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Association between aortic calcification, cardiovascular events and mortality in kidney and pancreas-kidney transplant recipients.

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Abstract

Background: Cardiovascular (CV) disease is the leading cause of death in kidney and simultaneous pancreas-kidney (SPK) transplant recipients. Assessing abdominal aortic calcification (AAC), using lateral spine x-rays and the Kaupilla 24-point AAC (0-24) score, may identify transplant recipients at higher CV risk.

Methods: Between the years 2000-2015, 413 kidney and 213 SPK first transplant recipients were scored for AAC at time of transplant and then followed for CV events (coronary heart, cerebrovascular or peripheral vascular disease), graft-loss and all-cause mortality.

Results: The mean age was 44 ± 12 years (SD) with 275 (44%) having AAC (26% moderate: 1-7 and 18% high: ≥8). After a median of 65 months (IQR 29-107 months), 46 recipient's experienced CV events, 59 died and 80 suffered graft loss. For each point increase in AAC, the unadjusted hazard ratios (HR) for CV events and mortality were 1.11 (95% CI 1.07-1.15) and 1.11 (1.08-1.15). These were similar after adjusting for age, gender, smoking, transplant type, dialysis vintage and diabetes: aHR 1.07 (95% CI 1.02-1.12) and 1.09 (1.04-1.13). For recipients with high versus no AAC, the unadjusted and fully-adjusted HR for CV events were 5.90 (2.90-12.02) and 3.51 (1.54-8.00), for deaths 5.39 (3.00-9.68) and 3.38 (1.71-6.70), and for graft loss 1.30 (0.75-2.28) and 1.94 (1.04-3.27) in age and smoking history-adjusted analyses.

Conclusion: Kidney and SPK transplant recipients with high AAC have 3-fold higher CV and mortality risk and poorer graft outcomes than recipients without AAC. AAC scoring may be useful in assessing and targeted risk-lowering strategies.

KEY WORDS; vascular calcification, cardiovascular disease, kidney transplant, simultaneous pancreas-kidney transplant, mortality.

Introduction

Patients with chronic kidney disease (CKD) have increased atherosclerosis, large-vessel remodelling or arteriosclerosis[1], a propensity for arterial calcification[2] and substantially higher risks for cardiovascular (CV) events[3]. Although kidney transplant recipients have improved survival compared to patients on dialysis, they nevertheless have 3-5 times higher CV risk than people from the age-matched general population[4,5]. For patients undergoing simultaneous pancreas-kidney (SPK) transplantation, this risk may be even greater due to the cumulative vascular burden associated with type 1 diabetes mellitus and end-stage kidney disease (ESKD)[6]. Age and prior CV events are predictive of outcomes[7], but further means to stratify risk and to target treatment strategies are poorly understood.

In the general population abdominal aortic calcification (AAC) is commonly present as focal intimal or atherosclerotic calcifications[8,9] and is associated with increased cardiovascular (CV) risk[10]. The development and progression of AAC is a dynamic, actively regulated process, and is commonly described in patients with ESKD [11,12], in whom the process of vascular calcification is exacerbated by abnormal mineral metabolism and alterations to local and systemic inhibitors of calcification[13]. By the time patients require kidney or SPK transplantation, endothelial dysfunction and atherosclerosis is common, with 50-60% having detectable vascular calcification [6,7,14]. Even after kidney transplantation, calcification of the thoracic aorta and coronary arteries progresses at median rates of 4 and 11%, respectively, per year[15].

AAC can be assessed from lateral spine X-rays that include the abdominal aorta, or from dual-energy X-ray absorptiometry (DXA) lateral spine images, using the Kauppila AAC-24 point semi-quantitative scale[16]. For this scoring method, the anterior and posterior walls of the aorta are divided into 4 regions corresponding to the L1-L4 vertebrae (8 segments). Each segment is scored zero if there is no calcification, 1 for $\leq 1/3^{rd}$ of the segment calcified, 2 for 1/3 to $\leq 2/3^{rds}$ calcified, and 3 for $>2/3^{rds}$ calcified. Scores for the 8 segments are then added for a maximum score of 24/24. In a study of 531 patients admitted for kidney (69%) and SPK (31%) transplantation[7], AAC was significantly associated with age, dialysis vintage, smoking, pre-existing vascular disease, and with diabetes for patients undergoing kidney only transplants[7].

To date, a number of studies have reported associations of AAC to cardiovascular risk and mortality. These include a retrospective study of 253 patients with 3 years median follow up [6], a study using dual-energy X-ray absorptiometry for AAC assessment [17], a study of 134

patients commencing 7 to 9 years after transplantation [18] and a retrospective study of 119 patients, which reported ACC was not predictive of patient survival in multivariable analyses [19]. To date, no study has reported on the association of AAC with cardiovascular or mortality outcomes in SPK recipients.

The primary aim of this study was to determine whether AAC scores at the time of kidney or SPK transplantation were associated with cardiovascular events and all-cause mortality. A secondary aim was to determine the association of AAC with death-censored kidney and/or pancreas graft loss.

Materials and Methods

The manuscript complies with the STROBE reporting guidelines for observational studies [20].

Statement of ethics

The study was approved by the Western Sydney Local Health District Human Research Ethics Committee (LNR/13/WMEAD/64) and complies with the 'Declaration of Istanbul on Organ Trafficking and Transplant Tourism'.

Study population

Recruitment of this cohort has been described previously [7]. Briefly, a lateral lumbar spine X-ray including the abdominal aorta was performed within four weeks of transplantation on 695/900 (77%) consecutive patients admitted to Westmead Hospital, Sydney, for kidney or SPK transplantation between 2000 and 2015. Patients without a lateral spine X-ray included those with post-operative complications, those who returned soon after transplantation to their referring renal unit and those who did not attend their scheduled visit to the clinic. Only first transplant recipients were included and patients with suspected or proven CV disease (coronary artery disease, cerebrovascular disease or peripheral vascular disease) and heart failure were excluded. The final dataset consisted of 623 transplant recipients (**Figure 1A**).

Study population demographics and comorbidities

Pre-transplant demographic and clinical data was collected directly from transplant recipients during their clinic visit within four weeks of transplant, and included body mass index (BMI), intercurrent illnesses including diabetes (none, type I and type II), information on smoking status (never, former and current) and pre-transplant medications. Prevalent co-morbidities and racial background were obtained through data linkage to the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry. Blood was collected within the 24 hours preceding transplantation for routine biochemistry, hormonal studies including intact-parathyroid hormone (PTH) and bone turnover markers as described previously[7].

Abdominal aortic calcification 24 scores (AAC24)

Lateral spine X-rays (example in **Figure 1B**) including the abdominal aorta were performed within 4 weeks of transplantation. AAC was quantified using an established 24 point scoring scale [16], assigned prospectively by an experienced clinician (GJE, MVD) at the immediate post-transplant consultation, with high blinded inter-observer consistency (Spearman's

rho=0.91, P<0.001), as described previously [7]. Suspected and proven CV disease was an exclusion criterion for this study. AAC was examined in three ways; i) semi-continuous variable on the AAC 24 point scale, ii) present vs. absent and iii) using previously published cut points from a prior study of kidney transplant recipients of no AAC, moderate AAC (score 1-7) and high AAC (score 8-24), respectively [6].

Cardiovascular events and all-cause mortality

The primary endpoints were CV events (coronary artery disease, cerebrovascular disease or peripheral vascular disease) and/or deaths (events) and all-cause mortality obtained from ANZDATA. For CV events, patients are classified as 'yes', 'no' or 'suspected'. Patients with 'suspected' or confirmed CV or a CV-related death after transplantation were deemed to have an incident CV event. Time to event data was calculated from transplant date to date of first CV event, date of death or the 31st of December 2015, whichever came first. Death–censored kidney graft loss, death-censored pancreas graft loss and any death-censored graft loss (kidney and/or pancreas) was considered a secondary outcome. Data on kidney and pancreas graft outcomes was obtained from the ANZDATA or the Australian and New Zealand Islet and Pancreas Transplant Registries and graft failure dates corresponded to dates of graft removal or return to dialysis (kidney) or the use of insulin more than 0.5 units per kg per day over a period of 90 consecutive days (pancreas).

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Statistical analysis

Baseline data are presented as mean ± SD, median and IQR or number and (%) where appropriate. The association of the presence of AAC (yes or no) or AAC24 severity (none, moderate or high) with incident CV events (hospitalization or death) was assessed in unadjusted and multivariable-adjusted Cox proportional hazards regression analyses. For the primary analyses for CV events, we treated deaths as censored. For the primary analyses with all-cause mortality we did not censor for graft loss. As a further analysis we censored at the time of kidney graft failure (death with a functioning kidney graft outcome, n=44 or death with any functioning kidney or pancreas graft outcome, n=41). To avoid overfitting models with low event rates (n=41-60), we performed multivariate Cox proportional hazards regression analyses adjusted for either age, or age, gender, smoking, transplant type, dialysis vintage and diabetes. In addition, multivariable models for graft loss included donor factors;

organ source (deceased or living), age and ischemia time (hours). For secondary outcomes of kidney graft loss or any graft loss (kidney and/or pancreas) we undertook forward stepwise Cox regression with age, gender, smoking history, transplant type, dialysis vintage, diabetes, organ source, donor age, ischemia time and HLA mismatch (0-6, number). The final model for both kidney and any graft loss (kidney and/or pancreas) included age and smoking history. We tested for linear trends across AAC categories by using the median AAC24 value for each category (low = 0, moderate = 3, or high = 11). Additionally, dose-response relationships between AAC scores and cardiovascular disease events and all-cause mortality outcomes were examined with restricted cubic splines [21]. Given the high risk of non-CV death, we performed competing-risks analyses based on Fine and Gray's proportional sub-distribution hazards model [22]. Cox proportional hazards assumptions were tested with the Schoenfeld residuals. No violations of the Cox proportional hazards assumptions were detected. Analyses were undertaken using SPSS Version 22 (2012, Armonk, NY: IBM Corp), STATA Version 13 (StataCorp LP, College Station, TX) or R (R Foundation for Statistical Computing, Vienna, Austria).

Results

Cohort characteristics

An overview of the study recruitment is provided in **Figure 1A**. The median follow up of transplant recipients was 65 months (IQR 29-107 months). SPK recipients were younger, had lower BMI, shorter dialysis vintage and were less ethnically diverse, all P<0.05, (**Table 1**). Medication data was available in 440 recipients. The percentage of patients prescribed calcium-based phosphate binders, calcitriol and cinacalcet prior to transplant was 75.9%, 44.6% and 5.2% respectively. There were no statistically significant differences in the risk of CV events (7.5% vs. 7.3%, P=0.930) or deaths (10.3% vs. 9.0%, P=0.598) between SPK and kidney transplant recipients. AAC24 scores were skewed in both the kidney transplant and the SPK transplant recipients.

Presence of AAC and cardiovascular events and all-cause mortality

Of 623 kidney and SPK transplant recipients, 275 (44%) had detectable and 348 (66%) had no detectable AAC at time of transplantation. For transplant recipients with no detectable AAC, 3.7% had a CV event while 5.5% died of any cause. For transplant recipients with detectable AAC, 12.0% had a CV event while 14.5% died of any cause. Kaplan Meier survival plots for time to CV events and to death are presented in **Figure 2 a & b**. When investigating kidney and SPK transplant recipients separately, similar findings were seen (**Figure 3 a-d**). No interaction was observed between AAC24 scores and transplant type for CV events (P=0.578) or all-cause mortality (P=0.153). Transplant recipient groups were therefore combined for the main analyses.

AAC scores as continuous measures

In unadjusted analyses for each 1 point increase in AAC24 score there was a 11% increase in risk of CV events (HR 1.11 95%CI [1.07-1.15], P<0.001 and all-cause mortality HR 1.11 95%CI [1.08-1.15], P<0.001). For each 1 point increase in AAC24 score there was a 7-8% increase in age and multivariable-adjusted risk of CV events (age-adjusted HR 1.08 95%CI [1.04-1.13], P<0.001 and multivariable-adjusted HR 1.07 95%CI [1.02-1.12], P=0.005). Similarly, for each 1 point increase in AAC24 score there was an 8-9% increase in age and multivariable-adjusted risk of all-cause mortality (age-adjusted HR 1.09 95%CI [1.06-1.13], P<0.001 and multivariable-adjusted HR 1.08 95%CI [1.04-1.13], P<0.001). In the multivariable-adjusted restricted cubic spline regression model there was an increasing

gradient of estimated CV event and all-cause mortality risk with increasing AAC24 scores (**Figure 4 a & b**).

Presence of AAC and CV events and all-cause mortality

In recipients with no AAC, the rate of CV events was 6.2, 95%CI (3.6-10.7) per 1000 person years and deaths was 9.0, 95%CI (5.7-14.1) per 1000 person years. By comparison, in recipients with AAC, the rates of CV events and deaths were 21.3, 95%CI (15.1-29.9) and 24.7, 95%CI (18.1-33.6) respectively. In univariate analysis recipients with any AAC had a HR of 3.50 95%CI (1.82-6.58) for CV events and 2.80 95%CI (1.62-4.83) for all-cause mortality (both P<0.001). In age and multivariable-adjusted analyses the presence of AAC was associated with at least twice the relative hazard of having a cardiovascular event or dying from any cause (**Table 2**).

Severity of AAC and cardiovascular events and all-cause mortality

Of the 623 patients, 348 (55.9%) had no AAC, 162 (26.0%) had moderate AAC (score 1-7) and 113 (18.1%) had high AAC (score 8-24). Using these cut points, Kaplan Meier survival estimates for CV events and all-cause mortality by the severity of AAC are presented in **Supplementary Figure 1**. The rate of CV events per 1000 person years was 6.2, 95%CI (3.6-10.7) in recipients with no AAC, 14.3, 95%CI (8.5-24.1) in recipients with moderate AAC and 33.2, 95%CI (21.2-52.1) in recipients with high AAC. The rate of all-cause mortality per 1000 person years was 9.0, 95%CI (5.7-14.1) in recipients with no AAC, 11.9, 95%CI (6.7-20.9) in recipients with moderate AAC and 45.8, 95%CI (31.7-66.4) in recipients with high AAC. In unadjusted Cox proportional hazards analysis, transplant recipients with high AAC had 5-6 times higher relative hazards of CV events and all-cause mortality (5.90 95%CI [2.9, 12.02] and 5.39 95%CI [3.00-9.68], both P<0.001). Recipients with moderate AAC had higher relative hazards for CV events than those with no AAC HR 2.22 95%CI (1.04-4.73), P=0.039. In age-adjusted models, transplant recipients with high AAC had at least 3 times the relative hazards for CV events and all-cause mortality compared to recipients with no AAC. This remained significant in multivariable-adjusted models (**Table 2**).

Graft loss

Overall 80 recipients lost any graft, comprising 42 [10.2%] of kidney recipients and 38 [17.8%] of SPK recipients, (P=0.007). Kidney graft loss occurred in 60 transplant recipients (kidney only 42 [10.2%] and SPK 18 [8.5%], P=0.567), while 20 SPK recipients lost their

pancreas graft and 4 lost both the pancreas and kidney. There was no significant increase in age-adjusted risk for death-censored a) kidney, b) pancreas, or c) any graft loss graft loss per 1 point increase in AAC24 score (age-adjusted HR 1.04 95%CI [0.99-1.09], P=0.136, HR 1.03 95%CI [0.94-1.12], P=0.552 and HR 1.04 95%CI [1.00-1.09], P=0.069, respectively). This was similar in multivariable-adjusted analyses. For transplant recipients with detectable versus no detectable AAC, there was no difference in graft loss in unadjusted (data not shown) age-adjusted or multivariable-adjusted analyses (**Supplementary Table 1**). In unadjusted analyses recipients with the most severe AAC (AAC24 ≥8) did not have increased relative hazards for graft loss compared to those with no AAC (HR 1.30 95%CI [0.75-2.28], P=0.351). However in age and smoking history-adjusted analyses, recipients with severe AAC had 1.9 times higher relative hazard for graft loss compared to those with no AAC (**Supplementary Table 1**).

Further analyses

When death from any non-CV cause was considered in competing risk analyses for CVD outcomes, findings were similar to the primary analyses (**Supplementary Table 2**). Similarly, when death from any cause was included in competing risks analyse for kidney graft loss or any graft loss, there was no alteration of the overall results (**Supplementary Table 2**). Finally, including death with a functioning kidney graft or death with any functioning graft in analyses, strengthened the observed association between AAC and mortality (severe AAC vs no AAC, aHR 4.42 [2.04-9.62], p<0.001).

Discussion

This prospective study highlights several important and novel findings. Firstly, for patients undergoing kidney and SPK transplantation, the presence and the severity of AAC was associated with CV events and mortality, with no significant differences between kidney and SPK transplant recipients over time. Secondly, we report a continuous, positive relationship of AAC scores to cardiovascular risk and mortality. Thirdly, we report for the first time that severe AAC is associated with kidney and/or pancreas graft loss. High AAC scores may be surrogates for reduced graft perfusion or a greater propensity for vascular damage.

Conventional risk factors that are markers of pathological processes leading to blood vessel damage consistently underestimate CV risk [23] or do not improve net reclassification compared to age, gender and eGFR in kidney transplant recipients[24]. Vascular calcification on the other hand is a structural measure of the amount of damage to the blood vessel and has been shown to be strongly associated with increased risk of CV events[6,17]. The increased risks in this study were particularly evident in those with AAC24 scores ≥8, similar to some earlier reports of transplant recipients. However, unlike those studies, we excluded people with prior transplantation or a history of CV disease, both of which could influence the accuracy of AAC to predict CV outcomes.

In a retrospective study of 253 kidney transplant recipients [6], the authors reported a relative HR of 1.09 per 1 point increase in AAC24 score with a univariate HR of 3.1 in kidney transplant recipients with high AAC. In a retrospective study of 119 older kidney transplant recipients [19], AAC24 scores >2 were associated with a relative risk of 3.8 for CV events, compared to those with AAC24 scores of 0-2. A study of 701 kidney transplant recipients using DXA images to assess AAC[17], found that after adjusting for CV risk factors, transplant recipients with higher AAC had an increased relative hazard of 2.78 for cardiovascular events, compared to recipients with no AAC. Taken together, these data and the current study support the concept that transplant recipients with AAC, and particularly those with high AAC scores, are at high risk for future CV events.

The Kidney Disease Improving Global Outcomes (KDIGO) CKD-MBD guidelines suggest that a lateral abdominal radiograph can be used to detect the presence or absence of vascular calcification in patients with CKD G3a–G5D, and that patients with known vascular calcification are at highest CV risk[25]. However, neither the KDIGO CKD-MBD nor transplantation guidelines[26] comment on the value of AAC screening to identify

individuals at high CV risk at the time of transplantation. While lateral spine radiographs are relatively low radiation, equivalent to approximately 20 days of natural background radiation [27], lateral DXA may also be used to evaluate AAC, with a much lower radiation exposure[24].

Because capturing these images is safe, simple and inexpensive, this study supports AAC screening in patients undergoing kidney or SPK transplantation. Once identified, patients at greatest risk could be targeted for intensive modification of 'traditional' CV risk factors, which may have greater impact on outcomes once the calcifying ESKD milieu improves. In addition, these patients could be targeted to assess modifications in the prescription of calcium and activated vitamin D, the addition of supplemental vitamin K or magnesium, and introduction of drugs with potential to delay progressive vascular calcification. Patients with high AAC scores might also be considered for more intensive monitoring of graft function

For patients with type 1 diabetes, successful SPK transplantation removes the need for insulin injections, restores normal glycaemic control and reverses systemic microvascular structural abnormalities [28]. SPK recipients have slower progression of coronary atherosclerosis (minimum obstruction diameter loss 0.037 mm/year vs 0.061 mm/year). When patients with type 1 diabetes undergoing SPK or kidney-only transplantation are compared, SPK recipient have greater regression of atherosclerosis (38% vs. 0%) [29]. Compared to kidney-only transplantation, these SPK recipients have improved long-term survival, predominantly from 5 years after transplantation [30]. However, we observed similar associations between AAC scores and incident CV events and mortality in both kidney-only and SPK recipients, suggesting that pre-transplant vascular damage is a major driver of later CV and mortality risk. Therefore strategies to monitor and intervene early to reduce pre-transplant AAC are warranted. Furthermore, our findings support the concept that AAC is a stable marker of long-term CV and all-cause mortality risk in bother groups of transplant recipients.

This study has some limitations and a number of strengths. Firstly, AAC prevalence in this study is likely to underestimate that of older dialysis patients, patients with type 2 diabetes mellitus or prevalent CV disease, who are often excluded from transplantation. Therefore our findings may underestimate the association of AAC, CV events and mortality in the general dialysis population and for transplant recipients with pre-existing CV disease. As indicated in the methods, some transplanted patients were not included in these analyses, which may have introduced selection bias. Also, the relatively young age of these kidney and

SPK recipients resulted in a low rate of CV events and deaths. Furthermore, we did not collect or adjust for pre-transplant CV risk factors such as low density lipoprotein cholesterol or CV medication use such as statins, which may have attenuated the relationship between AAC and CV events. Due to patient numbers, we undertook minimally adjusted models for associations of AAC to graft survival that did not include induction therapy or immunosuppressive medications and pre-transplant laboratory data. Including these may have attenuated the observed associations. Finally, our findings may not be generalisable to studies using other imaging modalities or scoring systems.

Study strengths include it being the largest and first prospective study using standard X-ray to assess patient and graft outcomes, and the first to include a large cohort of SPK recipients. Secondly, we describe the continuous, positive relationship between AAC scores and cardiovascular event and all-cause mortality risk. Additional strengths include comprehensive, accurate pre and post-transplant data collection in the clinic and in real time by the ANZDATA Registry. Finally, this is the first study to perform competing risks analysis or death with a functioning graft analyses.

In conclusion, in a large cohort of kidney and SPK transplant recipients, AAC on lateral spine radiographs identified transplant recipients at high risk of cardiovascular events and all-cause mortality. For secondary outcomes, recipients with severe AAC at transplantation also had significantly poorer graft outcomes compared to those with no AAC. In patients with high AAC scores detected at the time of kidney or SPK transplantation, future studies should evaluate whether, compared to usual care, intensive interventions aimed to reduce CV risk and progressive vascular calcification might impact incident CV events and mortality.

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Data sharing statement: Due to ethical restrictions related to patient privacy, raw data are available upon request, subject to standard approval from the data custodian: Prof. Grahame Elder g.elder@garvan.org.au.

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Table 1. Baseline characteristics of the study population stratified by abdominal aortic calcification (AAC) scores.

	Whole cohort* (n=623)	Kidney only (n=410)	Simultaneous pancreas-kidney (n=213)
Age, years, mean ± SD	44.1 ± 11.9	47.0 ± 12.8	38.5 ± 7.0
Gender, (%)			
Female (%)	257 (41.3)	161 (39.3)	96 (45.1)
Male, (%)	366 (58.7)	249 (60.7)	117 (54.9)
Body mass index, kg/m^2, mean ± SD†	25.9 ± 4.4	26.6 ± 4.6	24.5 ± 3.5
Dialysis type, number (%)**			
Haemodialysis (%)	329 (53.8)	230 (57.1)	99 (47.6)
Peritoneal dialysis (%)	185 (30.3)	119 (29.5)	66 (31.7)
Pre-emptive (%)	97 (15.9)	54 (13.4)	43 (20.7)
Dialysis vintage, months, median [IQR]	20.0 [6.0-48.0]	29.0 [9.0-60.5]	12.0 [3.0-30.0]
Ethnicity, number (%)			
Asian (%)	80 (12.8)	77 (18.8)	3 (1.4)
Caucasian (%)	496 (79.6)	297 (72.4)	199 (93.4)
Other (%)	47 (7.5)	36 (8.8)	11 (5.2)
Smoking history, number (%)‡			
Never (%)	389 (63.1)	261 (64.1)	128 (61.2)
Previous (%)	180 (29.2)	114 (28.0)	66 (31.6)
Current (%)	47 (7.6)	32 (7.9)	15 (7.2)
Diabetes, number (%)			
Never, (%)	352 (56.5)	352 (85.9)	0 (0)
Type I (%)	225 (36.1)	12 (2.9)	213 (100)
Type II (%)	46 (7.4)	46 (11.2)	0 (0)
Calcium, (mmol/L), median [IQR]	2.30 [2.19-2.43]	2.30 [2.19-2.44]	2.31 [2.21-2.39]
Phosphorus, (mmol/L), median [IQR]	1.60 [1.28-1.95]	1.55 [1.24-1.89]	1.69 [1.37-2.02]
Parathyroid hormone, (pmol/L), median [IQR]	34.2 [15.5-63.8]	35.8 [14.5-70.7]	32.7 [18.0-51.7]
Alkaline phosphatase, (U/L), median [IQR]	102 [75-145]	92 [70-138]	120 [93-154]
Donor factors			
Donor age, years, mean ± SD	41.3 ± 16.0	48.5 ± 13.7	27.3 ± 9.4
Donor ischemia time, hours, mean ± SD	8.4 ± 4.7	7.5 ± 5.1	10.4 ± 2.8
Donor type			

Deceased donor,	421 (67.6)	208 (50.7)	213 (100)
Living donor,	202 (32.4)	202 (49.3)	0 (0)
HLA-mismatches	3.6 ± 1.8	3.2 ± 1.8	4.3 ± 1.2

Data expressed as mean ± SD, median [IQR=interquartile range] or number and (%). * For patients undergoing simultaneous pancreas-kidney transplants, the cause of ESKD was type 1 diabetes mellitus. For patients undergoing kidney only transplants, the most common causes of ESKD were glomerulonephritis, polycystic kidney disease and vesicoureteric reflux.
†Data available for 488 recipients. **Data available for 611 recipients. ‡Data available for 616 recipients.

Table 2. Cox regression for CV events or all-cause mortality stratified by the presence and severity of abdominal aortic calcification (AAC).

	Number (%)	Age-adjusted HR (95% CI)	P value	Multivariable-adjusted HR (95% CI)*	P value
Presence of AAC (any)					
Cardiovascular event	46				
No AAC (AAC24 score 0)	13/348 (3.7)	1 (reference)		1 (reference)	
Any AAC (AAC24 score 1-24)	33/275 (12.0)	**2.53 (1.29-4.96)**	**0.007**	**2.23 (1.11-4.50)**	**0.024**
All deaths	59				
No AAC (AAC24 score 0)	19/348 (5.5)	1 (reference)		1 (reference)	
Any AAC (AAC24 score 1-24)	40/275 (14.5)	**2.07 (1.16-3.68)**	0.014	1.81 (0.99-3.31)	0.053
Severity of AAC					
Cardiovascular event	46				
No AAC (AAC24 score 0)	13/348 (3.7)	1 (reference)		1 (reference)	
Moderate AAC (AAC24 score 1-7)	14/162 (8.6)	1.79 (0.83-3.87)	0.141	1.71 (0.78-3.75)	0.183
High AAC (AAC24 score ≥8)	19/113 (16.8)	**4.04 (1.89-8.67)**	**<0.001**	**3.51 (1.54-8.00)**	**0.003**
P for trend†		**<0.001**		**<0.001**	
Any death	59				
No AAC (AAC24 score 0)	19/348 (5.5)	1 (reference)		1 (reference)	
Moderate AAC (AAC24 score 1-7)	12/162 (7.4)	1.09 (0.52-2.28)	0.815	1.05 (0.50-2.22)	0.902
High AAC (AAC24 score ≥8)	28/113 (24.8)	**3.88 (2.05-7.34)**	**<0.001**	**3.38 (1.71-6.70)**	**<0.001**
P for trend†		**<0.001**		**<0.001**	

Abbreviations: AAC; Abdominal aortic calcification, CV; Cardiovascular event, HR; hazard ratio. *Cox proportional hazards regression analyses were adjusted for age or age, gender, smoking history, type of kidney transplant (kidney only or SPK), dialysis vintage and diabetes. Values in bold p<0.05 compared to recipient with no AAC. †P values are a trend test using the median values of each AAC category in the Cox proportional hazards models.

Figure legend

Figure 1. Overview of study including; A) Flowchart of the study participants, B) Example of lateral spine radiograph showing predominantly linear AAC typical of chronic kidney disease.

Figure 2. Kaplan Meier Survival plots (n=623) by the presence or absence of AAC for a) cardiovascular (CV) events (n=46) and b) deaths (n=59). Vertical lines indicate censored individuals.

Figure 3. Kaplan Meier Survival plots by presence of AAC for cardiovascular (CV) events A) kidney only (n=410) and B) simultaneous pancreas-kidney transplant (n=213) and all cause mortality C) kidney only (n=410) and D) simultaneous pancreas-kidney transplant (n=213). Vertical lines indicate censored individuals.

Figure 4. Multivariable-adjusted restricted cubic spline regression for the association between AAC24 scores and a) cardiovascular events and b) all-cause mortality. Adjusted for age, gender, smoking history, type of kidney transplant (kidney only or SPK), dialysis vintage and diabetes.

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A)

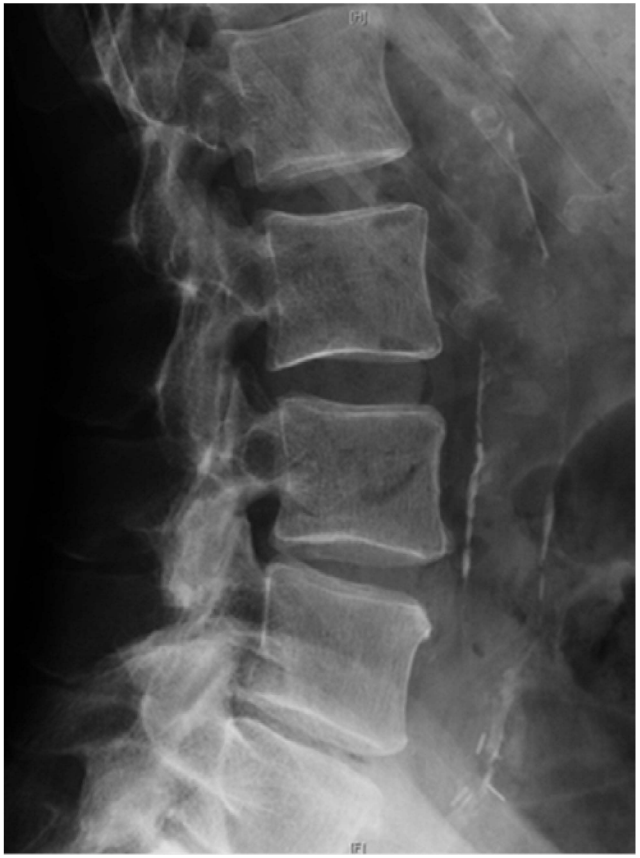
695 kidney or simultaneous pancreas-kidney (SPK) recipients with AAC assessed within 1 month of surgery

39 not first transplant
21 history of CVD
4 not first transplant + history of CVD
8 missing exclusion criteria data

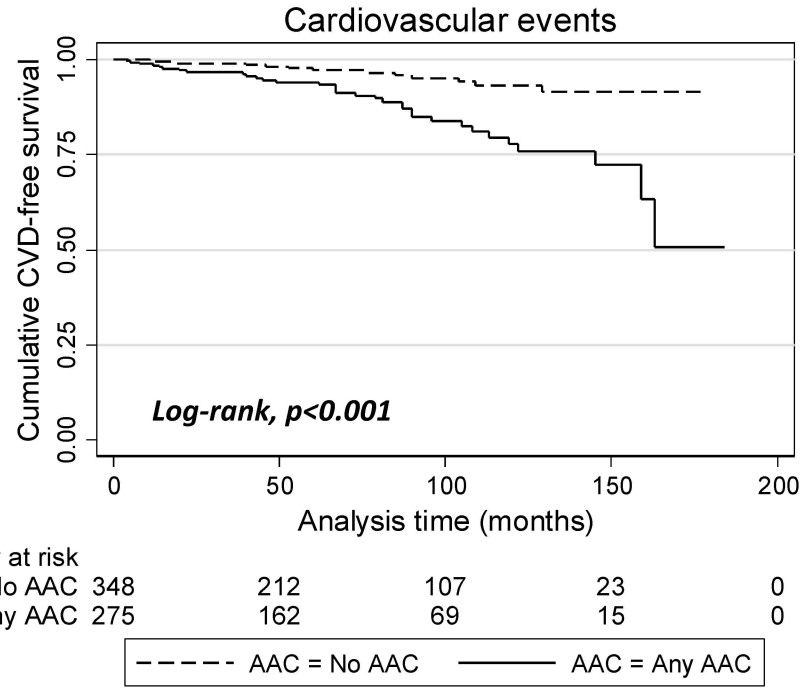
623 recipients with first transplant (410 kidney and 213 SPK)

Kidney graft loss, n=60
Pancreas graft loss, n=24
Any graft loss, n=80
Cardiovascular events, n=46
Deaths, n=59

B)



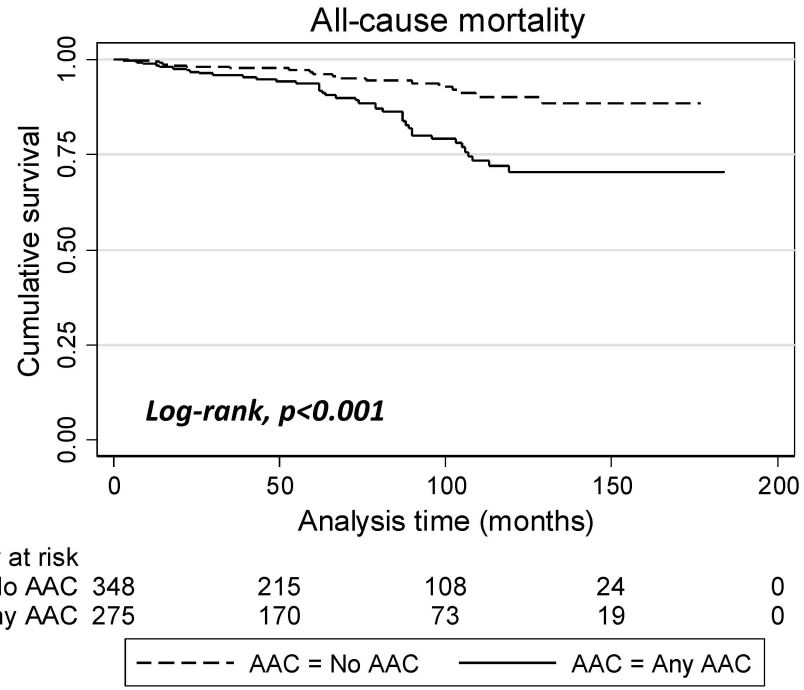
A)



Number at risk					
AAC = No AAC	348	212	107	23	0
AAC = Any AAC	275	162	69	15	0

AAC = No AAC AAC = Any AAC

B)



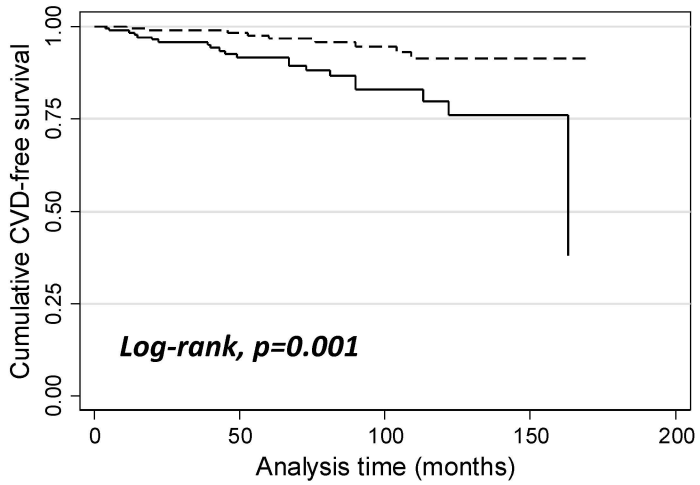
Number at risk					
AAC = No AAC	348	215	108	24	0
AAC = Any AAC	275	170	73	19	0

AAC = No AAC AAC = Any AAC

Kidney only

Simultaneous pancreas-kidney

A)



Number at risk					
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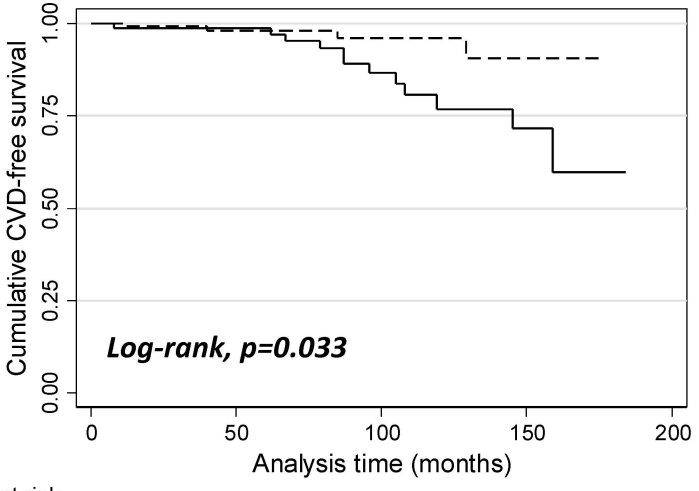
AAC = Any AAC	190	103	38	6	0

AAC = No AAC — AAC = Any AAC

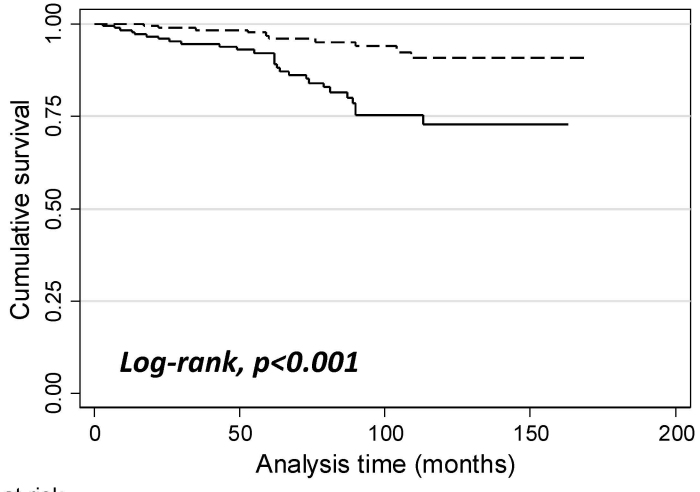
B)



Number at risk					
AAC = No AAC	128	70	40	7	0
AAC = Any AAC	85	59	31	9	0

AAC = No AAC — AAC = Any AAC

C)



Number at risk					
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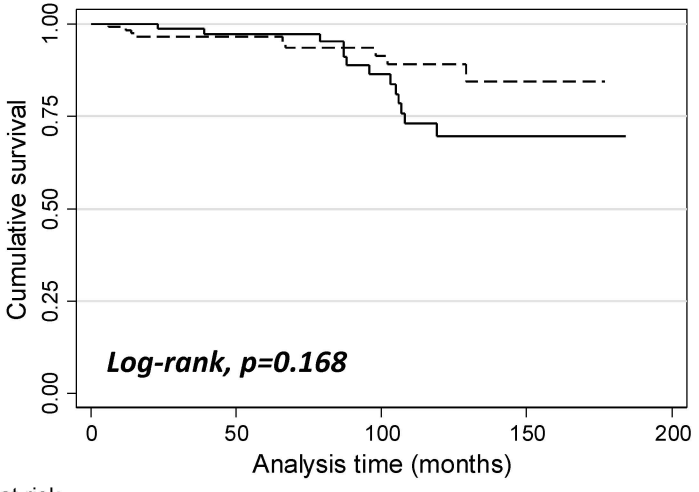
AAC = Any AAC	190	110	41	9	0

AAC = No AAC — AAC = Any AAC

D)



Number at risk					
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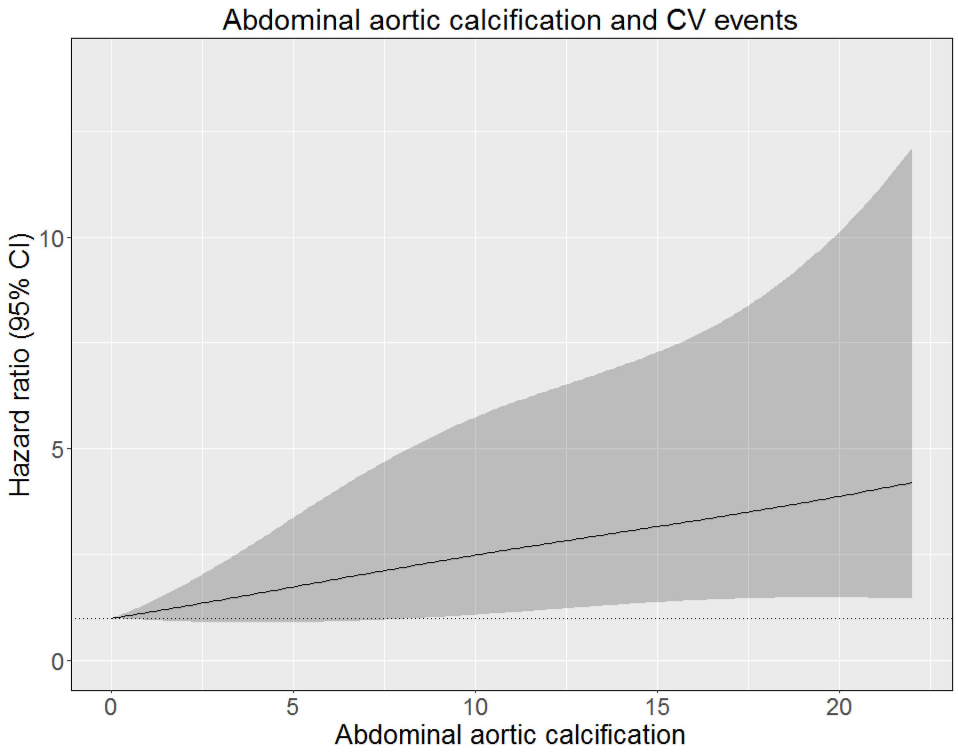
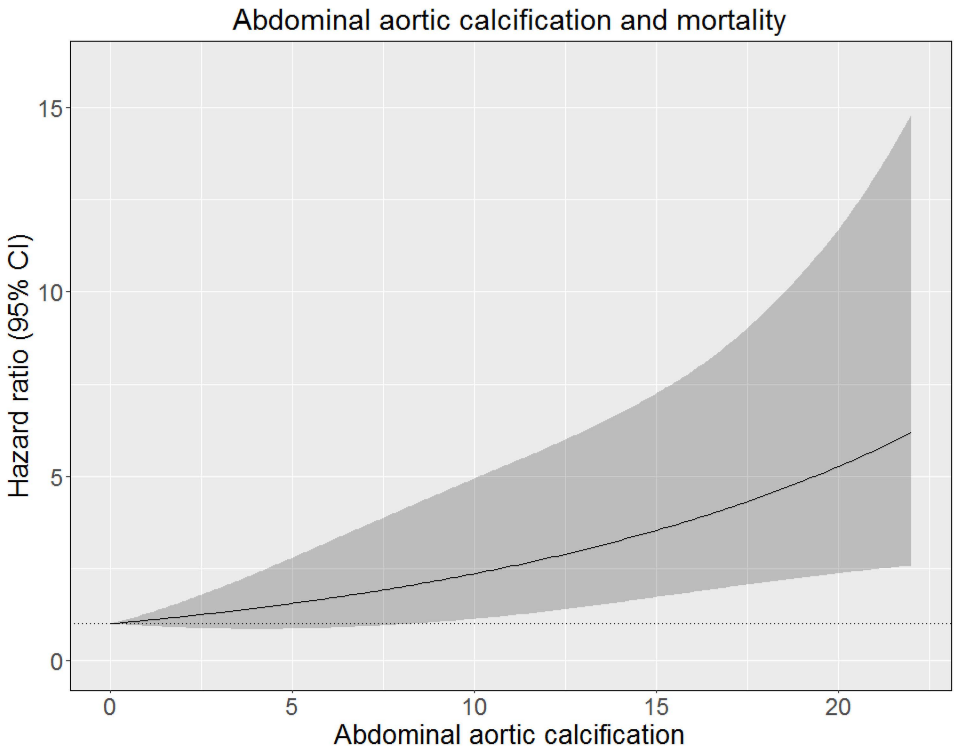
AAC = Any AAC	85	60	32	10	0

AAC = No AAC — AAC = Any AAC


Abdominal aortic calcification and CV events
Hazard ratio (95% CI)
0
5
10
0
5
10
15
20
Abdominal aortic calcification


Abdominal aortic calcification and mortality
Hazard ratio (95% CI)
0
5
10
15
0
5
10
15
20
Abdominal aortic calcification