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Inadequacy of Cardiovascular Risk Factor Management in Chronic Kidney Transplantation -- Evidence from the FAVORIT Study

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Abstract

Background—Kidney transplant recipients (KTRs) have increased risk for cardiovascular disease (CVD). Our objective is to describe the prevalence of CVD risk factors applying standard criteria and use of CVD risk factor lowering medications in contemporary KTRs.

Methods—The Folic Acid for Vascular Outcome Reduction in Transplantation study enrolled and collected medication data on 4,107 KTRs with elevated homocysteine and stable graft function an average of 5 years post-transplant.

Results—CVD risk factors were common (hypertension or use of blood pressure lowering medication in 92%, borderline or elevated LDL or use of lipid-lowering agent in 66%, history of diabetes mellitus in 41%, and obesity in 38%); prevalent CVD was reported in 20% of study participants. National Kidney Foundation blood pressure (BP) guidelines (BP < 130/80 mm Hg) were not met by 69% of participants. Uncontrolled hypertension (BP of 140/90 mm Hg or higher) was present in 44% of those taking anti-hypertension medication; 18% of participants had borderline or elevated LDL, of which 60% were untreated, and 31% of the participants with prevalent CVD were not using an anti-platelet agent.

Conclusion—There is opportunity to improve treatment and control of traditional CVD risk factors in kidney transplant recipients.

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Keywords

Kidney transplantation; cardiovascular disease; cardiovascular risk factors; medications; medical management

Introduction

Cardiovascular disease (CVD) is much more common among kidney transplant recipients than the general population (1–3). This burden is not entirely explained by traditional risk factors such as hypertension, dyslipidemia, and diabetes (4). Other factors may be involved, particularly those which may influence systemic inflammation including graft rejection, infection, and use of immunosuppressive medications (1–3).

Kidney transplantation reduces CVD risks in patients with end-stage renal disease (5). Compared to patients on a transplant wait list, kidney transplant recipients experience a marked reduction in the CVD death rate, especially from adolescence onward (6). Despite this benefit, kidney transplant recipients, particularly those age 25 to 55 years, have substantially more CVD mortality than their age, gender, and race matched non-dialysis counterparts. Some of the increased risk for CVD in the kidney transplant population could be related to lower levels of kidney function, as compared to the general population (7–9). In the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) study, we demonstrated increased risk in both CVD and all-cause mortality, with the association between estimated glomerular filtration rate (eGFR) and CVD being comparable in magnitude to that of systolic blood pressure and age (10). Consequently, efforts should be focused to control traditional cardiovascular risk factors in kidney transplant recipients including blood pressure, cholesterol, and glucose, and to counsel patients to increase their physical activity, stop smoking, and achieve or maintain acceptable body weight (11).

We describe the use of CVD risk-reducing medications in kidney transplant recipients overall, by country, and in subgroups defined by graft vintage and presence of risk factors including diabetes. As a multi-national study, FAVORIT provides a unique opportunity to consider the similarities and meaningful differences in participant characteristics including CVD risk factors and use of risk factor lowering medications. Participant grouping by graft vintage is useful in considering medications that include agents or classes with varied availability and use over the past two decades.

Materials and Methods

Details regarding the design of the clinical trial and general baseline data have been published elsewhere (12, 13). Briefly, the FAVORIT study was a randomized, double-blind controlled clinical trial to evaluate the impact of homocysteine-lowering vitamin therapy on cardiovascular disease in stable kidney transplant recipients. Study participants were enrolled from August 2002 through January 2007 at 27 clinical sites in the United States, two sites in Canada and one site in Brazil. We report data from the baseline visit. The study was approved by the applicable ethics board or institutional review board at each

participating site, and each study participant provided written informed consent prior to enrollment.

Male and female kidney transplant recipients who were 35 to 75 years of age with elevated total homocysteine levels (≥ 11 μmol/L for women; ≥ 12 μmol/L for men) and stable graft function were eligible. All participants were required to be at least 6 months post-transplant and have a Cockcroft-Gault (14) estimated creatinine clearance (Ccr) of 30 mL/min or greater (25 mL/min or greater for women recruited after July 2005 to reflect the generally lower Ccr distribution in females). Patients with recent CVD events or CVD-related procedures that would temporarily increase the risk of a cardiovascular event and those with chronic illness limiting life expectancy to less than two years were ineligible.

During the baseline visit, data collection included information on health history and medication use, a brief physical examination, and a lipid profile. Kidney graft vintage was defined as the time (years) between the most recent transplant prior to enrollment and date of randomization. Graft vintage tertiles were rounded to nearest whole year to identify cut points for categorization. Cardiovascular disease history was assessed from medical record review and participant report. Height and weight were obtained with shoes removed, but while wearing street clothes. Two blood pressure measurements were taken approximately 5–10 minutes apart, with the average being used for analysis. Blood pressure (BP) was classified as *elevated* if it was 130/80 mm Hg or greater. (15) Participants were considered to have *prevalent* hypertension if regular use of a prescription blood pressure lowering medication was reported or if systolic BP was 140 mm Hg or greater, or diastolic BP was 90 mm Hg or greater. Participants who were taking an anti-hypertensive medication and had a baseline systolic BP of 140 mm Hg or greater or a diastolic BP of 90 mm Hg or greater were considered to have *uncontrolled* hypertension. Obesity was defined by a body mass index of 30 or higher.

Prescription medications taken regularly during the past month were recorded by study staff during participant interview. Risk factor lowering medications categorized and recorded were as follows:

- **blood pressure lowering medications**: angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), beta blockers, dihydropyridine calcium channel blockers, non-dihydropyridine calcium channel blockers, loop diuretics and other diuretics
- **lipid lowering medications**: HMG COA reductase inhibitors, bile acid sequestrants, niacin, gemfibrozil, fenofibrate, bezafibrate, clofibrate, probucol and ezetimibe
- **anti-platelet medications**: aspirin, clopidogrel, ticlopidine and other anti-platelet agents
- **anti-diabetic agents:** insulin, sulfonylureas, rosigliatazone, pioglitazone, metformin, and other anti-diabetic agents

Serum creatinine, homocysteine and lipid panel were analyzed at a central laboratory (Jean Mayer USDA Human Nutrition Research Center on Aging, Boston, Massachusetts).

Homocysteine data in this report are from the screening visit which occurred up to 120 days prior to randomization. Homocysteine was measured by high-performance liquid chromatography with fluorescence detection. Baseline creatinine was measured by a modified Jaffe method using an Olympus U400 analyzer that met isotope-dilution mass spectrometry standards. The Chronic Kidney Disease Epidemiology Collaboration equation (16, 17) was used to calculate eGFR that, in turn, was used to classify participants by stage of kidney disease (18). Cholesterol, high density lipoprotein (HDL) and triglyceride levels were assessed by direct measurement using an Olympus U400 analyzer. Low density lipoprotein (LDL) was measured directly if triglyceride was 400 mg/dL or higher; otherwise it was calculated. (19) LDL levels of 130 mg/dL (3.4 mmol/L) were considered elevated. (20, 21)

All statistical analyses were computed using SAS, version 9.2 (SAS Institute, Cary, NC). P-values for country and disease history comparisons of categorical variable were based on chi-square test for homogeneity unless any cell counts were less than 10 in which case Fisher's Exact Test was used. Analysis of variance (ANOVA) F test was used for evaluating continuous variables, with transformations to normalize variables with severely skewed distributions. Age did not require transformation; homocysteine was transformed using the negative reciprocal; other continuous variables were log transformed.

Results

Study Subjects

A total of 7,273 patients were screened, of which 4,753 met eligibility criteria for Ccr and elevated homocysteine level. Of these, 4,110 participants met additional eligibility criteria and were enrolled. Three subjects with missing medication data were excluded. Baseline participant characteristics are summarized in Table 1. We report on 1,527 women and 2,580 men with a mean age of 52 years (SD=9.4) who were enrolled on average 5 years after kidney transplantation. Statistically significant differences in participant characteristics by country are evident, though the magnitude may not be clinically relevant. Baseline characteristics were also examined by categorized graft vintage (data not shown). Subjects did not differ in age, sex, smoking history, prevalence of hypertension, history of diabetes mellitus, CVD history, and BMI across graft vintage categories. However, there were fewer participants of non-white race among those transplanted more than 6 years (19%) than among those with more recent transplants (29%) and those with graft vintage of 2–6 years (26%, $p<0.001$). Older graft vintage was also associated with lower mean eGFR (46 ml/min per 1.73 m^2; $p<0.001$) and lower mean triglyceride levels (188 mg/dL; $p<0.002$) than the intermediate (50 ml/min per 1.73 m^2; 197 mg/dL) and younger (51 ml/min per 1.73 m^2; 214 mg/dL) graft vintage categories.

CVD, Risk Factors and Medication Use

At study entry, 820 participants (20%) reported a history of CVD, including 566 participants (14%) with previous myocardial infarction or coronary heart disease. Ninety-two percent of those enrolled had prevalent hypertension; 69% had blood pressure of 130/80 mm Hg or higher. Uncontrolled hypertension, history of diabetes mellitus, and obesity were common

risk factors present in 44%, 41% and 38%, respectively in this cohort; elevated LDL (130 mg/dL or higher) was present in 18% of participants.

Table 2 summarizes medication use at baseline. Overall, 89% of participants were taking a blood pressure (BP) - lowering medication, 55% a lipid-lowering agent, and 29% an anti-diabetic medication. Of 1,662 participants with a history of diabetes, 72% were prescribed an anti-diabetic agent. Specific medication use frequently differed by graft vintage. The association between graft vintage and use of CVD risk factor lowering medications was inconsistent and *unrelated* to overall use of BP-lowering medications, whereas lipid-lowering agent use was *less* prevalent and anti-platelet use, primarily aspirin use, was *more* prevalent among those with grafts in place less than 2 years than in participants with older vintage grafts. For example, among participants with a graft vintage of two or more years, at least 58% took a lipid lowering medication in comparison to 48% of those with grafts in place less than two years. Conversely, anti-platelet use was more prevalent among those more recently transplanted (47%) than among participants with older vintage grafts (40%–42%). Anti-diabetic agent use was most prevalent among those receiving grafts within the past 2 years (33%) versus those with grafts more than 6 years (26%), perhaps reflecting survivor bias. Among immunosuppression medications, while prednisone use was consistently high across all graft vintage categories (90–92%), cyclosporine A use was more prevalent in participants transplanted at least 6 years (68%) whereas use of mycophenolate mofetil (77%) and tacrolimus (59%) were more frequent among those with more recent transplants.

Medical management of risk factors—Medical management of CVD risk factors is summarized in Table 3. Of 2,817 participants with elevated blood pressure (130/80 mm Hg or higher), 90% were using at least one blood pressure lowering medication, and 61% were taking two or more medications. Of those using one or more anti-hypertensive medications, 70% had blood pressure of 130/80 mm Hg or higher and 44% had blood pressure of 140/90 mm Hg or greater. Elevated low density lipoprotein (LDL ≥ 160 mg/dL) was identified in 209 participants, of which only 85 (41%) reported regular use of a lipid-lowering agent. Of the 2,164 participants who were taking a lipid-lowering agent and had baseline cholesterol data, 87% had a baseline LDL less than 130 mg/dL and only 4% had LDL levels of 160 mg/dL or greater. Only 159 participants reported regular use of more than one lipid lowering medication; of these, 143 (90%) had baseline LDL less than 130 mg/dL.

CVD risk factor lowering medication use was more prevalent among participants with a prior history of CVD events or procedures (Table 4). This association was most evident for use of anti-platelet agents with 69% of subjects with a history of CVD using an anti-platelet agent in comparison to only 36% of those without a CVD history. Also among those with a CVD history, 66% were taking a lipid-lowering medication and 93% were using an anti-hypertensive medication versus 53% and 87%, respectively, of those participants without a history of CV events or procedures. Use of CVD risk factor lowering medications was greater among participants with a history of diabetes in comparison to those without diabetes. Participants with a history of both diabetes and CVD (n=496) were most likely to be using blood pressure lowering medication, lipid-lowering medication, or anti-platelet

agents, whereas those with neither risk factor (n=2,110) were least likely to use these medications.

Discussion

The FAVORIT study reveals that traditional CVD risk factors continue to be over-represented in the kidney transplant population. Although the burden of CVD (20%), diabetes mellitus (41%), borderline or elevated LDL or use of lipid-lowering medication (66%), and obesity (38%) is substantial approximately 9 out of 10 participants had hypertension defined as blood pressure >140/80 mmHg. Of greatest concern is the level of uncontrolled elevated blood pressure that remains after medical management is attempted: 70% of participants taking at least one blood pressure lowering medication had a blood pressure level that failed to meet the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKOQI) (15) recommended target of less than 130/80 mm Hg.

The use of cardiovascular risk reducing medications in renal transplant recipients remains a challenging problem. This is in large part due to the numerous medications prescribed, concerns about patient adherence, medication tolerability and drug: drug interactions that are integral to management of the renal transplant recipient. Patients are often taking two or three immunosuppression medications, two or three anti-infective agents, a proton pump inhibitor or an H_2 blocker, as well as other medications for medical co-morbidity management. Common comorbidities include hypertension, diabetes, and dyslipidemia. Thus, patients may often be taking 6–10 medications directly related to transplantation before a clinician considers the addition of cardiovascular risk-reducing therapies. Moreover, drugs such as HMG-CoA reductase inhibitors (statins) may interact with cyclosporine (22), and cause myopathy or liver enzyme elevations, and bile acid sequestrants may interfere with drug absorption (23). These concerns may limit implementation of these drugs. Additionally, drugs such as renin angiotensin system blockers, which have proven beneficial in the general population for treating heart (24–26) and kidney disease progression (27, 28), may be associated with acute changes in serum creatinine or potassium, and cause a mild reduction in serum hemoglobin (29). As a consequence, clinicians may be willing to tolerate higher levels of blood pressure, and greater degree of lipid abnormalities given concerns about drug: drug interactions, patient tolerability and the concern that prescribing more medications may lead to medication non-adherence.

Cardiovascular disease is the leading cause of death with a functioning graft in the renal transplant population (30). Transplant recipients often present for transplantation with increased CV risk (31), and the majority of patients have hypertension and/or diabetes. Despite the improved life expectancy post-transplantation (30) the underlying CV risks can be compounded by post-transplant risk factors; inadequately controlled hypertension, suboptimal diabetes control, hyperlipidemia, chronic kidney disease and ongoing tobacco use (32). In addition, hyperhomocysteinemia has been a postulated risk factor for atherosclerosis and was the impetus for the implementation of this study (33, 34). Chronic kidney disease in itself has been postulated to contribute to cardiovascular risk (4, 7, 8).

Cardiovascular disease influences the candidacy for transplant. This may explain part of the variation by country in history of CVD that we report. Also, the observed differences by country in the history of diabetes may reflect some variation in definitions, comorbidities, and associated eligibility for transplant between centers.

Our study captures a different population than the recent study (11) that retrospectively evaluated cardiovascular medication use in 14,236 transplant patients from the PORT (Patient Outcomes in Renal Transplantation) study. Pilmore and colleagues report a study that included a lower proportion of patients with cardiovascular disease (4.7% previous MI, 6.8% a revascularization procedure, and 3.7% history of stroke) and smaller percentage of diabetes at the time of transplant (27.9%) than was observed in our chronic stable renal transplant cohort. Therefore, participants in our prospective FAVORIT study were inherently at higher risk for cardiovascular events than the patients in the retrospective PORT study.

Anti-platelet therapy is a mainstay of cardiovascular disease prevention and is standard of care in patients with known CVD. The overall use of acetylsalicylic acid (ASA) was suboptimal for a population with high CVD risk, but varied by graft vintage. The greater use of ASA among recent recipients (45%) in comparison to those greater than six years from transplant (38%) may reflect either greater confidence in using ASA early post transplantation, transplanting a higher risk population, or possibly ASA being stopped for intolerance or other reasons and not being restarted in patients who were further out from transplant. Another consideration is that the ASA use may be an extension of its use to maintain graft patency, unrelated to use as a cardiovascular risk lowering agent. Our study demonstrates that those patients at greatest risk for a cardiovascular event, those with diabetes with known CVD, are most likely to be using antiplatelet therapy (73%) in contrast to the lowest risk patients, the non-diabetic, with no history of CVD (29%).

Hypertension is a leading cause of chronic kidney disease and a risk factor for cardiovascular disease. Blood pressure control in kidney transplant recipients is particularly challenging. The KDOQI (15) recommendations included that most transplant recipients be treated with a regimen drawn from calcium channel blockers, diuretics, ACEi, ARBs, and beta blockers to reach a target blood pressure less than 130/80 mm Hg. Patients less than two years from transplant were more likely to be on a beta-blocker and less likely to be on a diuretic than participants greater than six years out from transplant. The more frequent use of beta blockers in the population of subjects within two years of transplant may reflect a practice of using perioperative beta blockers for cardioprotection. The use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers may have been limited in the past out of concern for elevating the serum creatinine and causing hyperkalemia. This is most problematic in the first 6–12 weeks post-transplant. Use of ACEi and ARBs are felt to offer both renal and cardio-protective benefits once renal function has stabilized. Our cohort includes only patients with stable renal function, greater than six months from transplant and therefore reflects the greater comfort level in using these agents. Nevertheless, the use of this class of agent was relatively low in our cohort despite the purported benefit of ACEi and ARB in stabilizing renal function.

The focus of this paper is to evaluate the use of cardiovascular disease risk-lowering medications in stable renal transplant recipients. Of greatest interest is the frequency of use of these medications in patients with a known history of cardiovascular disease and those at greatest risk for cardiovascular events, specifically diabetic patients. Beta-blocker use for those with known cardiovascular disease imparts improved survival. While our study identified a sizable proportion of participants with a history of CVD who were not taking a beta blocker, we did not ascertain the reasons why such medications were not prescribed or being used by participants.

The strength of this study is in the design, size, and diversity. It aimed to capture a specific population of renal transplant recipients with elevated homocysteine and to evaluate cardiovascular events in a rigorous and standardized fashion. The FAVORIT trial is the largest known trial designed specifically to evaluate cardiovascular outcomes in renal transplant recipients. The mixture of clinical sites and large number of participants provides an excellent cohort for examining contemporary characteristics of renal transplant recipients and associations of the characteristics with cardiovascular and renal outcomes.

The main issue is what is the impediment to maximizing appropriate care of the renal transplant patient? There are likely several contributing factors, not the least of which is who is taking primary responsibility of the patient's medical care? Primary care physicians are often reluctant to adjust medication out of concern for disturbing the delicate balance of medications inherent to a transplant recipient. Transplant physicians are often focused on the primary issues related to managing renal function. There is also concern about polypharmacy with the number of medications a patient must take and the associated drug interactions. Improvement in care of renal transplant patients should not be overlooked as health care systems and guidelines are updated. For example, electronic medical record systems might be customized to prompt transplant physicians to consider CV risk reduction strategies at specific milestones post-transplant. As concerns about the early risks of infection and rejection are lessened, increasing attention can focus on prevention of CVD and other longer term complications. A collaborative management approach is essential to optimize medical management of the kidney transplant recipient.

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Table 1

Baseline Characteristics by Country

Characteristic	Overall n=4107	United States n=2997	Brazil n= 612	Canada n= 498	p-value
Age --- yr	52 ± 9.4	52 ± 9.4	49 ± 8.5	53 ± 10.2	<0.001
Female sex	1527 (37.2 %)	1144 (38.2 %)	214 (35.0 %)	169 (33.9 %)	0.091
Non-white race	998 (24.5 %)	749 (25.2 %)	181 (29.6 %)	68 (13.7 %)	<0.001
Graft Vintage --- yr	5 ± 5.0	5 ± 4.9	5 ± 3.9	7 ± 6.5	<0.001
Smoking history					
Never smoker	2001 (49.3 %)	1496 (50.1 %)	282 (46.1 %)	223 (48.4 %)	ns
Current smoker	450 (11.1 %)	334 (11.2 %)	64 (10.5 %)	52 (11.3 %)	
Former smoker	1611 (39.7 %)	1159 (38.8 %)	266 (43.5 %)	186 (40.3 %)	
Blood Pressure < 130/80 mm Hg	1255 (30.8 %)	1028 (34.5 %)	74 (12.1 %)	153 (32.1 %)	<0.001
Prevalent hypertension	3778 (92.0 %)	2765 (92.3 %)	569 (93.0 %)	444 (89.3 %)	0.053
History of diabetes	1662 (40.5 %)	1332 (44.5 %)	178 (29.1 %)	152 (30.6 %)	<0.001
Medical History					
Previous MI/CHD	566 (13.8 %)	470 (15.7 %)	46 (7.5 %)	50 (10.2 %)	<0.001
Previous stroke/CBVD	271 (6.6 %)	215 (7.2 %)	44 (7.2 %)	12 (2.5 %)	<0.001
Previous AAA repair/LEAD	163 (4.0 %)	146 (4.9 %)	8 (1.3 %)	9 (1.8 %)	ns
Previous CVD (any of above)	820 (20.0 %)	664 (22.2 %)	91 (14.9 %)	65 (13.3 %)	<0.001
Previous renal arterial revascularization	67 (1.6 %)	28 (0.9 %)	32 (5.2 %)	7 (1.4 %)	ns
Body Mass Index (kg/m^2)	29 ± 6.2	30 ± 6.5	27 ± 4.5	28 ± 5.9	<0.001
Lipid Profile					
Total cholesterol (mmol/L)	4.8 ± 1.1	4.8 ± 1.1	5.0 ± 1.3	4.6 ± 1.0	<0.001
HDL (mmol/L)	1.2 ± 0.4	1.2 ± 0.4	1.1 ± 0.3	1.2 ± 0.4	0.002
LDL (mmol/L)	2.6 ± 0.9	2.6 ± 0.9	2.9 ± 1.0	2.4 ± 0.7	<0.001
Triglycerides (mmol/L)	2.2 ± 2.1	2.3 ± 2.3	2.1 ± 1.3	2.2 ± 1.5	ns
Screening homocysteine (mmol/L)					
Female	16.2 ± 5.7	16.2 ± 5.7	16.1 ± 6.8	16.5 ± 4.2	0.086
Male	17.6 ± 6.5	17.5 ± 6.6	17.6 ± 7.2	17.8 ± 5.1	ns
eGFR (ml/min/1.73 m^2)	49 ± 17.7	49 ± 17.7	52 ± 17.5	46 ± 17.7	<0.001
CKD Stage					

Characteristic	Overall n=4107	United States n=2997	Brazil n= 612	Canada n= 498	p-value
Stage 1T (eGFR 90+ ml/min/1.73 m^2)	114 (2.8 %)	80 (2.7 %)	22 (3.6 %)	12 (2.5 %)	<0.001
Stage 2T (eGFR 60–89 ml/min/1.73 m^2)	823 (20.5 %)	591 (20.2 %)	150 (24.5 %)	82 (17.1 %)	
Stage 3T (eGFR 30–59 ml/min/1.73 m^2)	2563 (63.8 %)	1877 (64.2 %)	389 (63.6 %)	297 (61.9 %)	
Stage 4T (eGFR 15–29 ml/min/1.73 m^2)	505 (12.6 %)	372 (12.7 %)	48 (7.8 %)	85 (17.7 %)	
Stage 5T (eGFR <29 ml/min/1.73 m^2)	10 (0.2 %)	3 (0.1 %)	3 (0.5 %)	4 (0.8 %)	

Note: Values expressed as mean ± standard deviation or number (percent) of non-missing data.

Abbreviations: MI/CHD-myocardial infarction/coronary heart disease; CBVD-cerebrovascular disease; AAA-abdominal aortic aneurysm repair; LEAD-lower extremity arterial disease; CVD-cardiovascular disease; HDL-high density lipoprotein cholesterol; LDL-calculated or direct low density lipoprotein cholesterol; eGFR-estimated glomerular filtration rate; CKD-chronic kidney disease.

Table 2

Medication Use by Graft Vintage

	Overall		Graft Vintage (y)						
			0.5 – <2		2 – 6		> 6		
Medication	**N**	**%**	**N**	**%***	**N**	**%***	**N**	**%***	**p-value****
Immunosuppressive	**4085**	100	**1194**	100	**1486**	100	**1405**	100	ns
Cyclosporine A	**2081**	51	**405**	34	**718**	48	**958**	68	<0.001
Tacrolimus	**1551**	38	**703**	59	**632**	43	**216**	15	<0.001
Sirolimus	**342**	8	**151**	13	**136**	9	**55**	4	<0.001
Mycophenolate Mofetil	**2672**	65	**919**	77	**1119**	75	**634**	45	<0.001
Azathioprine	**733**	18	**102**	9	**162**	11	**469**	33	<0.001
Prednisone	**3720**	91	**1080**	90	**1346**	91	**1294**	92	ns
Blood Pressure Lowering	**3620**	89	**1041**	87	**1326**	89	**1253**	89	ns
ACE Inhibitors	**1336**	33	**291**	24	**521**	35	**524**	37	<0.001
Angiotensin Receptor Blockers	**545**	13	**114**	10	**196**	13	**235**	17	<0.001
Beta Blockers	**2306**	56	**739**	62	**851**	57	**716**	51	<0.001
DHP-CCB	**1430**	35	**419**	35	**502**	34	**509**	36	ns
NDHP-CCB	**242**	6	**60**	5	**80**	5	**102**	7	0.014
Loop Diuretics	**1222**	30	**351**	29	**418**	28	**453**	32	0.095
Other Diuretics	**401**	10	**85**	7	**161**	11	**155**	11	0.001
Lipid Lowering	**2264**	55	**577**	48	**857**	58	**830**	59	<0.001
HMG COA Reductase Inhibitors	**2146**	53	**539**	45	**816**	55	**791**	56	<0.001
Other Lipid Lowering	**290**	7	**71**	6	**110**	7	**109**	8	0.078
Anti-Platelet Agents	**1744**	43	**564**	47	**623**	42	**557**	40	<0.001
Aspirin	**1685**	41	**541**	45	**607**	41	**537**	38	<0.001
Clopidogrel	**99**	2	**36**	3	**28**	2	**35**	2	ns
Other Anti-platelet	**34**	1	**7**	1	**9**	1	**18**	1	0.045
Anti-Coagulants	**197**	5	**58**	5	**66**	4	**73**	5	ns
Warfarin	**193**	5	**57**	5	**65**	4	**71**	5	ns
Heparin	**6**	0	**1**	0	**1**	0	**4**	0	ns
Anti-Diabetic Agents	**1196**	29	**391**	33	**443**	30	**362**	26	<0.001

	Overall		Graft Vintage (y)						
			0.5 – <2		2 – 6		> 6		
Medication	**N**	**%**	**N**	**%***	**N**	**%***	**N**	**%***	**p-value****
Insulin	**904**	22	**310**	26	**326**	22	**268**	19	<0.001
Sulfonylureas	**312**	8	**87**	7	**117**	8	**108**	8	ns
Rosigliatazone	**74**	2	**22**	2	**36**	2	**16**	1	ns
Pioglitazone	**62**	2	**18**	2	**27**	2	**17**	1	ns
Metformin	**68**	2	**21**	2	**24**	2	**23**	2	ns
Other Anti-Diabetic Agents	**30**	1	**5**	0	**17**	1	**8**	1	ns

Abbreviations: ACE Inhibitors: angiotensin-converting enzyme inhibitors; DHP-CCB: Dihydropyridine Calcium Channel Blockers; NDHP-CCB: Non-Dihydropyridine Calcium Channel Blockers.

Note: Data for 21 participants with missing graft vintage are omitted from this table.

* Denominator is number of participants in the vintage category.

** P-value is from the Cochran-Armitage test for trend; ns: p >0.10.

Table 3

Risk Factor Lowering Medication Use by Risk Factor Status

	Risk factor lowering medication use*								
	Overall		United States		Brazil		Canada		
Baseline Status	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**p-value**
Systolic BP									
≥ 130 mmHg	2221 (91 %)	219 (9 %)	1572 (91 %)	153 (9 %)	410 (91 %)	42 (9 %)	239 (91 %)	24 (9 %)	ns
< 130 mmHg	1383 (85 %)	249 (15 %)	1085 (86 %)	174 (14 %)	125 (78 %)	35 (22 %)	173 (81 %)	40 (19 %)	0.009
Diastolic BP									
≥ 80 mmHg	1622 (88 %)	212 (12 %)	984 (88 %)	129 (12 %)	442 (89 %)	56 (11 %)	196 (88 %)	27 (12 %)	ns
< 80 mmHg	1981 (89 %)	255 (11 %)	1673 (89 %)	198 (11 %)	92 (81 %)	21 (19 %)	216 (86 %)	36 (14 %)	0.011
SBP ≥ 130 or DBP ≥ 80 mm Hg									
Yes	2526 (90 %)	291 (10 %)	1764 (90 %)	192 (10 %)	478 (89 %)	60 (11 %)	284 (88 %)	39 (12 %)	ns
No	1078 (86 %)	177 (14 %)	893 (87 %)	135 (13 %)	57 (77 %)	17 (23 %)	128 (84 %)	25 (16 %)	0.044
Low-density lipoprotein									
≥ 4.1 mmol/L	85 (41 %)	124 (59 %)	56 (40 %)	84 (60 %)	25 (45 %)	31 (55 %)	4 (31 %)	9 (69 %)	ns
3.4 – 4.1 mmol/L	191 (39 %)	296 (61 %)	126 (39 %)	196 (61 %)	52 (41 %)	76 (59 %)	13 (35 %)	24 (65 %)	ns
< 3.4 mmol/L	1888 (59 %)	1318 (41 %)	1438 (61 %)	909 (39 %)	154 (36 %)	272 (64 %)	296 (68 %)	137 (32 %)	<0.001
Prevalent CVD									
Yes	569 (69 %)	251 (31 %)	458 (69 %)	206 (31 %)	62 (68 %)	29 (32 %)	49 (75 %)	16 (25 %)	ns
No	1175 (36 %)	2099 (64 %)	872 (37 %)	1457 (63 %)	197 (38 %)	324 (62 %)	106 (25 %)	318 (75 %)	<0.001

*Risk factor lowering medications are as follows. For elevated blood pressure (BP):ACE inhibitors, angiotensin receptor blockers, beta blockers, dihydropyridine calcium channel blockers, non-dihydropyridine calcium channel blockers, loop diuretics and other diuretics. For elevated LDL: HMG COA reductase inhibitors, bile acid sequestrants, niacin, gemfibrozil, fenofibrate, bezafibrate, clofibrate, probucol and ezetimibe. For prevalent cardiovascular disease (CVD): aspirin, clopidogrel, ticlopidine and other anti-platelet agents.

Table 4

CVD Risk Factor Lowering Medication Use by Prevalent CVD and History of Diabetes

	History of CVD							No History of CVD							
	Overall		DM History		No DM History			Overall		DM History		No DM History			
Medication	**N**	**%***	**N**	**%***	**N**	**%***	**p-value****	**N**	**%***	**N**	**%***	**N**	**%***	**p-value****	**p-value†**
Blood Pressure Lowering	**764**	93	**468**	94	**296**	91	0.096	**2862**	87	**1032**	89	**1830**	87	0.111	<0.001
ACE Inhibitors	**295**	36	**183**	37	**112**	35	0.497	**1043**	32	**389**	33	**654**	31	0.154	0.025
Angiotensin Receptor Blockers	**113**	14	**75**	15	**38**	12	0.173	**433**	13	**191**	16	**242**	11	<0.001	0.667
Beta Blockers	**569**	69	**341**	69	**228**	70	0.623	**1741**	53	**621**	53	**1120**	53	0.882	<0.001
Other Blood Pressure Lowering	**524**	64	**336**	68	**188**	58	0.005	**2000**	61	**762**	65	**1238**	59	<0.001	0.138
Lipid Lowering	**539**	66	**336**	68	**203**	63	0.149	**1723**	53	**668**	57	**1055**	50	<0.001	<0.001
HMG COA Reductase Inhibitors	**507**	62	**315**	64	**192**	59	0.242	**1636**	50	**634**	54	**1002**	48	<0.001	<0.001
Other Lipid Lowering	**87**	11	**57**	11	**30**	9	0.310	**202**	6	**85**	7	**117**	6	0.045	<0.001
Anti-Platelet Agents	**569**	69	**362**	73	**207**	64	0.006	**1175**	36	**553**	48	**622**	29	<0.001	<0.001

*Denominator is number of participants with non-missing medication data in the corresponding column.

**P-value is from Pearson chi-square test if expected cell counts > 10; else from Fisher's Exact Test for comparing medication use by DM status within history of CVD stratum.

†P-value is from Pearson chi-square test if expected cell counts > 10; else from Fisher's Exact Test for comparing medication use among those with a history of CVD verses those without a history of CVD.