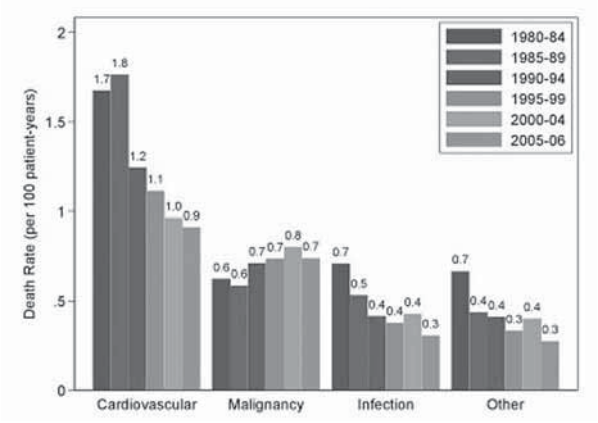
Results: There is a significant reduction in the death rate since 1990 compared to earlier eras with an ongoing reduction in the most recent decade (Figure below); Incidence Rate Ratio (IRR) 0.54; *p=0.000*). In comparison, there is no change in the rate of deaths from malignancy (IRR 1.18; *p=0.287*).



Factors associated with cardiovascular death after transplantation are: age over 45 years (RR 3.03, CI 1.15 – 8.0; *p=0.025*), diabetes as the cause of ESRF (RR 3.56; CI 1.52 – 8.35; *p=0.0035*) and presence of cardiovascular disease at the onset of ESRF (RR 2.7, CI 1.47 – 4.97; *p=0.0014*).

Conclusions: The rate of death from cardiovascular disease appears to be declining, in contrast to malignancy. Ongoing research is required to determine the cause of this observation.

604 METABOLIC SYNDROME AND CARDIOVASCULAR DISEASE RISK IN RENAL TRANSPLANT RECIPIENTS IN THE ALERT TRIAL: EFFECTS OF STATIN TREATMENT

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Background: Metabolic Syndrome (MS) is a risk factor for cardiovascular disease (CVD) and diabetes mellitus in the general population. Renal transplant recipients (RTR) have unfavorable metabolic conditions, partly due to immunosuppression.

Aim: To study MS as CVD risk factor in RTR. To investigate the effect of fluvastatin treatment in CVD prevention in RTR with MS.

Methods: In total, 1708 stable RTR without diabetes mellitus in the ALERT trial were randomized to treatment with fluvastatin or placebo. Follow-up was 7-8 years (ALERT-extension trial). MS was defined at baseline using ATPIII definition. Major adverse cardiac event (MACE) was the primary study end-point.

Results: In the ALERT study, 29% of the non-diabetic RTR had MS. MACE risk was increased in RTR with MS [RR (95% CI)] 1.67 (1.27-2.20). RTR with MS also had increased RR for non-fatal myocardial infarction (MI) 1.84 (1.20-2.88) and cardiac death 2.22 (1.44-3.42). Statin treatment was associated with considerable reduction in cardiovascular event probability among RTR patients with MS (Table).

Table. Cumulative 8-year probability of an event (%)

	MS and placebo	MS and statin	No MS and placebo	No MS and statin
MACE	27	14	12	10
Non-fatal MI	11	4.5	5	3.5
Cardiac Death	13	6	5	3.5

Conclusion: RTR with MS are at high risk for CVD. RTR with MS are easily identifiable group of patients who benefit from statin treatment.

605 ANTIHYPERTENSIVE THERAPY FOR KIDNEY TRANSPLANT RECIPIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Aims: To assess the relative effects of different classes of antihypertensive agents on patient and graft survival, graft function, cardiovascular events, acute rejection, proteinuria, blood pressure and anaemia in kidney transplant recipients.

Data sources: A comprehensive search of MEDLINE, EMBASE, CENTRAL, DARE, Science Citation Registry, reference lists of identified studies and abstracts of conference proceedings.

Methods: We included randomised trials of any antihypertensive agent in kidney transplant recipients which were administered for two weeks or more, compared with placebo/no treatment or another class of antihypertensive agent. Summary estimates of treatment effects were combined using a random effects model and expressed as relative risks for dichotomous outcomes and weighted mean difference for continuous outcomes, both with 95% CI.

Results: Data from a total of 60 trials of 76 intervention comparisons involving 3627 participants were retrieved. Indication for treatment varied: hypertension 25 trials (1407 participants), erythrocytosis six trials (111 participants), left ventricular hypertrophy two trials (131 participants), and chronic allograft nephropathy one trial (28 participants). In the majority (37 trials, 2291 participants), the indication was not provided or treatment was investigated for effect on reducing concomitant cyclosporin use. Calcium channel blocker (CCB) therapy was the most commonly allocated treatment (1612 participants, 49 trials), followed by ACE inhibitors (ACEi; 706 participants, 27 trials) and angiotensin receptor-2 blockers (ARB; 367 participants, 16 trials). As trials permitted use of additional agents to treat hypertension, similar blood pressure control was achieved among all studied drug class comparisons.

Recipients allocated to ACEi, compared to placebo or no treatment had lower GFR (WMD -6.0 ml/min, 95% CI -11.9 to 0.0), higher serum potassium (WMD 0.44 mmol/L, 95% CI 0.10 to 0.78) and lower haemoglobin (WMD -8.7 g/L, 95% CI -12.1 to -5.3). Recipients allocated to CCB, compared to placebo or no treatment, had lower risk of graft loss (RR 0.71, 95%CI 0.53 to 0.94), higher GFR (WMD 4.8 ml/min, 95%CI 1.9 to 7.6 ml/min) and lower creatinine (WMD -6.5 mmol/L, 95%CI -11.9 to -1.1). Recipients allocated to CCB compared to ACEi experienced less acute rejection (RR 0.61, 95%CI 0.46 to 0.82), had higher GFR (WMD -10.6 ml/min, 95% CI 6.0 to 15.2), lower creatinine (WMD -12.9 mmol/L, 95% CI -17.6 to -8.1), more proteinuria (WMD 0.28 g/24h, 95% CI 0.10 to 0.47), less hyperkalaemia (RR 0.27, 95% CI 0.13 to 0.53) and higher haemoglobin (WMD 11.5 g/L, 95%CI 7.2 to 15.8).

Conclusions: These data indicate that CCB should be favoured as first line treatment in kidney recipients requiring antihypertensive treatment, and suggest that CCB may prevent graft loss and improve graft function in kidney transplant recipients, irrespective of indication. Further prospective randomised trials in patients receiving newer immunosuppression regimens are required.

606 GENETICS OF NEW-ONSET POST TRANSPLANT DIABETES MELLITUS (NOPTDM)

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Background: The development of diabetes after transplantation is a significant problem that dramatically increases patient morbidity and mortality. The principle cause of NOPTDM is the use of diabetogenic drugs, especially steroids and calcineurin inhibitors (CNIs), and yet only a proportion of recipients develop the disease. This suggests an individuality in susceptibility that may have a genetic component.

Patients and methods: Therefore we tested the association of known genetic markers for type II diabetes (DM2) and mature onset diabetes of the young (MODY) with NOPTDM in renal transplant recipients. NOPTDM was defined as blood glucose >125 mg/dl at more than one time point, starting 30 days post-transplant. Patients were followed for at least 1 year after grafting. We identified

117 patients with NOPTDM and 295 controls (never hyperglycaemic) from a pool of 1153 patients transplanted between 01/01/2001 and 09/30/2005.

Results: Amongst the genes associated with NOPTDM were genes affecting beta cell K-channel function (KCNJ11, p=0.008), insulin gene activation (HNF1A, p=0.002) insulin response (IRS1, p=0.008) and regulatory feedback of insulin action (TCF7L2, p=0.001). Each of these genes is responsive to either NF-AT or glucocorticoid, and therefore influenced by CNIs or steroids.

Conclusions: NOPTDM genes can be defined as follows: (1) the gene is important in glucose homeostasis, (2) there are alleles of the gene that confer a risk of diabetes and (3) the gene is directly susceptible to the immunosuppressive drugs used to treat the patient. Given the strength of association, for example TCF7L2 has an Odds Ratio of 13.72 (95% CI 3.13-60.21), genetic information on the recipient may dictate the selection and dose of immunosuppressive agents for individual recipients.

607 LATE STEROID WITHDRAWAL AND CARDIOVASCULAR EVENTS IN KIDNEY TRANSPLANT RECIPIENTS

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Introduction: Cardiovascular events (CVE) are the leading cause of morbidity and mortality in kidney transplant recipients. The adverse effects of long-term therapy with steroids on cardiovascular risk factors have motivated increasing interest in steroid withdrawal (SW). The objective of this study was to compare the incidences of CVE (fatal and non-fatal cardiac and cerebrovascular events) and all-cause mortality between patients who had undergone SW at 1 year post-transplant and control patients who continued on steroids.

Methods: The study cohort included 400 consecutive adult recipients of a kidney transplant between January 1, 1993 and December 31, 1998 who qualified for SW at 1 year after transplantation. Candidates for SW included those with no more than 2 previous acute rejections, a stable serum creatinine of less than 2.0 mg/dl, and ability to tolerate full doses of azathioprine or mycophenolate mofetil, and to maintain adequate levels of cyclosporine or tacrolimus. At 1 year post-transplant 188 patients subsequently underwent SW, while 212 patients continued on steroids. Cox proportional-hazards analysis was used to estimate cardiac events (new-onset angina pectoris, acute myocardial infarct, coronary angioplasty or by-pass surgery, or cardiac death), cerebrovascular events (transient ischemic attack, cerebrovascular accident, carotid endarterectomy, or death from a cerebrovascular event) and all-cause mortality hazard ratios (HR) for patients who had undergone SW versus controls who continued on steroids beyond 1 year.

Results: The average duration of follow-up was 61 months for the entire cohort, with average follow-up of 63 months for SW group and 59 months for control patients. There were 44 (11%) cardiac events, 18 (4.5%) cerebrovascular events, and 41 deaths (10.3%). The composite outcome of CVE and all-cause mortality was reached in 26 (13.8%) subjects who had undergone SW and 50 (23.6%) controls (P = 0.013). In adjusted analyses, SW was associated with decreased risk for the composite outcome (HR 0.46, 95% confidence interval [CI] 0.28-0.76, P = 0.003), cardiac events (HR 0.48, 95% CI 0.28-0.84, P = 0.009), and all-cause mortality (HR 0.27, 95% CI 0.12-0.59, P = 0.001). There was no association of SW with the risk for cerebrovascular events (HR 1.76, 95% CI 0.45-7.01, P = 0.42). Steroid continuation was associated with increased body mass index, increased frequency of newly-diagnosed hypertension, and higher cumulative rate of new-onset diabetes mellitus when compared with SW (+0.50 ± 0.17 kg/m2 vs. -0.11 ± 0.18 kg/m2, 37.8% vs. 25.3%, and 8.0% vs. 1.1%, respectively; P < 0.05).

Conclusion: In this retrospective analysis, SW at 1 year post-transplant was associated with decreased risk for future CVE and all-cause mortality. Late SW had a positive influence on some of the risk factors associated with cardiovascular disease, specifically new-onset diabetes mellitus.

608 CARDIOVASCULAR EVENTS AND MORTALITY IN RENAL TRANSPLANT RECIPIENTS: EARLY CORTICOSTEROID CESSATION REGIMENS VERSUS CHRONIC CORTICOSTEROID THERAPY

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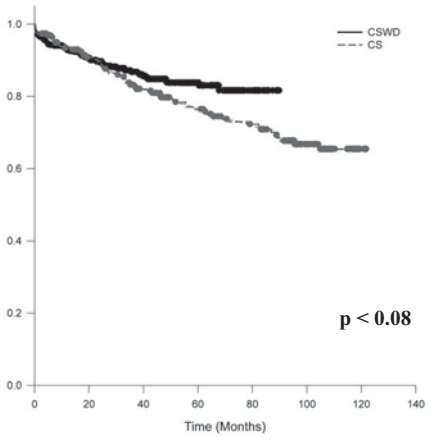
Background: Cardiovascular (CV) risk reduction has been a primary reason for pursuing early corticosteroid withdrawal (ECSWD) in renal transplant (RTx). To date, actual cardiovascular event (CVE) data (rather than CV risk) has not been reported for ECSWD. Therefore, we analyzed and compared actual CVE, CV-related survival, and overall patient survival in ECSWD (≤7 days) versus chronic corticosteroid (CCS) therapy.

Methods: CVE and heart failure (HF) data were prospectively collected. CVE were defined as sudden death, myocardial infarction, angina, and cerebrovascular accident/transient ischemic attack. HF events were defined as pulmonary edema or clinical HF diagnosis. Statistical analyses included Student's t-test, Cox Proportional-hazards Regression, and Kaplan Meier (KM) survival estimates and time to CVE.

Results: Data on 693 RTx pts (471 ECSWD and 222 CCS pts) were analyzed. Demographic data and results are presented in Table 1. Mean follow-up in all pts was 1420 ± 958 days. No difference was observed in HF events between groups (5.7% ECSWD v 6.8% in CCS group, p<0.57). CCS pts experienced more CVE (27.5% v 13.4% in ECSWD), despite a higher proportion of pre-existing cardiovascular disease (CVD) in ECSWD pts (15% v 7% in CCS). CVE-free survival was numerically greater in ECSWD pts and approached significance on KM analysis (Figure) (p<0.08). A trend toward better pt survival by KM was observed for ECSWD (p<0.11).

Demographics and Results

	CS Group (n=222)	CSWD group (n=471)	p
Male	49%	60%	0.007
African American	27%	21%	0.08
Mean Age (yrs)	46.4 ± 12	48.7 ± 12.9	0.03
Pretxp FRS	7.8 ± 6.7	8.2 ± 7.4	0.49
Pretxp CVD	7%	15%	0.003
Pretxp DM	26%	31%	0.14
% pts w/ CVE	27.5%	13.4%	<0.0001
Mean #CVE/pt	1.6 ± 1	1.3 ± 0.6	<0.0001



Conclusions: RTx recipients receiving ECSWD experienced: 1) fewer CVE and 2) a trend toward overall better pt survival. These differences in CVE and pt survival do not present until at least 3 yrs PTx; therefore, require long term follow-up to become evident.