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Safety Events in Kidney Transplant Recipients: Results from the Folic Acid for Vascular Outcome Reduction in Transplant (FAVORIT) Trial

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Abstract

Background—Kidney transplant recipients are at increased risk for adverse safety events related to their reduced renal function and many medications.

Methods—We determined the incidence of adverse safety events based on previously defined Agency for Healthcare and Research Quality (AHRQ) ICD-9 code-derived patient safety indicators (PSI) in the Folic Acid for Vascular Outcome Reduction in Transplant (FAVORIT) trial participants who had a hospitalization stratified by tertiles of estimated glomerular filtration rate. We also examined the frequency of Micromedex defined two precautionary drug-drug interactions, and two medications whose use may be contraindicated due to reduced GFR from the FAVORIT trial Medication Thesaurus at baseline, and annually among 4110 participants. Logistic regression was used to examine the relationship between patient safety events and baseline demographic and clinical variables at a participant level. Event rates were estimated at participant and visit levels.

Results—Of the 2514 patients with a hospitalization, 978 (38.9%) experienced an AHRQ PSI. Factors which were associated with more common AHRQ PSI included: US location, history of cardiovascular disease or diabetes, and lower tertile of estimated GFR. At a participant level, 2524 of the 4110 participants (61.4%) were taking a CNI and a statin, 378 (9.2%) were taking

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azathioprine and an ACE inhibitor, 171 (12.9%) were taking a sulfonylurea), 45 (3.4%) were taking metformin despite a baseline GFR below 40 ml/min/1.73m^2.

Conclusions—We conclude that patient safety events are not uncommon in kidney transplant recipients. Careful monitoring is necessary to prevent adverse outcomes.

Keywords

Medication error; Medication Safety; Transplantation

Introduction

Patients with chronic kidney disease (CKD) are at increased risk for adverse safety events related to their care [1-3] however little work has been done to determine the impact of these safety events on CKD outcomes. This is particularly relevant in kidney transplant recipients who often have reduced estimated glomerular filtration rate (GFR) where medication dosage adjustment may be required, and there is increased risk of drug: drug interactions [4]. Moreover it remains unanswered how precautionary statements issued by Micromedex about potential drug-drug interactions in transplant recipients translate into patient safety events in this population. This study aimed to identify the frequency of general patient safety events as determined by hospital-based ICD-9 codes, as well as the frequency of usage of commonly administered medications which are ill-advised in individuals with reduced GFR. We postulated that a high frequency of published precautionary drug interactions would be present as part of this population's usual medical management profile, and questioned whether these exposures may be associated with adverse events.

Results

Patient characteristics

Participant characteristics are shown in Table 1. The mean age was 52 years with a predominance of males (63%) and approximately 25% non-white race. The majority of the participants (73%) were from the United States, but there was substantial representation from Brazil (15%), and Canada (12%). The graft vintage was on average five years. Many of the patients had a history of cardiovascular disease (20%), diabetes mellitus (40%), and hypertension (92%). Only 11% were current smokers and mean baseline GFR was 49 ml/min/1.73m^2. Follow-up ranged from 0-6.8 years yielding a mean of 4.0 +/− 1.5 years. During follow-up, 62% of the participants were hospitalized at least once, and accrued a total of 7939 hospitalizations.

Overall safety events

There were a substantial number (39%) of participants who were hospitalized with AHRQ PSI (Table 2). Overall, about 20% of all hospitalizations events were considered as PSI events. It is important to note, that patients in the lowest tertile of estimated GFR, experienced more AHRQ PSI at the participant level and hospitalizations considered as PSI events. The rates for AHRQ PSI at the three tertiles of GFR were significantly different from each other for both participant level ($p<.0001$) and hospitalizations ($p=.0004$).

There was frequent use of statins with CNI (61% at the participant level) as well as sulfonylureas (13%) and metformin (4%) at the participant level) (Table 3). Patients with the lowest tertile of GFR experienced no more participant level and visit level patient safety events, while receiving metformin or sulfonylurea drugs' compared to those patients in the higher GFR tertiles.

Demographics and clinic characteristics: AHRQ Patient Safety Indicators

Overall, patients with diabetes or cardiovascular disease (CVD) were more likely to experience AHRQ PSI at the patient level (Table 4). Interestingly, transplant patients from Canada and Brazil were less likely to experience patient level AHRQ events compared to patients from the US. Also, patients with higher GFR were less likely to experience events. We also evaluated GFR as a continuous variable, rather than as tertiles, and observed that for each 1ml / min / 1.73 m2 increase in estimated GFR that the odds ratio for an event was 0.99 (0.98-0.99), p<.001.

As seen in Table 5, the incidence of myopathy was low and was not associated with the use of a CNI and a statin. The use of an ACE inhibitor with azathioprine was associated with an increased risk of shock/sepsis, p=0.04. Patients in the lowest tertile of GFR taking a sulfonylurea or metformin experienced more diabetic ketoacidosis/coma than those patients in the middle or higher tertiles of GFR. On the other hand, the risk of hypoglycemia was higher in the middle tertiles of GFR.

Drug interaction: CNI and a statin

Participants of older age or with known CVD were more likely to receive a combination of a CNI and a statin (SDC, Table 1). Interestingly patients of African heritage were less likely to receive both, as well as were individuals from Brazil. Canadians were more likely to receive a statin and a CNI compared to the US participants. Likewise, patients with history of diabetes, or who were overweight, were more likely to receive a statin and a CNI, as were patients with higher baseline GFR.

Drug interaction: Azathioprine and an ACE inhibitor

The combination of azathioprine and an ACE inhibitor was more common in Brazil, in patients with older graft vintage, and in current smokers (SDC, Table 2). This drug combination was less common in Canada compared to the US, in patients with lower baseline GFR, as well as those with hypertension.

Potential Safety events: Diabetic Patients on a sulfonylurea

Older participants, patients of African heritage, and higher BMI were more likely to receive a sulfonylurea with a reduced baseline GFR. This was also more commonly seen in Canada, compared to US or Brazil (SDC, Table 3). Not surprisingly, history of diabetes and overweight patients were more likely to receive a sulfonylurea.(SDC, Table 3).

Potential Safety events: Diabetic Patients on Metformin

Older patients, those patients with higher BMI, and non-US patients were commonly prescribed metformin. Males were less likely to receive metformin. Patients with a higher

GFR were more likely to receive metformin compared to those with a lower GFR. (SDC, Table 4).

Discussion

Recipients of kidney transplants are at increased risk for adverse safety events related to the many medications that they receive for their immunosuppression and medical comorbidity. Moreover, many of these patients have estimated GFR in the lower tertile, <40 ml/min/1.73 m^2. Little information exists in the literature as to the relationship between medication misuse, drug: drug interactions, and adverse outcomes. To our knowledge, this is the first report which has examined the frequency of Micromedex precautionary drug interactions and the use of medications which may be contraindicated in kidney transplant patients due to reduced estimated GFR. Herein, we describe that patient safety exposures are not uncommon, and some exposures may put patients at much greater risk for adverse outcomes, whereas others do not.

Overall, we noted that about 20% of all hospitalizations were considered as PSI events. Not surprisingly, patients with reduced estimated GFR, diabetes or CVD were more likely to experience AHRQ PSI likely related to greater use of medications for treatment of these comorbidities. Higher GFR was associated with reduced risk of PSI events, as were non-US patients. Interestingly, the lower risk of PSI in non-US patients was evident despite greater use of statins, sulfonylureas, and metformin in Canadian patients. With the expanding circle of health care providers involved in the clinical care of kidney transplant recipients, the opportunity for medication misuse and patient safety events is substantial. In addition, the large number of newer medications for immunosuppression, infection, and medical co-morbidities places an increasing burden on prescribers to be sure about medication interactions (especially with the immunosuppression medications) and use in patients with reduced renal function. Our observations in this trial provide important perspectives in this regard and indicate the need for continued surveillance and better strategies to facilitate education for both patients and healthcare providers.

We specifically chose to examine two common Micromedex defined precautionary drug: drug interactions: those patients taking a CNI and a statin and those taking azathioprine and an ACE inhibitor. CNI alter statin metabolism and may enhance their overall effect, but also increase their risk of inducing myopathy and possibly even rhabdomyolysis[12-14]. Although statins are of great use in reducing the risk of cardiovascular events in both the general population, as well as in the transplant population [17, 18], the therapeutic index has been questioned by some. Jardine [19] has noted that there are more myopathic events in patients receiving statins with cyclosporine. In the FAVORIT trial, more than 25% of patients were receiving both drugs which resulted in comparable visit level event and non-event exposures. Overall, there were only 44 AHRQ PSI myopathy events, which is remarkably low considering the exposure. Although there was a trend toward more patients receiving a CNI and a statin to experience myopathy, due to the low event frequency, this was not statistically significant. These observations would suggest that the concern of clinically significant myopathy requiring hospitalization with the concomitant use of a CNI and a statin is quite low [15, 16]and is more than offset by the beneficial effects of statins on

cardiovascular risk in renal transplant recipients. Nonetheless, caution is required, especially with the use of higher doses of statins.

Likewise, we examined the percentage of patients receiving both azathioprine, and an ACE inhibitor, which is also listed as “medication error” by Micromedex. This combination may increase the risk of leukopenia and anemia. Although not well recognized in current literature due to the diminished use of azathioprine, there are many patients with older grafts who receive both medications. In our cohort, 378 patients were receiving both, albeit with a low visit level event to non-event ratio. There did not appear to be a correlation between taking these two drugs and AHRQ hospitalization events of shock or sepsis, with only 316 total events, of which only 19 occurred in patients taking both drugs. This would indicate that this interaction is unlikely to be of clinical concern. Unfortunately, we did not capture transfusion events in our data set to see if the use of the two drugs influenced the need for transfusions. Interestingly, mycophenolate mofetil and mycophenolic acid are the two antimetabolites which are most commonly used in transplantation today, yet are not listed in Micromedex as a “medication error” with a renin-angiotensin system blocking drug.

The use of sulfonylureas, particularly glyburide, and metformin in kidney transplant patients may be more complicated, especially in those patients with lower GFR [8-11] Although the FAVORIT medication thesaurus would not allow distinctions between type of sulfonylureas, it was evident that the use of these drugs, even in the lower tertile of estimated GFR, was not associated with an increased risk of patient safety events. Since the FAVORIT study start was in 2005, it is likely that many of the patients were receiving older sulfonylureas such as glyburide, which does require dosage adjustment in patients with reduced renal function [9]. Thus, there were a sizeable number of visit level event exposures during the course of the FAVORIT trial. This was of particular concern, as it has been described in literature that hypoglycemia and lactic acidosis can occur with use of these types of oral anti-diabetic medications in patients with reduced GFR[11]. Although we could not distinguish between the types of acidosis based on the AHRQ ICD-9 codes, it was apparent that diabetic ketoacidosis/coma was nearly three times more common in patients taking these drugs, as compared to those not taking them, and occurred more frequently in patients in the lowest tertile of estimated GFR. Hypoglycemia can occur in patients taking these drugs, which would necessitate some caution, with the use of these drugs in patients with reduced estimated GFR. Moreover, a study in diabetic patients with chronic kidney disease demonstrated increased one day mortality in those individuals reduced GFR experiencing hypoglycemia [20]. However, we did not observe an increased risk of hypoglycemia with the use of these drugs in our lowest estimated GFR tertile group.

In summary, these descriptive data provide the first opportunity to examine the frequency of precautionary medication exposures in a large cohort of prevalent kidney transplant recipients from three different countries. This data set also provides an opportunity to examine between country differences, as well as clinical factors and patient characteristics which predispose to these exposures. Our results indicate that there is a high frequency of published (Micromedex) precautionary drug interactions as part of the usual pharmacy profile in kidney transplant patients. Our data suggests that some of these precautionary

statements are of less clinical relevance than previously thought. But, others are of substantial concern.

The strength of our observations stems from the well described cohort of transplant recipients from diverse backgrounds, and the detailed efforts to capture all hospitalization data. More than 4000 participants were followed for more than four years. The limitations of our observations are related to the categorization of drugs within the Medication Thesaurus, which frequently lumped classes of medications together for simplicity, the lack of notation of dose, the categorization of ICD-9 codes, and the care and the completeness of the coding process, and the limitation of relying only on hospitalization data, which represents only a small portion of general renal transplant recipient care. Further, the opportunity to examine individual medications of concern such as glyburide, among the sulfonylureas, was not possible. In addition, other types of medication, such as potassium-sparing diuretics, may put patients at greater risk for adverse outcomes such as potassium sparing diuretics, however our Medication Thesaurus was not designed to examine all of the many individual medications that were used in our patients. Our results also underscore the difficulties in identifying relevant drug interactions and safety events even in the context of a prospective cohort study.

Our relatively limited description of exposures in renal transplant recipients likely only scratches the surface of potential adverse events in this population. The frequency of these events is sufficient to raise concern about our current clinical practice and how we may best protect our patients from patient safety events related to misuse of medications in this at risk population.

Methods

The study was conducted using data obtained from the Folic Acid for Vascular Outcome Reduction in Transplant (FAVORIT) trial, a multi-center, multi-country, double-blind, randomized controlled clinical trial conducted to determine whether lowering homocysteine levels with vitamin therapy would reduce the rate of pooled atherosclerotic cardiovascular disease outcomes in 4110 kidney transplant recipients with mean follow-up of four years [5]. Details of the study design have been previously published [5]. The trial received approval from institutional review boards or ethical boards from all thirty clinical sites.

Study participants

Kidney transplant recipients between the ages of 35 and 75 years who were at least 6 months post-transplant were screened for eligibility. Study criteria required: elevated homocysteine levels and stable kidney function with an estimated GFR >30 ml/min/1.73m^2 through July 7, 2005, after which the cut-point for women was reduced to >25 ml/min/1.73m^2. Estimated GFR utilized for screening was the Cockroft-Gault formula. Baseline data utilized the CKD-EPI formula to calculate estimated GFR [6]. Race and ethnicity were self-determined.

Baseline and follow-up

The trial enrolled participants between August 2002 and January 2007. Follow-up contacts occurred every six months through January 2010 to obtain study-related outcomes through June 2009.

Safety Events Ascertainment

We initially evaluated the incidence of adverse safety events based on Agency for Healthcare and Research Quality (AHRQ) [7] patient safety indicators (PSI) in the FAVORIT participants who had a hospitalization [7] stratified by estimated GFR. For the determination of ICD-9 derived safety events, the AHRQ was integrated with FAVORIT hospitalization ICD-9 data.

Next, we also examined the frequency of use of sulfonylureas (particularly glyburide) and of metformin in kidney transplant recipients stratified by estimated GFR due to the increased reported risk of hypoglycemia and lactic acidosis, respectively [8-11]. Information on the specific sulfonylurea type used was not available in this dataset.

Lastly, we focused on the frequency of two Micromedex precautionary drug-drug interactions including: the use of statins and calcineurin inhibitors (CNI), and angiotensin-converting enzyme (ACE) inhibitors with azathioprine. These two drug-drug interactions were chosen due to the increased risk of myopathy and rhabdomyolysis with concurrent use of CNI [12-14], and the greater reported risk of anemia and leukopenia when ACE inhibitors are combined with azathioprine. Our medication thesaurus did not provide distinction about the type of medication, nor the dose[15, 16].

Statistical analysis

The use of medication at a participant level was determined at baseline and at each follow-up visit. A participant was recorded as having used the medication if he used it at least on one occasion. Logistic regression was utilized to examine the relationship between outcome variables and a variety of baseline demographic and clinical variables at a participant level. Data at the visit level for each patient were tabulated as the number of visits with events out of the total number of visits for that patient. The rates at the visit level were estimated using logistic regression with over dispersion. Presence of an ICD-9 code was compared in groups with and without the medication exposure, where exposure was determined based on the follow-up visit preceding the occurrence of the ICD-9 event. Patients were stratified by estimated GFR (ml/min/1.73m^2) into tertiles: low (mean 31.02, 9.5-39.1), middle (mean 46.32, 39.2-53.8) and high (mean 68.6, 53.9-131.8). Analyses were performed at both the patient, and visit level. All analyses were performed using SAS statistical software (SAS Institute Inc., SAS® 9.2, Cary, NC, USA).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Reference List

1. Chapin E, Zhan M, Hsu VD, Seliger SL, Walker LD, Fink JC. Adverse safety events in chronic kidney disease: the frequency of "multiple hits". Clin J Am Soc Nephrol. Jan; 2010 5(1):95–101. [PubMed: 19965526]
2. Fink JC, Brown J, Hsu VD, Seliger SL, Walker L, Zhan M. CKD as an underrecognized threat to patient safety. Am J Kidney Dis. Apr; 2009 53(4):681–8. [PubMed: 19246142]
3. Seliger SL, Zhan M, Hsu VD, Walker LD, Fink JC. Chronic kidney disease adversely influences patient safety. J Am Soc Nephrol. Dec; 2008 19(12):2414–9. [PubMed: 18776123]
4. Manitpisitkul W, McCann E, Lee S, Weir MR. Drug interactions in transplant patients: what everyone should know. Curr Opin Nephrol Hypertens. Sep; 2009 18(5):404–11. [PubMed: 19593130]
5. Bostom AG, Carpenter MA, Kusek JW, et al. Homocysteine-lowering and cardiovascular disease outcomes in kidney transplant recipients: primary results from the Folic Acid for Vascular Outcome Reduction in Transplantation trial. Circulation. Apr 26; 2011 123(16):1763–70. [PubMed: 21482964]
6. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. May 5; 2009 150(9):604–12. [PubMed: 19414839]
7. Department of Health and Human Services and Human Services Agency for Healthcare Research & Quality. AHRQ quality indicators-guide to patient safety indicators. Agency for Healthcare Quality and Research; Rockville, MD: Feb 20. 2006 [3.0]Ref Type: Online Source
8. Holstein A, Hammer C, Hahn M, Kulamadayil NS, Kovacs P. Severe sulfonylurea-induced hypoglycemia: a problem of uncritical prescription and deficiencies of diabetes care in geriatric patients. Expert Opin Drug Saf. Sep; 2010 9(5):675–81. [PubMed: 20553106]
9. Holstein A. Impact of renal impairment on the risk of severe hypoglycaemia associated with the use of insulin and glyburide. Nephrol Dial Transplant. May; 2011 26(5):1748–9. [PubMed: 21372261]
10. Laforest C, Saint-Marcoux F, Amiel JB, Pichon N, Merle L. Monitoring of metformin-induced lactic acidosis in a diabetic patient with acute kidney failure and effect of hemodialysis. Int J Clin Pharmacol Ther. Feb; 2013 51(2):147–51. [PubMed: 23149294]
11. Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. Diabetes Care. Jun; 2011 34(6):1431–7. [PubMed: 21617112]
12. Asberg A. Interactions between cyclosporin and lipid-lowering drugs: implications for organ transplant recipients. Drugs. 2003; 63(4):367–78. [PubMed: 12558459]
13. Christians U, Jacobsen W, Floren LC. Metabolism and drug interactions of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in transplant patients: are the statins mechanistically similar? Pharmacol Ther. Oct; 1998 80(1):1–34. [PubMed: 9804052]

14. Lemahieu WP, Hermann M, Asberg A, et al. Combined therapy with atorvastatin and calcineurin inhibitors: no interactions with tacrolimus. Am J Transplant. Sep; 2005 5(9):2236–43. [PubMed: 16095503]
15. Gossmann J, Kachel HG, Schoeppe W, Scheuermann EH. Anemia in renal transplant recipients caused by concomitant therapy with azathioprine and angiotensin-converting enzyme inhibitors. Transplantation. Sep; 1993 56(3):585–9. [PubMed: 8212154]
16. Kirchertz EJ, Grone HJ, Rieger J. Successful low dose captopril rechallenge following drug-induced leucopenia. Lancet. Jun 20; 1981 1(8234):1362–3.
17. Holdaas H, Fellstrom B, Jardine AG, et al. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. Lancet. Jun 14; 2003 361(9374):2024–31. [PubMed: 12814712]
18. Holdaas H, Fellstrom B, Cole E, et al. Long-term cardiac outcomes in renal transplant recipients receiving fluvastatin: the ALERT extension study. Am J Transplant. Dec; 2005 5(12):2929–36. [PubMed: 16303007]
19. Jardine A, Holdaas H. Fluvastatin in combination with cyclosporin in renal transplant recipients: a review of clinical and safety experience. J Clin Pharm Ther. Dec; 1999 24(6):397–408. [PubMed: 10651972]
20. Moen MF, Zhan M, Hsu VD, et al. Frequency of hypoglycemia and its significance in chronic kidney disease. Clin J Am Soc Nephrol. Jun; 2009 4(6):1121–7. [PubMed: 19423569]

Table 1

Baseline Characteristics of Study Participants

Characteristics	n (%) or mean ± SD (n=4110)
Age in years	**52 ± 9.4**
Female sex	**1528 (37.2)**
Nonwhite race	**998 (24.5)**
Country	
Brazil	**612 (14.9)**
Canada	**498 (12.1)**
United States	**3000 (73.0)**
Graft vintage in years	**5 ± 5.0**
History of CVD	**820 (20.0)**
History of diabetes mellitus	**1663 (40.5)**
Hypertension	**3778 (92.0)**
Body mass index (kg/m^2)	**29 ± 6.2**
Current Smoker	**451 (11.1)**
Baseline creatinine (μmol/L)	**1.7 ± 0.6**
Baseline eGFR (mL/min per 1.73 m^2)	**48.9 ± 17.7**
Baseline CKD Stage	
Stage 1 (eGFR 90 mL/min per 1.73 m^2)	**115 (2.9)**
Stage 2 (eGFR 60-89 mL/min per 1.73 m^2)	**822 (20.4)**
Stage 3 (eGFR 30-59 mL/min per 1.73 m^2)	**2571 (63.9)**
Stage 4 (eGFR 15-29 mL/min per 1.73 m^2)	**507 (12.6)**
Stage 5 (eGFR <15 mL/min per 1.73 m^2)	**10 (0.3)**

Abbreviations: CVD = Cardiovascular Disease

Table 2

Agency for Healthcare Research Quality (AHRQ) Patient Safety Indicators (PSI) stratified by tertile of GFR

	AHRQ Patent Safety Indicator (PSI) Present			
	Yes		No	
	N	%	N	%
Participant Observed Rate	**978**	**38.9**	**1536**	**61.1**
Low tertile GFR	**406**	**45.2**	**492**	**54.8**
Middle tertile GFR	**290**	**36.8**	**497**	**63.2**
High tertile GFR	**255**	**33.5**	**507**	**66.5**
Hospitalizations Observed Rate	**1606**	**20.2**	**6333**	**79.8**
Low tertile GFR	**663**	**22.4**	**2334**	**77.6**
Middle tertile GFR	**468**	**19.7**	**1865**	**80.3**
High tertile GFR	**423**	**17.5**	**1905**	**82.5**

p-value <.0001 for participant observed differences in rates for GFR, P value = 0.004 for hospitalization observed differences in rate for GFR. Based on chi-square test GFR=estimated glomerular filtration rate

Table 3

Overall Safety Events in FAVORIT Participants

	Participant		Visit [+]	
	N	%	N	%
Drug Interaction				
CNI and Statin	**2524/4110**	**61.4**	**7898/16327**	**47.4**
AZA and ACEI	**378/4110**	**9.2**	**1036/16327**	**6.3**
Metformin Use Stratified by GFR tertile	**Participant[*]**		**Visit[**]**	
Low tertile GFR	**45/1325**	**3.4**	**104/5081**	**2.0**
Middle tertile GFR	**54/1322**	**4.1**	**124/5330**	**2.5**
High tertile GFR	**65/1359**	**4.7**	**140/5496**	**2.6**
Sulfonyluree use Stratified by GFR tertile	**Participant[***]**		**Visit[****]**	
Low tertile GFR	**171/1325**	**12.9**	**388/5081**	**7.6**
Middle tertile GFR	**182/1322**	**13.8**	**429/5337**	**7.9**
High tertile GFR	**180/1369**	**13.1**	**425/5496**	**7.5**

CNI=calcineurin inhibitor, AZA=azathioprine, ACEI=angiotensin-converting enzyme inhibitor, GFR=estimated glomerular filtration rate

[+] Rates computed using proc logistic scale=Williams.

[*] p value = 0.08,

[**] p value = 0.09,

[***] p value = 0.80,

[****] p value = 0.72

Table 4

Demographics and Clinical Characteristics: AHRQ Patient Safety Indicators

Characteristic	Likelihood Estimate	95% Confidence Interval
Age (years) quartile		
<44 (Reference)	**1.00**	
45-54 vs. <44	**0.87**	**(0.68-1.10)**
55-64 vs. <44	**0.95**	**(0.74-1.22)**
>64 vs. <44	**1.05**	**(0.77-1.43)**
Female (reference)	**1.00**	
Male	**1.04**	**(0.87-1.25)**
Caucasian (reference)	**1.00**	
African heritage	**1.05**	**(0.84-1.32)**
Other	**0.93**	**(0.64-1.36)**
Location		
US (Reference)	**1.00**	
Canadian	**0.41**	**(0.29-0.57)***
Brazil	**0.18**	**(0.13-0.26)***
No history of CVD	**1.00**	
History of CVD	**1.39**	**(1.13-1.71)***
No history of diabetes	**1.00**	
History of diabetes	**1.25**	**(1.04-1.49)****
Smoking		
Never smoker (Reference)	**1.00**	
Current smoker	**1.25**	**(0.94-1.66)**
Ever smoker	**1.13**	**(0.93-1.36)**
BMI (kg/m^2) tertile		
Lowest (15.8-25.8) (Reference)	**1.00**	
Middle (25.9-30.6)	**1.14**	**(0.91.-1.42)**
Highest (30.7-57.5)	**1.14**	**(0.91-1.41)**
Graft Vintage tertile		
Lowest (0.3-2.2) (Reference)	**1.00**	
Middle (2.3-6.0)	**0.96**	**(0.78-1.19)**
Highest (6.1-46.2)	**1.01**	**(0.82-1.25)**
No prevalent hypertension	**1.00**	
Prevalent hypertension	**0.94**	**(0.66-1.35)**
Glomerular Filtration Rate tertile		
Lowest (9.5-39.1) (Reference)	**1.00**	
Middle (39.2-53.8)	**0.69**	**(0.56-0.85)***
Highest (53.9-131.8)	**0.59**	**(0.48-0.73)***

Abbreviations: AHRQ=Agency for Healthcare and Research Quality, US=United States, CVD=cardiovascular disease, BMI=body mass index

*
p-value < 0.01,

** **p-value <0.05.**

Table 5

Medication Administration and Agency for Healthcare and Research Quality ICD-9 code Derived Patient Safety Indicator Events

Event		Participants taking both CNI and Statin				
		Yes		No		
		N	%	N	%	p-value
Myopathy	Yes	30	1	14	1	0.35
	No	2494	99	1572	99	
		Participants taking both ACEI and AZA				
		Yes		No		
		N	%	N	%	p-value
Shock/Sepsis	Yes	19	5	297	8	0.04
	No	359	95	3435	92	

	Participants taking Sulfonylurea or Metformin stratified by tertile of GFR				
	Yes		No		
	N	%	N	%	p value
Diabetic Ketoacidosis/Coma*					
Low tertile GFR.....Yes	70	34.5	133	65.5	<.0001
..... No	207	18.5	915	81.5	
Middle tertile GFR.....Yes	70	32.9	171	15.4	<.0001
..... No	143	67.1	938	84.6	
High tertile GFR.....Yes	61	28.1	197	17.1	.0001
..... No	156	71.9	955	82.9	
Hypoglycemia**					
Low tertile GFR.....Yes	6	3.0	32	2.8	0.83
..... No	197	97.0	1090	97.2	
Middle tertile GFR ..Yes	10	4.7	13	1.2	0.002
..... No	203	95.3	1096	98.8	
High tertile GFR..... ..Yes	8	3.7	18	1.6	0.052
..... No	209	96.3	1134	98.4	

CNI – calcineurin inhibitor, AZA = azathioprine, ACEI = angiotensin-converting enzyme inhibitor GFR=estimated glomerular filtration rate.

* **p value = 0.34**