22. Koch M, Mengel M, Poehnert D *et al*. Effects of everolimus on cellular and humoral immune processes leading to chronic allograft nephropathy in a rat model with sensitized recipients. *Transplantation* 2007; 83: 498–505
23. Battaglia M, Stabilini A, Migliavacca B *et al*. Rapamycin promotes expansion of functional CD4+CD25+FOXP3+ regulatory T cells of both healthy subjects and type 1 diabetic patients. *J Immunol* 2006; 177: 8338–8347
24. Meister S, Schubert U, Neubert K *et al*. Extensive immunoglobulin production sensitizes myeloma cells for proteasome inhibition. *Cancer Res* 2007; 67: 1783–1792
25. Maseda D, Meister S, Neubert K *et al*. Proteasome inhibition drastically but reversibly impairs murine lymphocyte development. *Cell Death Differ* 2008; 15: 600–612
26. Everly MJ, Everly JJ, Susskind B *et al*. Bortezomib provides effective therapy for antibody- and cell-mediated acute rejection. *Transplantation* 2008; 86: 1754–1761
27. Trivedi HL, Terasaki PI, Feroz A *et al*. Abrogation of anti-HLA antibodies via proteasome inhibition. *Transplantation* 2009; 87: 1555–1561
28. Arpinati M, Chirumbolo G, Nicolini B *et al*. Selective apoptosis of monocytes and monocyte-derived DCs induced by bortezomib (Velcade). *Bone Marrow Transplant* 2009; 43: 253–259
29. Blanco B, Perez-Simon JA, Sanchez-Abarca LI *et al*. Bortezomib induces selective depletion of alloreactive T lymphocytes and decreases the production of Th1 cytokines. *Blood* 2006; 107: 3575–3583

Received for publication: 3.3.10; Accepted in revised form: 6.4.10

Nephrol Dial Transplant (2010) 25: 3773–3778
doi: 10.1093/ndt/gfq268
Advance Access publication 25 May 2010

Coronary artery calcification: a strong predictor of cardiovascular events in renal transplant recipients

Pauline TH Nguyen[1]*, Séverine Henrard[2]*, Emmanuel Coche[3], Eric Goffin[1], Olivier Devuyst[1] and Michel Jadoul[1]

[1]Nephrology, Cliniques Universitaires St Luc, Université catholique de Louvain, Brussels, Belgium, [2]Epidemiology and Biostatistics, Ecole de santé publique, Université catholique de Louvain, Brussels, Belgium and [3]Medical Imaging, Cliniques Universitaires St Luc, Université catholique de Louvain, Brussels, Belgium

Correspondence and offprint requests to: Michel Jadoul; E-mail: michel.jadoul@uclouvain.be
*Both authors equally contributed to this work.

Abstract

Background. Coronary artery calcification (CAC) independently predicts cardiovascular events (CVE) in the general population. Whether this applies to renal transplant recipients (RTR) is unknown. This prospective study assessed the prognostic impact of CAC on CVE in RTR.

Methods. We followed up a published cohort of 281 prevalent RTR. At baseline, 16-slice chest spiral computerized tomography scan was performed and classical as well as CKD-related risk factors were recorded. Major CVE (MCVE) was defined as cardiovascular death, myocardial infarction, stroke or transient ischaemic attack. All CVE (ACVE) included MCVE and revascularizations. Prognostic factors were assessed by univariate and multivariate Cox regression.

Results. During 2.3 ± 0.5 years of follow-up, 16 patients died from CV ($n = 8$) or non-CV causes ($n = 8$). Thirty-one RTR developed at least one CVE (first CVE cardiac in 15, peripheral in 12 and cerebrovascular in 4) for a total of 36 CVE. Thirty-month CV survival, MCVE-free survival and ACVE-free survival was 96.4, 93.9 and 87.9%, respectively. By multivariate analysis, the independent predictors of ACVE were CAC score (hazards ratios [HR] = 1.40 [1.12; 1.75] for a 2.72-fold increase in CAC, $P < 0.003$) and history of CVE (HR = 2.76 [1.21; 6.39], $P < 0.02$).

Conclusion. Our study shows for the first time that CAC is a strong independent predictor of CVE in RTR.

Keywords: coronary artery calcification; kidney transplantation; vascular calcification

Introduction

In the general population, the presence and extent of coronary artery calcification (CAC) independently predict an increased risk of cardiac events [1]. Several studies have assessed the prevalence of CAC in renal transplant recipients (RTR) [2–6], but the prognostic value of CAC in RTR is unknown. We recently performed a large cross-sectional study of the prevalence and determinants of CAC and thoracic aorta calcifications (AoC) in RTR [5] and hypothesized that the presence and extent of CAC and/or AoC would predict cardiovascular events (CVE) in RTR. We report the preliminary results in this cohort followed up for an average of 2.3 years.

Materials and methods

Patients

From 3 February 2004 to 27 January 2005, all RTR with a functional graft attending our outpatient clinic for an annual or bi-annual in-depth control were asked to enter the study. The protocol was approved by the local ethics committee and written informed consent was obtained from all patients. Exclusion criteria were age under 18, residing abroad or being a recipient of a multiorgan transplant [5].

Spiral CT scan

All subjects underwent chest spiral computerized tomography (CT) on a 16-slice scanner (16 Brilliance Power; Philips Medical Systems, Cleveland, OH) with retrospective cardiac gating, as previously described [5]. Calcium mass scores were expressed as milligrammes of hydroxyapatite.

Clinical and outcome variables

Medical charts were reviewed by a single investigator; blood sampling and all paraclinical investigations were performed on the day of inclusion. Blood pressure was measured by a nurse, after a 5-min rest in a seated position, before the nephrologist's examination, with a validated automatic device (Omron® M5-I, Hoofddorp, The Netherlands), according to the JNC VII protocol [7]. Glomerular filtration rate (eGFR) was estimated by the abbreviated MDRD equation [8]. Key demographic, clinical, medical history and drug treatment characteristics were recorded [5]. The cumulative dosage of steroids (expressed as grammes of prednisolone) was recorded from the date of (last) TP. CVE were defined as myocardial, cerebrovascular or lower limb necrosis or revascularization or documented transient ischaemic attack (TIA) [9]. Three outcomes were considered. The first one was CV death. The second one was major CVE (MCVE), including CV death and all spontaneous CVE. The third one was all CVE (ACVE) and included both MCVE and revascularizations.

CVE were prospectively recorded from inclusion until 20 December 2006.

Biological samples

Blood samples were obtained under fasting conditions in order to measure in blood or serum, using standard laboratory methods, haemoglobin, hsCRP (DadeBehring, Deerfield, IL), homocysteine, creatinine, glucose, total cholesterol, HDL cholesterol, magnesium, bioactive (whole) PTH (Nichols, San Juan Capistrano, CA), 25(OH) vitamin D_3 and 1,25$(OH)_2$ vitamin D_3 (Diasorin, Stilwater, MN). Proteinuria was measured on a 24-h urine collection.

Statistical analysis

Variables presenting a right-skewed distribution were log-transformed and expressed as geometric mean and geometric standard deviation.

Prognostic factors were assessed using Cox proportional hazards regression, both by univariate and multivariate analyses. Variables considered as potential predictor(s) of CVE, including CV death, MCVE and ACVE, were CAC (in milligrammes of hydroxyapatite), AoC (in milligrammes of hydroxyapatite), gender, age (in years), a history of CVE, diabetic status, smoking status, systolic blood pressure (SBP; in millimetres of mercury), diastolic blood pressure (DBP; in millimetres of mercury), pulse pressure (PP; in millimetres of mercury), heart rate (in beats per minute), body mass index (BMI; in kilogrammes per square metre), proteinuria (in grammes per 24 h), serum creatinine (in milligrammes per decilitre), GFR (in millilitres per minute per 1.73 m^2), CRP level (in milligrammes per decilitre), glycaemia (in milligrammes per decilitre), total cholesterol (in milligrammes per decilitre), HDL cholesterol (in milligrammes per decilitre), haemoglobin (in grammes per decilitre), homocysteine (in micromoles per litre), magnesium (in milliequivalents per litre), bioactive PTH, 25 (OH) vitamin D_3 (in nanogrammes per millilitre) and 1,25$(OH)_2$ vitamin D_3 (in nanogrammes per millilitre).

Variables with a P-value ≤ 0.20 in univariate analysis were submitted to a multivariate regression. A common fit between backward and forward elimination procedure using Akaike's information criterion was used to select independent multivariate predictors. In the 281 patients, 25 variables were recorded but a few data were missing in 15 patients; there were 8 missing data for 25(OH) vitamin D_3 and 1,25$(OH)_2$ vitamin D_3, 3 missing data for proteinuria and 5 missing data for total cholesterol and HDL cholesterol. Sensitivity to missing data was assessed using multiple imputation methods and comparisons between estimated Cox regressions with and without imputations. The final multivariate regression includes all patients without missing data for the selected variables. The proportional hazards assumption was checked using correlations between scaled Schoenfeld residuals and ranked time-to-event and using graphical display of residuals against ranked time-to-event. Results are reported as hazards ratios (HR) with 95% CI, reflecting the risk multiplication induced by a one-unit increase in predictor on a linear scale and a 2.72 times increase in predictor on a natural log scale. All statistical analyses were performed using SAS software release 9.1.3. All tests were two-tailed and a P-value < 0.05 was considered as significant.

Results

Population characteristics

The characteristics of the cohort at inclusion were reported earlier [5]. Briefly, the population was 98% Caucasian, 61% male, 15% diabetic, aged 53 ± 13 years and transplanted for 8.3 ± 6.9 years after having been dialysed for 2.4 ± 2.4 years. A history of CVE was present in 87 patients (31%). These 87 patients had experienced a median of 1 CVE [range 1–7]. Thirteen percent (n = 37) had a HDL cholesterol level ≤ 40 mg/dl. Other descriptive statistics are presented in Table 1.

CAC and AoC were 52.2 (4.9) and 99.3 (8.2) mg, respectively [5].

Angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers were the most frequently prescribed antihypertensive drugs (n = 166, 59%), followed by β-blockers (n = 100, 36%) and calcium channel blockers (n = 95, 34%). Loop diuretics were prescribed to 19% (n = 52) and statins to 39% (n = 110).

CVE (CV death, MCVE and ACVE)

During 100% complete follow-up of 2.3 ± 0.5 years, 16 patients died. Eight deaths had a CV cause: six cardiac deaths [sudden death (n = 4), heart failure (n = 2); in

Table 1. Characteristics of the RTR cohort (n = 281)

Variables	Mean ± SD
SBP, mmHg	136 ± 21
DBP, mmHg	82 ± 12
PP, mmHg	54 ± 16.4
CRP, mg/dl[a]	0.17 (3.6)
Glycaemia, mg/dl[a]	97.9 (1.3)
Calcium level, mg/dl	9.5 ± 0.6
Phosphorus level, mg/dl	3.1 ± 0.8
25(OH) vitamin D_3, ng/ml	17.0 ± 9.5
1,25$(OH)_2$ vitamin D_3, pg/ml	33.7 ± 17.2
Bioactive PTH, pg/ml[a]	43.9 (2.0)
Proteinuria, g/24 h[a]	0.17 (2.9)
Haemoglobin, g/dl	13.2 ± 1.6
BMI, kg/m^2	26.4 ± 4.5
Tacrolimus	48%
MMF	53%
Cyclosporin	52%
Time after last TP, years	7.6 ± 6.4
Steroids cumulative dosage, g	18.6 ± 18.3

[a]Geometric mean (SD).

Table 2. Distribution of first CVE per patient according to the vascular bed

Affected vascular bed	CV death, *n* (%)	MCVE, *n* (%)	ACVE, *n* (%)
Cardiac	6 (75.0)	9 (60.0)	15 (48.4)
Cerebrovascular	1 (12.5)	4 (26.7)	4 (12.9)
Peripheral	1 (12.5)	2 (13.3)	12 (38.7)
Total	8	15	31

two of these six patients, death occurred after revascularization (one cardiac and one peripheral)], one death from a stroke and one from a mesenteric infarction. Eight patients died from non-CV causes: five from infection (one endocarditis, three sepsis and one pneumonia) and three from neoplasia (one lymphoma, one squamous cell carcinoma of the tongue and one prostate cancer).

MCVE included the six cardiac deaths and three non-fatal myocardial infarctions, the fatal stroke and three non-fatal CVA and/or TIA as well as the fatal mesenteric infarction and a spontaneous radial artery occlusion. ACVE included all MCVE as well as 7 cardiac revascularizations without myocardial infarction (1 patient underwent revascularization after myocardial infarction and revascularization was performed in 1 patient who later died from heart failure) and 10 peripheral revascularizations (followed by sudden death in 1 patient). A total of 36 CVE were thus observed in 31 patients (Table 2), but analyses for MCVE or ACVE were performed using the time to first event. The incidence of a first CVE was 4.89 events per 100 patient-years.

The respective fractions of cardiac, cerebrovascular and peripheral events vary between the outcomes (Table 2), with a majority of cardiac events for all three outcomes.

Predictors of and survival free of CV death, MCVE and ACVE

At 30 months, CV survival was 96.4% (95% CI, 92.6–98.3%), survival free of MCVE was 93.9% (95% CI, 89.8–96.4%) and survival free of ACVE was 87.8% (95% CI, 83.0–91.4%) (Figure 1).

Variables associated with CV death by univariate analysis were a higher CAC score, a history of CVE, a higher AoC score, a higher glycaemia, older age, a higher haemoglobin level, a higher PTH level and diabetes (Table 3). HR reported in Table 3 represent the risk multiplication for a one-unit increase in non-transformed variables or a 2.72-fold increase in variables on a natural log scale.

Variables associated with MCVE by univariate analysis were a higher CRP level and a higher proteinuria.

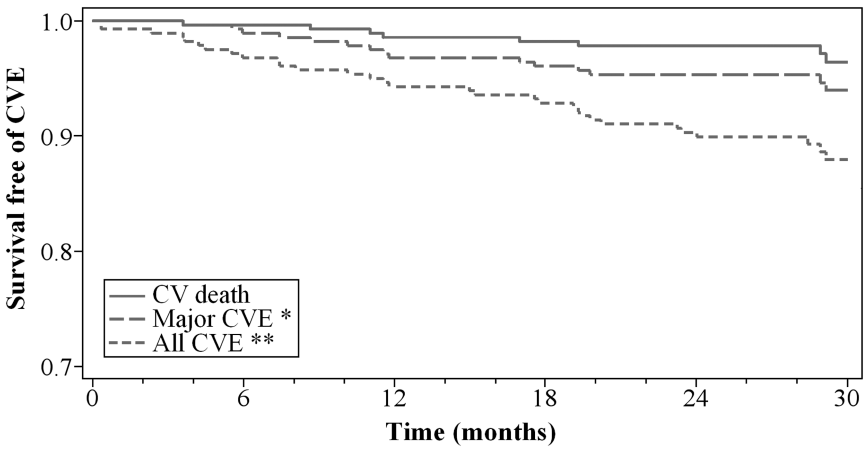
Variables associated with ACVE were, again, higher CAC and AoC scores, a history of CVE, a higher SBP, older age, a higher pulse pressure (PP), a lower 25(OH) vitamin D_3 level, a higher glycaemia, male gender, a higher CRP level, a higher PTH level, diabetes, a higher DBP and a higher homocysteinaemia (Table 3).

Variables not significantly associated with any outcome were smoking, heart rate, creatinine serum level, eGFR and magnesium serum level.

By multivariate analysis (Table 4), the independent predictors of ACVE were a higher CAC score, P = 0.003, HR = 1.40 [1.12; 1.75] on a natural log scale and a history of CVE, P = 0.016, HR = 2.76 [1.21; 6.39]. Final multivariate regressions were computed using all 281 patients.

For ACVE, there were 31 events and correlations of the scaled Schoenfeld residuals with ranked time-to-event were also not significant (P = 0.98 for CAC and P = 0.76 for history of CVE). Moreover, there was no increase or decrease with time on Schoenfeld residuals plots.

Using multivariate analysis stratified by CAC score (with a cut-off of 100 mg of hydroxyapatite, chosen for illustrative purpose) [10] and presence or absence of a history of CVE (Figure 2), survival free of ACVE at 30 months was highest (95.9%) in patients without these two risk factors. Survival was slightly lower in patients with only one of these two risks factors: 93.8% in the presence of a history of CVE and 91.3% in the presence of a high CAC score. Survival free of ACVE at 30 months was



* CV death, infarction, CVA/TIA and peripheral events
** Major CVE and revascularisation

Fig. 1. Survival free of CV death, MCVE and ACVE.

Table 3. Predictors of cardiovascular (CV) death, MCVE and ACVE using univariate Cox regression

	CV death			MCVE			ACVE		
Variables	HR	[95% CI]	P-value	HR	[95% CI]	P-value	HR	[95% CI]	P-value
CAC, mg hydroxyapatite[a]	2.13	[1.21; 3.75]	0.009				1.59	[1.29; 1.96]	<0.001
AoC, mg hydroxyapatite[a]	1.63	[1.12; 2.37]	0.011				1.36	[1.16; 1.58]	<0.001
Age, years	1.12	[1.03; 1.22]	0.005				1.05	[1.02; 1.08]	0.003
Male gender				2.55	[0.71; 9.13]	0.15	2.88	[1.18; 7.02]	0.020
History of CVE	15.4	[1.9; 125.2]	0.011	2.41	[0.85; 6.89]	0.10	5.13	[2.41; 10.9]	<0.001
SBP, mmHg	1.01	[0.98; 1.04]	0.39				1.02	[1.01; 1.04]	0.001
DBP, mmHg	1.04	[0.99; 1.10]	0.14	1.04	[0.99; 1.08]	0.084	1.02	[1.00; 1.05]	0.11
PP, mmHg							1.02	[1.01; 1.04]	0.004
CRP, mg/dl[a]				1.62	[1.07; 2.45]	0.022	1.39	[1.05; 1.84]	0.023
Glycaemia, mg/dl[a]	7.31	[1.55; 34.4]	0.012	3.24	[0.71; 14.72]	0.13	3.42	[1.57; 9.21]	0.015
HDL cholesterol, ≤40 mg/dl				2.36	[0.66; 8.46]	0.19	1.66	[0.64; 4.32]	0.30
Homocysteinemia							2.35	[0.75; 7.35]	0.141
Calcium level, mg/dl	1.67	[0.49; 5.69]	0.42	1.00	[0.39; 2.56]	0.99	1.01	[0.54; 1.89]	0.99
Phosphorus level, mg/dl	0.48	[0.15; 1.57]	0.23	0.51	[0.21; 1.24]	0.14	0.69	[0.40; 1.19]	0.18
25(OH) vitamin D_3, ng/ml	0.86	[0.75; 1.00]	0.053	0.95	[0.89; 1.03]	0.21	0.93	[0.87; 0.98]	0.008
1,25$(OH)_2$ vitamin D_3, pg/ml	0.98	[0.93; 1.03]	0.42						
Bioactive PTH, pg/ml[a]	2.30	[0.86; 6.16]	0.097				1.65	[1.00; 2.74]	0.05
Proteinuria, g/24 h[a]	2.10	[0.43; 10.25]	0.36	2.78	[1.04; 7.42]	0.041			
Diabetes	3.86	[0.92; 16.19]	0.064				2.24	[1.00; 5.02]	0.049
Haemoglobin, g/dl	1.67	[1.06; 2.63]	0.028						
BMI, kg/m^2				1.06	[0.96; 1.18]	0.27			
Tacrolimus	1.79	[0.43; 7.50]	0.43	0.80	[0.28; 2.29]	0.67	0.88	[0.44; 1.79]	0.73
MMF	1.46	[0.35; 6.12]	0.60	1.16	[0.40; 3.35]	0.78	0.81	[0.40; 1.64]	0.56
Cyclosporin	0.57	[0.14; 2.39]	0.44	0.93	[0.33; 2.66]	0.89	0.87	[0.43; 1.75]	0.69
Time after last TP, years	0.97	[0.85; 1.10]	0.61	1.05	[0.99; 1.12]	0.10	1.04	[0.99; 1.09]	0.14
Steroids cumulative dosage, g	0.99	[0.94; 1.03]	0.53	1.01	[0.99; 1.04]	0.26	1.01	[0.99; 1.03]	0.23

[a]Natural log-transformed variable.

significantly lower in patients with both risk factors (61.9% [95% CI, 46.7–74.0], log-rank P-value < 0.0001).

Discussion

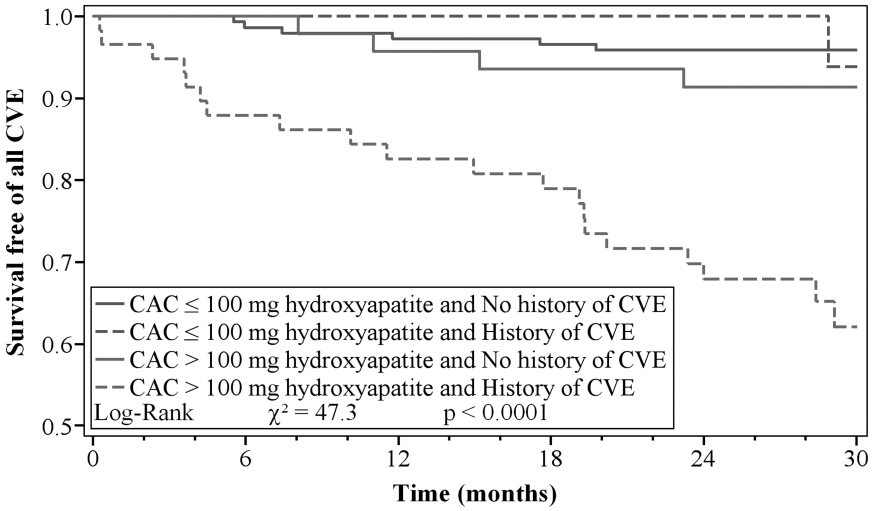
CV disease is not only highly premature in dialysed patients, but also in RTR compared with the general population [11]. CAC independently predicts CVE in the general population [1]. Recent evidence points to a similar impact of CAC as predictor of mortality, mainly CV, in haemodialysis [12]. However, whether CAC predicts CVE in RTR was unknown. In fact, a smaller-sized study (n = 112) recently identified AoC but not CAC as a predictor of CVE in incident RTR [13]. This discrepancy probably derives from the exclusion by DeLoach *et al*. of patients with a history of CVE, in contrast to our 'real-world', much larger cohort. Our study indeed shows that higher CAC, but not higher AoC, is associated with a markedly higher risk of CV mortality and of ACVE in prevalent RTR.

In fact, CAC is a strong predictor of CV mortality and ACVE in RTR, whereas the predictive role of classical CV risk factors such as older age, male gender, obesity, hypercholesterolaemia, smoking history or diabetes [14,15], apparent for some, but not all of them, by univariate analysis, was no longer significant by multivariate analysis. This most likely derives from the fact that CAC is strongly positively correlated with many classical or ESRD-specific risk factors, such as older age, male gender and longer time on dialysis [4,16], and probably, as intermediate outcome, 'in-

Table 4. Independent predictors of ACVE using multivariate Cox regression, and additive prognostic value of treatment data

	ACVE			Additional prognostic value		
Variables	HR	[95% CI]	P-value	HR	[95% CI]	P-value
CAC, mg hydroxyapatite	1.40	[1.12; 1.75]	0.003			
History of CVE	2.76	[1.21; 6.39]	0.015			
Calcium level, mg/dl				0.84	[0.46; 1.54]	0.58
Phosphorus level, mg/dl				0.83	[0.45; 1.56]	0.57
Tacrolimus				0.78	[0.38; 1.60]	0.49
MMF				1.00	[0.49; 2.05]	0.99
Cyclosporin				0.92	[0.45; 1.87]	0.82
Time after last TP, years				1.03	[0.98; 1.08]	0.21
Steroids cumulative dosage, g				1.01	[0.99; 1.02]	0.43

[a]Natural log-transformed variables.



Follow up (months)	0	6	12	18	24	30
CAC ≤ 100 mg of hydroxyap and No history of CVE	147	145	143	142	138	45
CAC ≤ 100 mg of hydroxyap and History of CVE	29	29	29	29	29	13
CAC > 100 mg of hydroxyap and No history of CVE	47	47	45	43	40	17
CAC > 100 mg of hydroxyap and History of CVE	58	50	49	44	36	15

Fig. 2. Survival free of ACVE, stratified by CAC score (with a cut-off of 100 mg of hydroxyapatite) and presence or absence of history of CVE.

cludes' or 'recapitulates' part of the risk associated with these factors. This study presents significant strengths. These include a relatively large sample size, a high participation rate of unselected patients, 100% follow-up of the included patients, the use of up-to-date sensitive multislice spiral CT [17] as well as the use of the calcium mass score, which is more accurate and reproducible than the conventional Agatston score [18–20]. Some limitations have to be acknowledged. The main one is the hitherto relatively short follow-up time and thus the limited number of events recorded, especially CV deaths; we thus refrained from performing a multivariate analysis of the predictors of death or MCVE. Secondly, our findings may not be generalized to some other populations of RTR as a result of the low prevalence of diabetic or black subjects in our cohort. Despite these limitations, calcium scoring of coronary artery could improve the assessment of CV risk in RTR. In conclusion, our preliminary results show that CAC, as assessed by multislice chest CT, is a strong predictor of CV mortality and of CVE in RTR, stronger than other well-known classical risk factors, and may become a useful tool for risk stratification in RTR.

Acknowledgements. The authors are grateful to the members of the UCL Nephrology Collaborative Group for the careful joint follow-up of RTR. This work was presented in abstract form as an oral communication at the 2008 American Society of Nephrology Meeting (Philadelphia). The study was partly funded by the Fonds spécial de Recherche of the Université catholique de Louvain and by the European Union FP6 program funding to Genecure.

Conflict of interest statement. None declared.

References

1. Pletcher MJ, Tice JA, Pignone M *et al*. Using the coronary artery calcium score to predict coronary heart disease events: a systematic review and meta-analysis. *Arch Intern Med* 2004; 164: 1285–1292
2. Goodman WG, Goldin J, Kuizon BD *et al*. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 2000; 342: 1478–1483
3. Ishitani MB, Milliner DS, Kim DY *et al*. Early subclinical coronary artery calcification in young adults who were pediatric kidney transplant recipients. *Am J Transplant* 2005; 5: 1689–1693
4. McCullough PA, Sandberg KR, Dumler F *et al*. Determinants of coronary vascular calcification in patients with chronic kidney disease and end-stage renal disease: a systematic review. *J Nephrol* 2004; 1: 205–215
5. Nguyen PT, Coche E, Goffin E *et al*. Prevalence and determinants of coronary and aortic calcifications assessed by chest CT in renal transplant recipients. *Am J Nephrol* 2007; 27: 329–335
6. Nitta K, Akiba T, Suzuki K *et al*. Assessment of coronary artery calcification in hemodialysis patients using multi-detector spiral CT scan. *Hypertens Res* 2004; 27: 527–533
7. Chobanian AV, Bakris GL, Black HR *et al*. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; 289: 2560–2572
8. Perico N, Gaspari F, Remuzzi G. Assessing renal function by GFR prediction equations in kidney transplantation. *Am J Transplant* 2005; 5: 1175–1176
9. Kasiske BL, Guijarro C, Massy ZA *et al*. Cardiovascular disease after renal transplantation. *J Am Soc Nephrol* 1996; 7: 158–165

10. Raggi P, Callister TQ, Cooil B *et al*. Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. *Circulation* 2000; 101: 850–855
11. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998; 32: S112–S119
12. Block GA, Raggi P, Bellasi A *et al*. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. *Kidney Int* 2007; 71: 438–441
13. De Loach SS, Joffe MM, Mai X *et al*. Aortic calcification predicts cardiovascular events and all-cause mortality in renal transplantation. *Nephrol Dial Transplant* 2009; 24: 1314–1319
14. De Mattos AM, Prather J, Olyaei AJ *et al*. Cardiovascular events following renal transplantation: role of traditional and transplant-specific risk factors. *Kidney Int* 2006; 70: 757–764
15. de Vinuesa SG Goicoechea M, Gomez-Campdera F, Luno J. Predictive cardiovascular risk factors in patients with chronic kidney disease (CKD). *Kidney Int* 2005; 93: S35–S38
16. Mehrotra R, Westenfeld R, Christenson P *et al*. Serum fetuin-A in nondialyzed patients with diabetic nephropathy: relationship with coronary artery calcification. *Kidney Int* 2005; 67: 1070–1077
17. Moe SM, O'Neill KD, Fineberg N *et al*. Assessment of vascular calcification in ESRD patients using spiral CT. *Nephrol Dial Transplant* 2003; 18: 1152–1158
18. Agatston AS, Janowitz WR, Hildner FJ *et al*. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990; 15: 827–832
19. Hong C, Bae KT, Pilgram TK. Coronary artery calcium: accuracy and reproducibility of measurements with multi-detector row CT-assessment of effects of different thresholds and quantification methods. *Radiology* 2003; 227: 795–801
20. Ulzheimer S, Kalender WA. Assessment of calcium scoring performance in cardiac computed tomography. *Eur Radiol* 2003; 13: 484–497

Received for publication: 23.9.09; Accepted in revised form: 23.4.10

Nephrol Dial Transplant (2010) 25: 3778–3786
doi: 10.1093/ndt/gfq229
Advance Access publication 28 April 2010

Long-term outcome of ABO-incompatible living donor kidney transplantation based on antigen-specific desensitization. An observational comparative analysis

Jochen Wilpert[1,5,*], Karl-Georg Fischer[1,*], Przemyslaw Pisarski[2], Thorsten Wiech[3], Michael Daskalakis[4], Anna Ziegler[1], Elke Neumann-Haefelin[1], Oliver Drognitz[2], Florian Emmerich[4], Gerd Walz[1] and Marcel Geyer[1]

[1]Renal Division, [2]Transplant Unit, Surgery Division, [3]Institute of Pathology and [4]Department of Transfusion Medicine, University Hospital Freiburg, Germany

Correspondence and offprint requests to: Marcel Geyer; E-mail: marcel.geyer@uniklinik-freiburg.de
[5]Present address: HBH-Kliniken Singen, Renal Division, Germany.
[*]Both authors contributed equally to this work.

Abstract

Background. ABO-incompatible living donor kidney transplantation based on specific conditioning has been successfully adopted by transplant centres worldwide. Excellent short-term results have been reported in small cohorts. However, long-term data and comparative analyses are still sparse. We report on the outcome of 40 consecutive ABO-incompatible living donor kidney transplant recipients and compare their clinical course to a control group of 43 ABO-compatible living donor transplant patients transplanted during the same time period.

Methods. This is an observational single-centre analysis of 40 consecutive patients undergoing ABO-incompatible kidney grafting between April 2004 and April 2009, using a protocol of rituximab, antigen-specific immunoadsorption, intravenous immunoglobulin, basiliximab induction and oral triple immunosuppression with tacrolimus, mycophenolic acid and prednisone. Forty-three ABO-compatible kidney transplant recipients served as controls. The control group had also received basiliximab induction and an identical initial maintenance immunosuppression. The two groups were observed for an average of 39 and 19 months, respectively.

Results. There was a significantly higher incidence of lymphoceles requiring surgical revisions in the ABO-incompatible group. However, this surgical complication did not affect patient or graft survival. Mean serum creatinine, estimated glomerular filtration rate and proteinuria did not differ between the two groups. Furthermore, ABO-incompatible and ABO-compatible patients had the same incidence of humoral and cellular rejections. Despite a more aggressive induction therapy, no differences in infectious or malignant complications were observed.

Conclusions. ABO-incompatible living donor kidney transplantation utilizing a combination of rituximab and antigen-specific immunoadsorption yielded results