts CV outcome in prevalent RTR [10–14]. Prevalent RTR, however, represent a selected population as they survived the "high"-risk immediate postoperative period. Prospective data in incident RTR are scarce, especially regarding the parameters of arterial stiffness and studies combining the two parameters in this population are completely lacking [11–17].

The present prospective observational study addresses the question to what extent vascular damage accrued prior to Tx contributes to an unfavorable CV outcome after Tx.

Materials and methods

Study population

A total of 253 patients receiving a single kidney transplant at the University Hospitals Leuven between October 2006 and March 2009 were enrolled in this prospective study. All subjects included provided signed informed consent at the time of listing.

In a subgroup of 115 patients, enrolled in the Arterial Stiffness and Calcification in RTR Study (ASCIT study; Trial registration: www.clinicaltrials.gov; study number: NCT00547040) measurements of vascular stiffness were performed. The study adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Catholic University of Leuven. Demographic and clinical data were retrieved from the patient files. Kidney allocation was performed according to the eurotransplant kidney allocation system (www.eurotransplant.org). In this system, the selection of potential recipients is based on medical urgency, % of panel reactive antibody level, HLA-A,-B,-DR matching between donor and recipient, ABO blood group rules, waiting time, and donor region. Selected potential recipients are ranked with the help of a point score system. The point score is calculated for all recipients, including 000-mismatched recipients. The recipient with the highest point score is ranked on top and receives the first offer.

Follow-up data were retrieved from the referring centers. Clinical data, extracted from the electronic medical files, included antihypertensive agents, age, body mass index, dialysis duration, dialysis modality, number of Txs, gender, smoking status, CV history, diabetes, and hypertension. CV history was defined as the occurrence of angiographic significant stenosis (>60%), myocardial infarction, percutaneous coronary artery intervention, cardiac surgery, peripheral artery disease, cerebrovascular disease, or significant (>70%) stenosis on carotid ultrasound. Tobacco use was categorized as "none," "past," or "current" smoking. Hypertension was defined as systolic blood pressure >140 or diastolic blood pressure >90 mmHg or the use of antihypertensive therapy. Delayed graft function was recorded as the need for dialysis in the first 7 days after Tx in the postoperative period. Estimated GFR (eGFR) at the time of pulse wave velocity (PWV) assessment was determined by Cockcroft and Gault formula.

Study end points

The primary end points for the study were CVEs. CVEs were defined as major adverse cardiac event (MACE) (coronary artery bypass surgery, percutaneous intervention or myocardial infarction, angor with ECG changes), cerebrovascular accidents or peripheral arterial disease (PAD; claudication with proven stenosis, vascular intervention), and sudden death. Time to first event was analyzed.

Aortic calcification

Aortic calcification was assessed by means of a lumbar X-ray at the time of admission for renal Tx. Calcification of the aorta was scored using a previously validated system in which both the location and the severity of calcific deposits at each lumbar vertebral segment (L1–L4) were evaluated [18]. The composite score for anterior–posterior severity was assigned here as the sum AC score. The scores of individual aortic segments both for the anterior and posterior walls were summed (with a maximum score of 24). Patients were categorized according to the following definitions: (i) below and above the median [referred to as severity AC (SAC)] and (ii) score: 0 (no calcification), 1: score: 1–7 (mild calcification), 2: score: 8–24 (moderate-to-severe calcification) with 8 being the median of patients with calcifications. Lateral lumbar radiographs were analyzed in a blinded fashion by one radiologist (SH). To evaluate intraobserver agreement, 20 X-rays were rescored. Only five X-rays were scored differently with a maximum difference of score ± 1.

Hemodynamic parameters

All hemodynamic measurements were performed by two trained investigators (KC and MD) during the second postoperative week (i.e. between 7 and 14 days; median time of 9 days) Hemodynamic measurements were made in a quiet, temperature-controlled room after 10 min of supine rest.

Blood pressure

Blood pressure was measured with a validated oscillometric device (Omron 507; Omron Corp, Kyoto, Japan) in the nonfistula arm. Blood pressure was calculated as the mean of three measurements taken 1 min apart.

Pulse wave velocity

The SphygmoCor system was used to assess PWV. To determine PWV, we recorded pressure waves at two sites sequentially: carotid-femoral for assessment of aortic PWV. The distance traveled by the pulse wave is measured as the distance between the recording site at the femoral artery to the suprasternal notch minus the distance between the recording site at the carotid artery to the suprasternal notch. PWV was calculated as the path length divided by transit time (m/s). Measurement of PWV values was conducted after abstinence from caffeine or smoking and after an overnight fast without intake of antihypertensive drugs. PWV were dichotomized above and below the median.

Statistics

Parameters are expressed as mean ± SD and median (interquartile range). Differences between groups were assessed by the Wilcoxon rank sum, *t*-test, or chi-squared test when appropriate. Correlations were assessed by the Spearman correlation index. Linear and logistic regression analyses were used to determine the parameters associated with calcification score and PWV.

Receiver operating characteristic (ROC) curves were used to compare the discriminative power of PWV and AC when used as a single parameter to predict outcome. Patient follow-up was censored at the time of graft failure, lost-to follow-up, or last visit (January 2012). Actuarial event-free survival curves were estimated using the Kaplan–Meier method and were compared using the log-rank test.

The Cox proportional hazard model was used to determine the association of AC and PWV with the risk of CVE. To avoid overfitting because of relatively low overall event rates, multiple models with acceptable number of variables were studied. The hazard ratio (HR) and 95% CI were calculated. A *P*-value of <0.05 was considered to be statistically significant. In case of posthoc pairwise comparisons, Bonferroni corrected *P*-values are reported.

Results

Baseline demographics

Patient demographics

Main demographic characteristics and relevant biochemistry of the total patient group are summarized in Table 1. The main cause of renal insufficiency was glomerulonephritis (27%). The majority of patients (93%) were transplanted with a kidney from a deceased donor. The majority of patients were treated with either tacrolimus (83%) or cyclosporine A (13%) in conjunction with mycophenolic acid and corticosteroids. The majority of hemodialysis patients (62%) were on conventional thrice-weekly hemodialysis. Hemodiafiltration, thrice-weekly nocturnal hemodialysis was performed in 34% and 4%, respectively.

Baseline calcifications

Aortic calcifications were present in 61% of RTR. Patients with AC score above the median were older, more over-

Table 1. Baseline demographics in the total patient population and according to CV event and hemodynamic parameters in the PWV subgroup.

	All	Event (n = 32)	No event (n = 221)	*P*-value
Male gender (%)	60	81	57	0.01
CV history (%)	23	75	15	<0.0001
Diabetes (%)	14	18	13	0.45
Hypertension (%)	76	94	74	0.01
Hyperlipidemia (%)	65	71	64	0.0048
Never smoking (%)	49	25	52	0.004
History of Tx (%)	13	25	11	0.03
Age (years)	54 (58)	63.5 (47)	53 (57)	<0.0001
Hemodialysis (%)	75	88	74	0.03
Dial duration (min)	36.6 (156)	37.1 (149.8)	31.5 (156)	0.9750
BMI (kg/m²)	24.7 (23)	24.6 (12)	24.7 (23)	0.5852
Hb (g/dl)	12.7 ± 1.5	13.4 ± 1.4	12.6 ± 1.5	0.005
CRP (mg/l)	3.2 (82)	3.5 (32)	2.9 (82)	0.4571
Total chol (mg/dl)	170.4 ± 43.8	150 ± 38	173 ± 44	0.0061
LDL chol (mg/dl)	84 ± 33	71 ± 32	86 ± 32	0.046
HDL chol (mg/dl)	48 ± 17	49 ± 17	48 ± 17	0.8
HbA1c (%)	5.4 (4.1)	5.5 (2.5)	5.3 (4.1)	0.0038
AC score	2 (24)	11 (24)	1 (21)	<0.0001
AC severity >2 (%)	50	91	43	<0.0001
AC present (%)	61	97	56	<0.0001
Antiplatelets (%)	41	77	35	<0.0001
PWV subgroup	All (n = 115)	Event (n = 13)	No event (n = 102)	
PWV (m/s)	7.6 ± 2	9.3 ± 2.8	7.4 ± 1.8	0.009
SBP (mmHg)	135 (91)	127 (45)	135 (91)	0.33
DBP (mmHg)	75.5 (54)	70 (32)	77 (54)	0.07
PP (mmHg)	55 (70)	58 (53)	55 (68)	0.76
Heart rate (min^{-1})	70.2 ± 11	70.2 ± 10.5	70 ± 11	0.88

Hct, haematocrit; CRP, C-reactive protein; BMI, body mass index; chol, cholesterol; AC, aortic calcification; PWV, pulse wave velocity; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; Dial, dialysis.

Table 2. Baseline demographics according to AC above or below the median.

	Below median (2)	Above median (2)	*P*-value
Male gender (%)	59	62	0.5366
CV history (%)	6	42	<0.0001
Diabetes (%)	11	18	0.1433
Hypertension (%)	66	86	0.0001
Hyperlipidemia (%)	56	73	0.0048
Never smoking (%)	57	40	0.0068
History of Tx (%)	9	17	0.0821
Age (years)	47.5(55)	61(39)	<0.0001
Hemodialysis (%)	74	77	0.7983
Dial duration (min)	33.4 (150)	39 (156)	0.1266
BMI (kg/m²)	23.4 (21.5)	25.2 (21.7)	0.0001
Hb (g/dl)	12.6 ± 1.5	12.8 ± 1.4	0.07
CRP (mg/l)	2.4 (82.4)	3.7 (43.9)	0.0118
Total chol (mg/dl)	171.4 ± 48	169 ± 40	0.8099
LDL chol (mg/dl)	84 ± 34	83.2 ± 32	0.9
HDL chol (mg/dl)	49.4 ± 17	48 ± 17	0.4
HbA1c (%)	5.2 (4.1)	5.4 (3.9)	0.0008
Antiplatelets (%)	28	54	<0.0001
PWV (m/s)	7.1 ± 1.7	8.2 ± 2.2	0.004

Hct, hematocrit; CRP, C-reactive protein; BMI, body mass index; chol, cholesterol; AC, aortic calcification; PWV, pulse wave velocity.

Table 3. Uni-and multivariate analyses of calcification above and below median (only significant values are shown).

	Analyses above and below median			
	Univariate		Multivariate	
Variable	OR	CI	OR	CI
Age (years)	1.118	1.085–1.152	1.109	1.075–1.145
CV history (absence versus presence)	0.081	0.035–0.188	0.145	0.058–0.364
Current or former smoker versus nonsmoker	1.991	1.207–3.284	2.119	1.110–4.043
Hypertension (absence versus presence)	0.304	0.162–0.571		
Log CRP	1.276	1.02–1.6		
PWV	1.336	1.08–1.65		
Hyperlipidemia (absence versus presence)	0.467	0.274–0.795		

CV, cardiovascular; CRP, C-reactive protein.

weight, and had higher values of C-reactive protein (CRP) and HbA1c. A larger proportion of patients with the higher score were hypertensive and current or former smokers. They also had a higher burden of CV diseases (Table 2). Older age, a CV history, prior or current smoking, hypertension, high CRP, higher PWV, and hyperlipidemia were found to be associated with AC score above median in univariate logistic regression. In the multivariable model, age, CV history, and smoking status were identified as independent determinants of AC (Table 3).

Arterial stiffness

Arterial stiffness was assessed in a subgroup of patients ($n = 115$). Patients with PWV above the median were older, more overweight, and had higher systolic blood pressure and a higher burden of CV diseases (Table 4). There was no difference in calculated creatinine clearance or eGFR and history of acute rejection or delayed graft function at the time of measurements (data not shown).

Multivariate logistic regression showed that CV history, increasing age, and systolic blood pressure were significant predictors of a PWV above the median. Similar independent determinants were identified in linear regression analysis (data not shown). Of note, AC were not retained in the multivariate model.

When we compared the group of patients who underwent PWV analysis to the total patient group, we found that the patients in the PWV group were younger ($P = 0.01$) and more on peritoneal dialysis ($P = 0.02$). There were no differences in presence of calcifications or AC score.

Event analysis

All patients were followed up for 36 ± 16 months. During this time period, 32 CVEs occurred. These CVEs were as follows: three patients died of CV causes, 17 patients experienced a MACE, nine patients suffered from PAD, and three patients had a cerebrovascular accident. Fifty percent of the events ($n = 16$) occurred within the first year after Tx. Table 1 demonstrates the baseline demographics, relevant biochemical and vascular parameters in patients with and without CVEs. Patients experiencing a CVE were characterized by a higher prevalence of traditional risk factors including male gender, hypertension, tobacco use, older age, hyperlipidemia, and CV history. In addition, these patients were characterized by a higher AC score and a faster PWV.

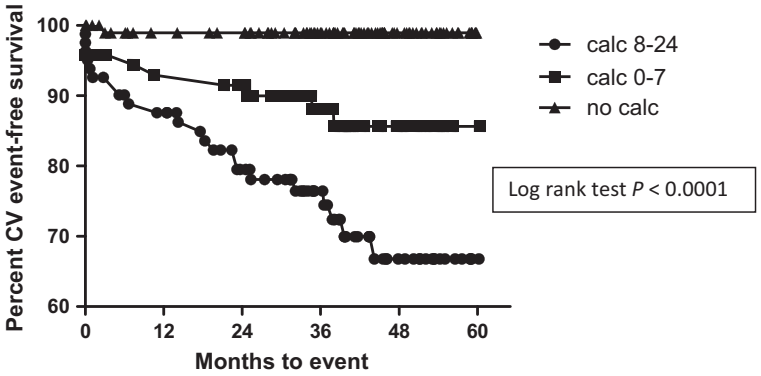
Calcification score

The AC score in patients with an event was significantly higher than in the patient population without an event (Table 1). Using ROCs, the area under the curve (AUC) for predicting CVEs for age was 0.71, the AUC for sum AC was 0.8. Unadjusted Kaplan–Meier cumulative-event curves according to the severity of calcifications in three groups are demonstrated in Fig. 1. There was a significant difference between the patients without calcifications and the groups with intermediate and severe calcifications. The difference between the patients with the highest scores and intermediate scores lost significance after Bonferroni correction ($P = 0.07$).

Table 4. Baseline demographics according to PWV levels above and below median.

	All (n = 115)	PWV ≤ 7.35 m/s	PWV > 7.35 m/s	P-value
Male gender (%)	65	74	56	0.05
CV history (%)	18	9	27	0.009
Diabetes (%)	11	10	11	0.9
Hypertension (%)	74	64	84	0.02
Hyperlipidemia (%)	60	59	62	0.73
Never smoking (%)	44	46	41	0.6
History of Tx (%)	10	12	9	0.5
Age (years)	51 (58)	44 (53)	57 (48)	<0.0001
Hemodialysis (%)	69	69	69	0.99
Dial duration (min)	40 (145)	38 (145)	57 (48)	0.25
BMI (kg/m²)	24.7 (17)	24 (15)	25 (16)	0.04
Hb (g/dl)	12.7 ± 1.5	12.5 ± 1.5	12.8 ± 1.5	0.07
CRP (mg/l)	3.2 (46)	2.5 (29.4)	3.1 (46)	0.42
Total chol (mg/dl)	166 ± 45	169 ± 39.5	164 ± 51	0.55
HDL chol (mg/dl)	48 ± 15	49.7 ± 17	46.5 ± 13	0.4
LDL chol (mg/dl)	81.1 ± 34	84.4 ± 33	78 ± 34	0.9
HbA1c (%)	5.4 (3.8)	5.3 (3.8)	5.4 (3.8)	0.1
SBP (mmHg)	135 (91)	132 (65)	136 (84)	0.05
DBP (mmHg)	77 (54)	77 (54)	75 (40)	0.6
AC score	2 (20)	0 (14)	6 (24)	0.0008
AC present	58	46	71	0.0086

Hb, hemoglobin; CRP, C-reactive protein; BMI, body mass index; chol, cholesterol; AC, aortic calcification; PWV, pulse wave velocity; SBP, systolic blood pressure; DBP, diastolic blood pressure.



Patients at risk	0	12	24	36	48
No Calc	99	88	85	63	28
Calc 0-7	72	63	60	41	22
Calc 8-24	82	69	58	39	17

Figure 1 Kaplan–Meier curve according to severity of calcifications.

Table 5 summarizes the univariate Cox-regression analyses. To avoid overfitting because of the rather low event rate, we performed multivariate Cox-regression analysis as follows. First, a basic multivariate model was built including age, CV history, and gender (Model 1). Then, AC score was added and found to be an independent predictor of outcome together with age and CV history (Model 2: age, CV history, gender, AC score). Finally, we added every other variable with $P < 0.2$ in univariate analysis (HbA1c, history of Tx, smoking status, Hb, and hypertension) to model 2. None of them remained in the final model (Table 6).

We found a negative interaction term of AC and CV history (PE-0.14) in our model indicating that the importance of AC as a predictor is attenuated in patients with CV history. To further investigate this, we used a multivariate

Table 5. Univariate Cox-proportional analysis.

Variable	Parameter estimate	*P*-value	HR	CI
AC present	3.07957	0.0024	21.749	2.97–159.4
AC score	0.16250	<0.0001	1.176	1.11–1.244
PWV	0.37	0.0009	1.45	1.16–1.8
PWV above median	1.60189	0.04	3.8	1.06–14
HbA1c	0.43920	0.0204	1.551	1.07–2.25
Age	0.06464	0.0002	1.067	1.03–1.1
Gender	1.07001	0.0182	2.915	1.2–7.08
History of Tx	0.61171	0.0471	1.844	1.01–3.37
Never smoking	−1.04497	0.0105	0.352	0.16–0.78
CV history	2.51785	<0.0001	12.402	5.56–27.67
Hb	0.34	0.004	1.4	1.12–1.77
Hypertension	1.67	0.02	5.3	1.27–22

AC, aortic calcification; PWV, pulse wave velocity; Hct, haematocrit; CV, cardiovascular; HR, hazard ratio.

Table 6. Cox regression models of factors predicting CV event.

Parameter	Unit increase	*P*-value	HR	95% CI
Model 1: Age, gender, CV history				
Age	Years	0.0350	1.043	1.003–1.085
CV history	1 vs. 0	<0.0001	9.130	3.991–20.885
Model 2: Model 1 plus sum AC				
CV history	1 vs. 0	<0.0001	6.865	2.746–17.17
Sum AC	1	0.0085	1.092	1.023–1.166
Model 3: model 1 plus severity AC				
CV history	1 vs. 0	<0.0001	7.235	3.066–17.08
severity AC	1 vs. 0	0.0241	4.323	1.212–15.42
Model 4: Model 2 plus interaction sum AC CV history				
CV history	1 vs. 0	<0.0001	23.233	4.994–108
Sum AC	1 vs. 0	0.0010	1.204	1.078–1.34
Sum AC × CV history		0.0392	0.87	0.762–0.99
Bivariate models in the PWV subgroup				
PWV	1 m/s	0.037	1.3	1.02–1.69
CV history	1 vs. 0	0.0003	9.8	2.9–33
PWV	1 m/s	0.0001	1.470	1.207–1.972
HbA1c	%	0.0037	1.145	1.045–1.255
PWV	1 m/s	0.01	1.4	1.1–1.84
Age	Years	0.7	1.010	0.958–1.07
PWV	1 m/s	0.08	1.24	0.97–1.6
AC		0.0031	1.16	1.05–0.27

AC, aortic calcification; PWV, pulse wave velocity; CV, cardiovascular; HR, hazard ratio.

Kaplan–Meier analysis stratified by the severity of AC score and presence or absence of CV history (Fig. 2). This demonstrates a 48-month CVE-free survival of 98.6% in the patient group with none of the risk factors. This was significantly different from the three other groups. In patients with CV history, the event-free survival was almost identical in the group with (52.8%) and without (53.0%) severe calcifications (P = NS). In the group without CV history there was a significant difference in survival between the patients with (79%) and without (98.6%) severe calcifications ($P = 0.005$).

Arterial stiffness

In the PWV subgroup only 13 events occurred. Using ROC-analysis, the AUC for the prediction of CVEs was 0.72 for PWV and 0.69 for age. Because of the low event number, we restrained from performing a full multivariate regression analysis, but instead built various bivariate models with variables with $P < 0.2$ in univariate analysis. These bivariate models are summarized in Table 6. PWV remained an independent predictor of CVEs, independent from all these variables but AC

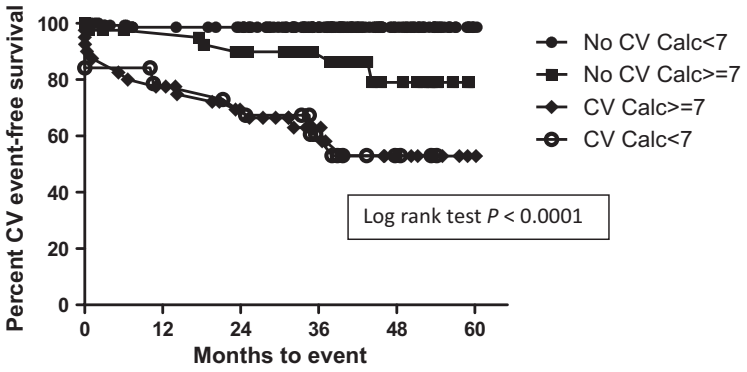
Discussion

The main findings of our study are that both ACs and increased stiffness are prevalent among RTRs and predict CV outcome beyond traditional risk factors.

Vascular calcifications were present in 61% of our incident RTR. Studies evaluating vascular calcification in RTR report prevalence ranging between 24 and 80% [13,16,17]. This large variation mainly reflects case-mix (age, transplant era, time since Tx) and differences in imaging method. Hernandez *et al.* [17] studied a large cohort of incident RTR and observed vascular calcifications in only 24.4%. However, patients in the latter study were younger and vascular calcification was assessed by plain anteroposterior X-ray of abdomen and pelvis. This method is less validated and possibly also less sensitive than conventional lateral lumbar X-ray used in our study [19]. Although multislice or electron-beam computed tomography (CT) remains the golden standard in detecting vascular calcification, lateral lumbar X-ray is less expensive, readily available, easy to perform and associated with lower radiation dose than conventional CT and similar radiation exposure as low-dose CT [20]. Moreover, Bellasi et al. found a very good correlation of lumbar X-ray with coronary calcification scores assessed by CT [21].

Not unexpectedly, tobacco use, older age, and CV history were identified as independent determinants of AC. Older age and tobacco use are classical CV risk factors. The observation of direct association between CV history and vascular calcifications is in agreement with previous studies in both hemodialysis and RTR [22,23]. These associations support the hypothesis that AC score might serve as a phenotype of vascular damage reflecting the cumulative exposure to harmful effects during patient's life.

In the present study, PWV as a measure of aortic stiffness was evaluated in a subgroup of 113 patients during the second postoperative week using the Sphygmocor device. In RTR, most data on PWV are from prevalent cohorts, mak-



Patients at risk	0	12	24	36	48
No CV Calc<7	146	133	128	91	39
No CV Calc≥7	48	44	40	30	12
CV Calc≥7	41	34	32	25	15
CV Calc<7	18	13	12	7	4

Figure 2 Kaplan–Meier curves according to severity of calcifications and cardiovascular history.

ing direct comparison rather difficult. For example, Verbeke *et al.* report a substantially higher PWV in a cohort of prevalent RTR [24]. Data on the long-term evolution of PWV after Tx are lacking or inconsistent [25–29]. Direct comparison between studies is furthermore hampered by methodological differences [30]. Overall, vascular calcification is more prevalent and PWV is faster in dialysis patients [6,9,31,32]. This is not unexpected as renal transplant candidates represent a highly selected subpopulation.

We identified AC score as a strong predictor of CVEs in incident RTR. We found this to be independent from classical risk factors such as HbA1c, age, gender, smoking status, previous history of renal Tx, and CV history. Our data confirm previous studies where coronary artery calcification (CAC) and AC were predictive of outcome in incident and prevalent RTR [15,16]. However, studies performed in the incident population, apart from the study of Hernandez *et al.*, were hampered by small patient size and the exclusion of patients with CV history. Moreover in these studies, both AC and CAC were assessed with electron beam CT, a method which is more costly and not as readily available as the scoring system using lumbar X-ray.

In contrast to other reports, we chose to include CV history in our model because of its clinical importance. We found ACs to be a risk factor of outcome independent of CV history in the multivariate model, but there was a negative interaction of CV history and AC indicating that the predictive value of AC is attenuated in patients with CV history.

Our findings regarding the predictive value of PWV are in line with previous studies in dialysis and prevalent RTR [6,9,10,14]. Data on the importance of PWV, assessed in the immediate postoperative period, are lacking. As for AC there was a clear increase in events along with the increase in PWV leading to an AUC of 0.72 in ROC analysis. In the calcification outcome in renal disease study, a negative interaction was found between PWV and AC score [9]. Unfortunately, because of the low event rate, we were not able to perform these analyses. Further research is needed to define the role of PWV as an independent predictor in incident RTR.

Several limitations need to be acknowledged. Firstly, our study consists of a Caucasian population almost exclusively transplanted with a cadaveric kidney so one should be cautious when extrapolating these results to other patient populations. Secondly, the total event number is rather low, especially in the PWV subgroup. As a consequence, we had to restrict the number of dependent variables in the multivariate model. Whether AC and PWV affect outcome independently remains to be investigated in a larger patient population. Finally, we lack information on thrombotic events of arteriovenous vascular access in HD patients. These thrombotic events are recognized a risk factor for future CV morbidity and mortality in the dialysis population. Strengths of our study include the relatively large sample size and the presence of data on both AC and PWV in a large subpopulation. Dissimilar to previous studies, we did not exclude patients with CV history and therefore our study better reflects the "real-life" situation.

In conclusion, our data indicate that AC and PWV, assessed at the time of Tx, are independent predictors of CVEs in a nonselected RTR population. Both parameters are readily available and easy to assess making them very attractive to help in stratifying the CV risk in incident RTR.

Authorship

KJC, SH and PE: participated in research design, performance of the study, writing of the article, data analysis and final approval of the submitted version. BB and DRK: participated in performance of the study, data analysis and final approval of the submitted version. BM, MN and YV: participated in performance of the study and final approval of the submitted version.

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