Metformin Use in the First Year after Kidney Transplant, Correlates and Associated Outcomes in Diabetic Transplant Recipients: A Retrospective Analysis of Integrated Registry and Pharmacy Claims Data

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Abstract

While guidelines support metformin as a therapeutic option for diabetic patients with mild-to-moderate renal insufficiency, the frequency and outcomes of metformin use in kidney transplant recipients are not well described. We integrated national U.S. transplant registry data with records from a large pharmaceutical claims clearinghouse (2008–2015). Associations (adjusted hazard ratio, $_{95\% \text{ LCL}}\text{aHR}_{95\% \text{ UCL}}$) of diabetes regimens (with and excluding metformin) in the first year post-transplant with patient and graft survival over the subsequent year were quantified by multivariate Cox regression, adjusted for recipient, donor, and transplant factors and propensity for metformin use. Among 14,144 recipients with pretransplant type 2 diabetes mellitus, 4.7% filled metformin in the first year posttransplant; most also received diabetes comedications. Compared to those who received insulin-based regimens without metformin, patients who received metformin

were more likely to be female, have higher estimated glomerular filtration rates, and been transplanted more recently. Metformin-based regimens were associated with significantly lower adjusted all-cause (aHR $_{0.18}0.41_{0.91}$), malignancy-related (aHR $_{0.45}0.45_{0.99}$), and infection-related (aHR $_{0.12}0.32_{0.85}$) mortality, and non-significant trends toward lower cardiovascular mortality, graft failure and acute rejection. No evidence of increased adverse graft or patient outcomes was noted. Use of metformin-based diabetes treatment regimens may be safe in carefully selected kidney transplant recipients.

Keywords

Diabetes mellitus; Kidney transplant; Metformin; Mortality; Pharmacy claims; Risk factors

INTRODUCTION

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend metformin as first-line therapy for type 2 diabetes[1] based on higher efficacy in glucose reduction, favorable effects on lipids, lower risk of side effects such as weight gain and hypoglycemia, and lower cost.[2] Large cohort studies have also demonstrated a survival benefit compared with the use of other diabetes treatment agents.[3]

While data support the benefits of metformin as a first-line agent for diabetes in the general population,[1] its safety, efficacy and association with clinical outcomes, are not well described among kidney transplant recipients. In transplant patients, immunosuppressive medications such as corticosteroids,[4] calcineurin inhibitors,[5] and mammalian target of rapamycin (mTOR) inhibitors[6,7] are associated with hyperglycemia that can worsen control of preexisting diabetes or lead to new-onset diabetes after transplant (NODAT).[8] In an observational study of kidney transplant recipients linking Scientific Registry of Transplant Recipients (SRTR) data to national pharmacy claims data, Stephen *et al.* found that of 51,523 recipients from 2001–2012, almost 10% received a metformin as part of their diabetic treatment regimen.[9] Metformin use was associated with improved allograft and patient survival.[9] A small retrospective single-center united States (U.S.) study examined the efficacy and safety of metformin and thiazolidinediones in kidney transplant recipients with either preexisting diabetes mellitus or NODAT over a mean follow-up of 16.4 months.[10] Although a decline in glomerular filtration rate (GFR) was noted in all patients with pre-transplant diabetes mellitus, only 3 of 11 patients had to stop metformin due to drop in GFR. In patients with NODAT, only 2 of 21 stopped metformin during follow-up. Both regimens were equally efficacious in glycemic control. The authors concluded that metformin use may be safe in diabetic kidney transplant recipients.[10] In a safety analysis of the Folic Acid for Vascular Outcome Reduction in Transplant (FAVORIT) trial, metformin use in kidney transplant recipients with lower GFR tertile (mean 31, range 9.5–39 ml/min per 1.73 m^2) was not associated with more adverse events, based on the Agency for Healthcare Research and Quality (AHRQ) Quality Indicators, compared with use in recipients with upper tertile GFR (mean 69, range 54–132 ml/min per 1.73 m^2), although there was a greater association with diabetic ketoacidosis/coma.[11]

Most of the evidence related to anti-glycemic medication use in transplant recipients comes from NODAT. [12] There is minimal data on patients with preexisting type 2 diabetes mellitus. In NODAT, sulfonylureas[13] are often used as the first-line oral agents, while meglitinides[14] are recommended as second-line agents due to safe renal profile but greater expense. Among patients that cannot use these two agents, the third-line agents usually include dipeptidyl peptidase-4 inhibitors[15] and alpha-glucosidase inhibitors. Thiazolinediones are usually avoided due to concerns about edema and bone loss [16]. Although recent data suggest renal benefit associated with sodium–glucose cotransporter 2 (SGLT-2) inhibitors in the general diabetic population with high cardiovascular risk[17] and those with early CKD,[18] there is minimal data on their use in the transplant population. The concern of lactic acidosis in patients with low GFR prompts many clinicians to avoid prescribing metformin in transplant recipients. This is despite recent data supporting the safety and efficacy of metformin use, in non-transplant patients with mild-to-moderate chronic kidney disease (CKD).[19] However, some experts caution against the use of metformin after kidney transplant due to heightened concerns of lactic acidosis as well as the relative inefficiency of metformin alone to provide adequate glycemic control exacerbated by immunosuppression.[20] On the other hand metformin has been proposed as a strategy to prevent NODAT by reducing beta-cell stress posttransplant.[21] Thus the potential risks and outcomes associated with metformin in kidney transplant recipients remain controversial.

To advance the understanding of the patterns of use, safety and outcomes associated with metformin treatment in kidney transplant recipients with pretransplant diabetes mellitus type 2, we examined a linkage of national transplant registry data with medical fill records from a large pharmaceutical claims clearinghouse. We examined the correlates of metformin use in the first year after transplant, and associations with graft and patient outcomes over the subsequent year.

METHODS

Data Sources

Data for this study was obtained from the SRTR.[22] The SRTR registry contains data on all transplant candidates, recipients, and donors in the United States (U.S), provided by the Organ Procurement and Transplantation Network (OPTN).[21] The Health Resources and Services Administration (HRSA) and U.S. Department of Health oversee OPTN and SRTR activities. SRTR kidney transplant data include baseline demographics such as recipient age at the time of transplant, sex, and race, as submitted by the hospital to the OPTN. The database also identifies acute rejection, graft failure, and death as reported by the hospital to the OPTN. The SRTR supplements graft failure records with Center for Medicare and Medicaid Studies end-stage renal disease reports and mortality data with the Social Security Death Master File.

Pharmacy fill data were assembled by linking SRTR records for kidney transplant recipients with billing claims from Symphony Health Solutions (SHS), a large U.S. pharmaceutical claims data warehouse that maintains prescription drug fill records including self-paid fills and those reimbursed by private and public payers. SHS comprises National Council for Prescription Drug Program format prescription claims aggregated from multiple sources

including claims warehouses, retail pharmacies, and prescription benefit managers for approximately 70% of U.S. retail pharmacy transactions. Individual claim records include the date of a given pharmacy fill with the national drug code identifying agent and dosage. After Institutional Review Board and HRSA approvals, SHS records were linked with SRTR records for kidney transplant recipients. We applied a deterministic de-identification strategy wherein patient identifiers (last name, first name, date of birth, sex, and ZIP code of residence) were transformed before delivery to the Saint Louis University researchers with Health Information Portability and Accountability Act and HITECH-certified encryption technology from SHS. The patient de-identification software employs multiple encryption algorithms in succession to guarantee that the resulting "token" containing encrypted patient identifiers can never be decrypted. However, the algorithm yields the same results for a given set of data elements, such that linkages by unique anonymous tokens are possible.

All direct identifiers were removed before the final dataset was available for analysis. Because of the large sample size, the anonymity of the patients studied, and the non-intrusive nature of the research, a waiver of informed consent was granted per the Department of Health and Human Services Code of Federal Regulations (Title 45, Part 46, Paragraph 46.116). The study was approved by the Institutional Review Board (IRB) at Saint Louis University and is in accordance with the Helsinki Declaration of 1975.

Sampling and Exposure Definitions

Patients selected for analysis had SRTR records of kidney-alone transplants between January 1, 2007 and December 31, 2013, were aged 10 years or older (the recommended age limit for metformin use), had type 2 diabetes mellitus as documented at listing or at transplant, had available pharmaceutical fill records for a minimum of 1 year after transplant, and filled a diabetes medication within the first year post-transplant (Figure 1). Patient clinical and demographic characteristics, as well as characteristics of the donated organ and other transplant factors, were extracted from the OPTN Transplant Candidate and Recipient Registration forms (Table 1). The primary exposure of interest was a pharmacy fill for metformin in the year after transplant, regardless of what other medications a patient received; insulin, glitazones, sulfonylureas, or other agents were also extracted. After identifying metformin exposure, we classified the most common regimen, insulin without metformin. We addressed concomitant use of multiple agents by defining mutually exclusive groups based on a hierarchy: metformin-based, insulin-based, glitazone-based, sulfonylurea-based, or other regimens (including dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1)-receptor agonists, meglitinides, alpha-glucosidase inhibitors, amylin analog, and SGLT-2 inhibitors) (Figure 1). In sensitivity analyses, we compared metformin to any non-metformin treatment regimen. The total metformin exposure in the first post-transplant year was quantified based on mg per pill and dispensed pill counts.

Acute Rejection, Graft Failure, and Death

The OPTN queries programs for information on acute rejection according to periods covered by specific reporting forms (0 to 6 months, 7 to 12 months, then annual periods), but dates of acute rejection within reporting periods are not collected. We defined acute rejection from SRTR records according to program reports that an acute rejection event occurred in a

reporting period, as per prior methods for identifying acute rejection from U.S. registry data. [23,24]

Patient death was defined as death from any cause. We examined cause-specific death related to infections, malignancy, cardiovascular/cerebrovascular, and other causes in a secondary analysis. Graft failure was defined as return to maintenance dialysis or "preemptive" re-transplant. To assess the implications of diabetes treatment in the first year posttransplant, we examined clinical outcomes from >1 to 2 years posttransplant. Recipients were censored at the first of outcome of interest, death, date of second transplant anniversary, or end of study period (January 31, 2015).

Statistical Analyses

Pharmacy claims and transplant recipient registry datasets were prepared in SAS 9.4 (SAS Institute, Cary, NC) and analyzed with RStudio version 1.0.143.0 (RStudio Inc., Boston, MA). Distributions of clinical and demographic traits among recipients in each diabetes treatment group were compared by the chi-square test for categorical variables and X test for continuous variables. Propensity models for the likelihood of metformin-based use in the first year posttransplant were constructed by multiple logistic regression. The average amount of metformin filled in the first year was explored in relation to first-anniversary estimated GFR (eGFR) level.

Cumulative patient death and graft failure from >1 to 2 years posttransplant according to diabetes treatment regimen was computed by the Kaplan-Meier method. Cox regression was used to estimate adjusted hazard ratio and define lower and upper confidence limits ($_{95\% \text{ LCL}}\text{aHR}_{95\% \text{ UCL}}$) for associations of diabetes treatments with these events. Multiple logistic regression modeling was used to quantify the adjusted odd ratio ($_{95\% \text{ LCL}}\text{aOR}_{95\% \text{ UCL}}$) of acute rejection from >1 to 2 years. Outcome models were also stratified by propensity for metformin use.

RESULTS

Distributions of clinical traits according to diabetic regimen in first year posttransplant

In the study period, 28,035 kidney-only transplant recipients with pre-transplant diabetes mellitus were recorded in the SRTR database. Of these, 21,847 had linked pharmacy fill activity covering their first year post-transplant, and 16,116 (78%) filled a diabetes medication in that period. The majority of these recipients had type 2 diabetes mellitus (n=14,144) of whom 665 had metformin fills, while the remainder filled non-metformin-based regimens (Table 1). The majority (91.6%) of patients who used metformin also received additional diabetes treatments (insulin 76.6%, sulfonylureas 48.9%, glitazones 12.4%, other diabetic agents 32.4%).

Patients who received metformin were more likely to be female (aOR $_{1.07}1.27_{1.50}$), have hypertension as the cause of end-stage renal disease (aOR $_{1.14}1.60_{2.18}$), have discharge eGFR >60 (vs. 30–60) ml/min per 1.73 m^2 (aOR $_{1.11}1.35_{1.64}$), and have undergone transplant in 2010–2012 (aOR $_{1.13}1.37_{1.67}$) or 2013–2015 (aOR $_{1.34}1.69_{2.13}$) compared with 2007–2009 (Table 1). Metformin-treated patients were less likely to have eGFR levels of

15–29 (aOR $_{0.54}0.69_{0.88}$) or <15 (aOR $_{0.47}0.60_{0.77}$) (vs. 30–60) ml/min per 1.73 m^2, or to have received expanded criteria deceased donor allografts compared with standard criteria (aOR $_{0.48}0.64_{0.84}$). The proportion of recipients prescribed Metformin decreased as level of eGFR declined (Figure 2).

Associations of metformin use in first year after kidney transplant with outcomes >1 to 2 years posttransplant

Incidence of acute rejection >1 to 2 years posttransplant was lower in patients who received metformin-based regimens compared with those who received insulin-based regimens without metformin (1.0% vs. 1.9%, P=0.18), although the trend was not statistically significant after covariate and propensity adjustment (aOR $_{0.20}0.59_{1.30}$) (**Figures 3 and 4A;** Appendix Table 1). All-cause graft failure >1 to 2 years posttransplant was significantly lower in patients who received metformin-based regimens in the first year compared with those who received insulin-based regimens (1.9% vs 4.2%, P=0.003), but this pattern was not significant after covariate and propensity adjustment (aHR $_{0.38}0.65_{1.14}$). Outcomes did not vary by level of metformin exposure (levels defined per Figure 2). Death-censored graft failure was not different in metformin-based regimens compared with insulin-based regimens. All-cause mortality in >1 to 2 years posttransplant was significantly lower in patients who received metformin-based regimens compared with those who received insulin-based regimens (0.9% vs 2.9%, P=0.002), and this pattern was significant after covariate and propensity adjustment (aHR $_{0.18}0.41_{0.91}$). Compared to insulin-based regimens without metformin, there was no significant difference in outcomes with glitazone-based, sulfonylurea-based, or other regimens excluding metformin (**Figure 3).** Associations of metformin with study outcomes were similar when compared to any non-metformin treatment regimen. Among metformin users, outcomes did not differ significantly according to whether metformin was received alone or with other classes of agents (P>0.05). Further, in contrast to patterns associated with metformin-based treatment, secondary analysis showed no difference in outcomes in patients who received sulfonylureas compared to any non-sulfonylurea agent.

Since we noted a significant reduction in all-cause mortality associated with metformin-based treatment in the first year after transplant, we also evaluated associations with causes of death as reported to the registry. After adjusting for baseline factors and propensity for metformin use, statistical significance was noted for malignancy-related death (aHR $_{0.45}0.45_{0.99}$), infection-related death (aHR $_{0.12}0.32_{0.85}$), and death from other causes (aHR $_{0.13}0.35_{0.94}$) (Figure 4B). Trends toward lower mortality were noted for death from cardiovascular disease (aHR $_{0.23}0.52_{1.18}$) and unknown causes of death (aHR $_{0.15}0.34_{1.07}$), but these did not reach statistical significance (Figure 4). Glitazone-based, sulfonylurea-based, and other diabetic regimens were not associated with any differences in cause-specific mortality compared with insulin-based regimens (Figure 4B).

Secondary analyses of all diabetic patients (n=16,116), including those with type 1 diabetes mellitus, showed similar associations of metformin use with subsequent mortality. There was no significant interaction of metformin use with diabetes type in survival analysis.

DISCUSSION

By linking national transplant registry data with pharmacy claims data, we identified, characterized, and studied outcomes associated with the anti-glycemic medication use in the first year after kidney transplant in a large, national, contemporary cohort with preexisting diabetes mellitus. Use of diabetes regimens including metformin was uncommon (4.7%) and inversely correlated with eGFR. Metformin use was not associated with any adverse patient or graft outcomes. In fact, despite prior concerns for safety, metformin-based regimens were associated with 59% lower mortality compared to insulin use without metformin. There were also non-significant trends toward lower risk of acute rejection and all-cause graft failure among patients managed with metformin compared to those who received insulin without metformin. Notably, this survival difference did not occur with other oral hypoglycemic-based regimens excluding metformin (glitazone-based, sulfonylurea-based, or other), consistent with reports in the general population.[3] Associations of metformin with study outcomes were similar when compared to any non-metformin treatment regimen.

Our work extends and confirms a prior analysis by Stephen et al.[9] examining pharmacy fill records in patients who underwent transplant before recent changes in guidelines for metformin prescribing in CKD.[25] The evolution in metformin guidelines motivated our study including more recent data, and argues for continued study over time. Differences in our current study compared with the work of Stephen et al. include our examination of a broader spectrum of outcomes including rejection and cause-specific death, categorization of patients who did not receive metformin into a variety of regimens, and focus on patients with established type 2 diabetes mellitus prior to transplant, whereas Stephen et al included those with both pre-transplant diabetes mellitus and NODAT. We also analyzed metformin use with respect to GFR categories including in patients with eGFR < 30 ml/min per 1.73m^2, for whom metformin use is currently contradicted by the FDA.[25] Importantly, primary inferences are consistent across both studies despite different samples and data sources.

The main anti-glycemic effect of metformin is inhibiting mitochondrial glycerophosphate dehydrogenase (mGPD), a liver enzyme involved in gluconeogenesis,[26] and enhancing insulin-mediated glucose utilization in peripheral tissues.[27] Metformin has been associated with lower all-cause mortality compared with insulin and other oral hypoglycemic agents in the general population.[3] In an observational study using a United Kingdom database of 78,241 patients treated with metformin, 12,222 matched patients with sulfonylurea, and 90,463 matched subjects without diabetes mellitus, metformin users were noted to have lower mortality compared with diabetic patients using sulfonylureas and with nondiabetic controls.[28] Metformin affects various cellular pathways associated with anti-aging, including inflammation, cell survival, autophagy, stress defense, and protein synthesis.[29] Observed survival benefits have been attributed to several reasons. Obesity is a risk factor for death,[30] and unlike insulin and sulfonylureas, which are associated with weight gain, metformin is associated with weight reduction.[31] Dyslipidemia is also a well-known risk factor for mortality, especially cardiovascular death.[32] Metformin improves the lipid profile by reducing serum low-density lipoprotein cholesterol concentrations, and increasing serum high-density lipoprotein cholesterol concentrations.[33] Metformin has also been associated with lower risk of cancer and reduction in cancer mortality in diabetic patients,[34] an effect

that may be mediated by regulation of AMP (adenosine monophosphate) -activated protein kinase (AMPK) through the tumor-suppressor liver kinase B1[35] Metformin is also known to have direct anti-inflammatory effects.[36]

The most common side effects associated with metformin are gastrointestinal (e.g., nausea, abdominal cramps, and diarrhea).[33] Less commonly, metformin has been associated with vitamin B12 deficiency and peripheral neuropathy.[37] The most concerning, albeit rare, side effect of metformin is lactic acidosis, which can be fatal.[38] Along with effects on gluconeogenesis, inhibition of mGPD also results in decreased conversion of lactate to pyruvate and release of lactate levels into the plasma. Metformin is renally excreted, and thus, despite its benefits, its use is limited in patients with kidney disease. The United States Food and Drug Administration (FDA) issued a black box warning regarding lactic acidosis risk with metformin in patients with GFR <30 ml/min per 1.73 m^2. [25] Despite these concerns, recent evidence supports that metformin can be safely used in patients with mild-to-moderate CKD.[39] Renal clearance of metformin declines by approximately 75% when the GFR falls below 60 ml/min per 1.73 m^2; however, the serum levels remain much lower than those associated with lactic acidosis.[40] A meta-analysis of 347 prospective trials and observational studies showed no increase in lactic acid levels or lactic acidosis with metformin use compared with other anti-glycemic regimens.[41] In 2012, the Kidney Disease Outcomes Quality Initiative (KDOQI) published an updated Clinical Practice Guideline for Diabetes and CKD[42] that questions application of creatinine-based guidelines to metformin use. A recent expert review based on current data recommended that metformin be continued in mild-moderate renal insufficiency with 50% dose reduction when GFR is 30 to 45, but avoided if GFR is <30 ml/min per 1.73m^{2,43}. In the updated metformin labelling in 2016, the FDA advised caution but did not contraindicate use of metformin at GFR levels of 30–60 ml/min per 1.73m^2.[25]

We hypothesized that due to safety concerns, the use of metformin in the kidney transplant population would be low. The observed frequency of 4.7% is substantially lower than use among patients with type 2 diabetes mellitus in the general population, and is consistent with prior studies of transplant recipients.[9] Often GFR in transplant recipients is <60 ml/min/1.73 m^2, a level associated with the diagnosis of CKD especially when recipient and donor age is > 60 years.[44] Not surprisingly, we observed graded declines in metformin use with lower levels of renal function and among recipients of expanded criteria donor kidneys. Moreover, since many type 2 diabetic patients with kidney failure require insulin before transplant, providers might be reluctant to change anti-glycemic therapies after transplant, particularly with the combined impact of higher insulin clearance from improved GFR and the hyperglycemic stresses of immunosuppression. Notably, there was a trend towards more metformin use in more recent years of the study, reflecting the general practices of more common metformin use in patients with mild/moderate kidney disease in recent times based on newer safety data.[25]

Although our data did not information on lactic acidosis, we examined mortality as a key safety measure. Metformin was not associated with increased risk of any cause of death, but rather was associated with significantly lower all-cause, malignancy-related, infection-related, and "other" deaths, and with trends toward lower risks of unknown and

cardiovascular death. While the potential mechanisms of cancer death are noted earlier, the reduction in infection-related death is an interesting finding. It is possible that the anti-inflammatory properties of metformin,[36] along with its ability to activate AMPK, a protein that is also involved in the pathogenesis of viral infections,[45] play a role. The trends toward reduced cardiovascular death may be a manifestation of the purported benefits on cardiovascular risk noted above, but given the lack of statistical significance, defining impact of this outcome in diabetic transplant recipients requires further study.

Regarding graft outcomes, we observed trends toward lower risk of graft failure and acute rejection with metformin-based regimens, but these patterns were not statistically significant in adjusted analyses. Potential mechanisms of allograft protection would include the ability of metformin to reduce kidney injury (possibly through AMPK activation[46,47] and its anti-inflammatory and immune modulatory effects (e.g. via AMPK-mTOR-STAT3 signaling[48] and T cell regulation.[49] Again, our study does not support definitive conclusions for effects on allograft health, but the absence of increased risk is reassuring for the overall safety profile.

In the general population, metformin is usually titrated to the maximally effective dose of 2000 to 2500 mg per day. In our study, we noted that most (>50%) patients on metformin received a lower dose (average <650 mg/day). This pattern occurred even when the GFR was >60 ml/min, when metformin dose reduction is not recommended, and might reflect the practice of transplant providers to start and maintain lower doses in this population. Interestingly, in our analysis, 1.5% of diabetic transplant recipients with GFR <30 ml/min per $1.73m^2$ were exposed to metformin in the first year post-transplant; significant portion of these to high doses (1500 mg/day) (**Figure 2**). Further study is warranted to determine optimal dosing of metformin in transplant recipients to maximize benefits and reduce risks of those treated with this agent.

Limitations of our study include our inability to compare metformin monotherapy with other monotherapies, primarily due to the small number patients receiving such regimens. Notably, other oral hypoglycemic medication groups (exclusive of metformin) were not associated with any effects on mortality compared with the insulin-based reference group. In a systemic review of 179 trials and 25 observational studies, metformin-based combination therapy had effects similar to those of metformin monotherapy.[50] We also could not stratify our analysis of mortality based on GFR subgroups of metformin dose, again due to the low number of metformin-treated patients. Future work should examine whether the mortality benefit of metformin persists in patients on higher doses and with lower GFRs. Although we adjusted for observed recipient, donor, and transplant factors, including the use of the propensity model to limit bias of "confounding by indication" the retrospective design poses inherent risk for residual confounding. It is noted that the metformin group was more likely to be female and have higher discharge/one-year eGFR; and less likely to have received expanded criteria allografts. Hence, it is possible that the despite measures to reduce confounding and bias, the mortality benefit in the metformin group was at least partially related to better overall health status. Findings may not be generalizable to patients who were not included in the linked databases. Further, we lacked laboratory values (e.g., hemoglobin A1c, glucose levels) to adjust for level of glycemic control, and the metformin-

treated patients may have had less severe diabetes mellitus. We also lacked granular measures of clinical complications such as lactic acidosis; however, we examined mortality and graft outcomes as safety measures. These observational findings need to be validated in studies using a longer exposure, ideally with prospective designs to minimize confounding. A pilot protocol for a randomized clinical trial (Transdiab), with a 12 month follow-up, designed to study the feasibility, safety, and efficacy of metformin in NODAT, was recently published.[51]

In conclusion, we found that in a national cohort of diabetic kidney transplant recipients, use of metformin-based diabetes therapy was uncommon, declined with lower levels of allograft function, and was not associated with increased risk of adverse patient or graft outcomes. Rather, metformin exposure was associated with reduced mortality and non-significant trends toward lower rates of rejection and graft loss. While these findings warrant replication in additional studies, examination of linked national registry and pharmacy fill records is an efficient strategy for identifying uncommon treatments in transplant recipients that can confirm, extend, and provide hypotheses for gold standard, but costly, clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ADA	American Diabetes Association
aHR	adjusted hazard ratio
AHRQ	Agency for Healthcare Research and Quality
aOR	adjusted odds ratio
CKD	chronic kidney disease
DPP-4	dipeptidyl peptidase-4
eGFR	estimated glomerular filtration rate
EASD	European Association for the Study of Diabetes

FAVORIT	Folic Acid for Vascular Outcome Reduction in Transplant
FDA	Food and Drug Administration
GFR	glomerular filtration rate
HRSA	Health Resources and Services Administration
GLP-1	glucagon-like peptide-1
KDOQI	Kidney Disease Outcomes Quality Initiative
mGPD	mitochondrial glycerophosphate dehydrogenase
mTOR	mammalian target of rapamycin
NODAT	new-onset diabetes after transplantation
OPTN	Organ Procurement and Transplantation Network
SGLT-2	sodium–glucose cotransporter 2
SHS	Symphony Health Solutions
SRTR	Scientific Registry of Transplant Recipients
U.S.	United States

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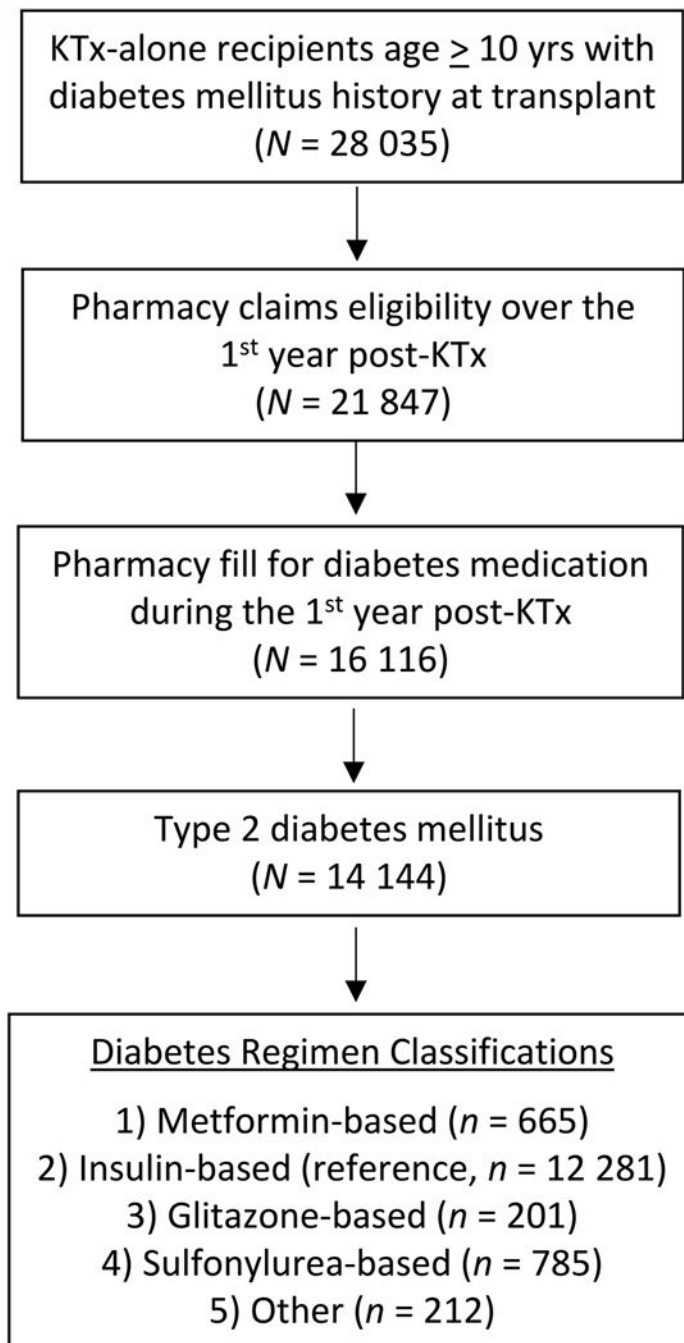
Figure 1.

Sampling scheme for mutually exclusive regimens. Metformin-based includes any metformin use, regardless of comedications. Insulin-based includes insulin and any other drug, except metformin. Glitazone-based includes glitazones and any other drug, except metformin and insulin. Sulfonylurea-based includes sulfonylurea and any other drug, except metformin, insulin or glitazones. "Other" diabetes treatment regimens include dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1)- receptor agonists,

meglitinides, alpha-glucosidase inhibitors, amylin analog and sodium-glucose co-transporter 2 (SGLT2) inhibitors.
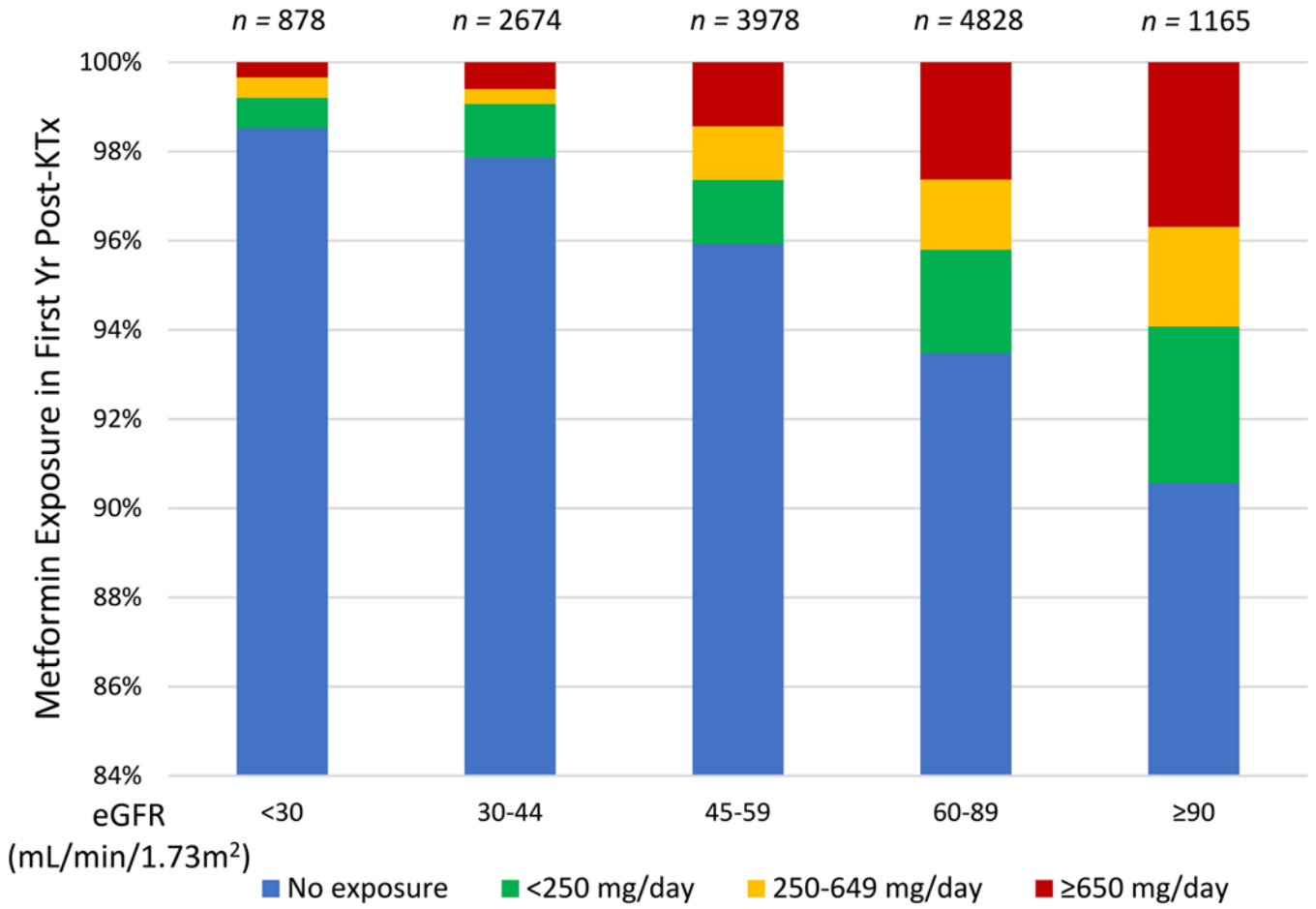
Figure 2.
Metformin exposure over the first year post-transplant by eGFR. Compared to eGFR ≥90ml/min/1.3 m^2, use patterns differed at levels <60 ml/min/1.73 m^2.
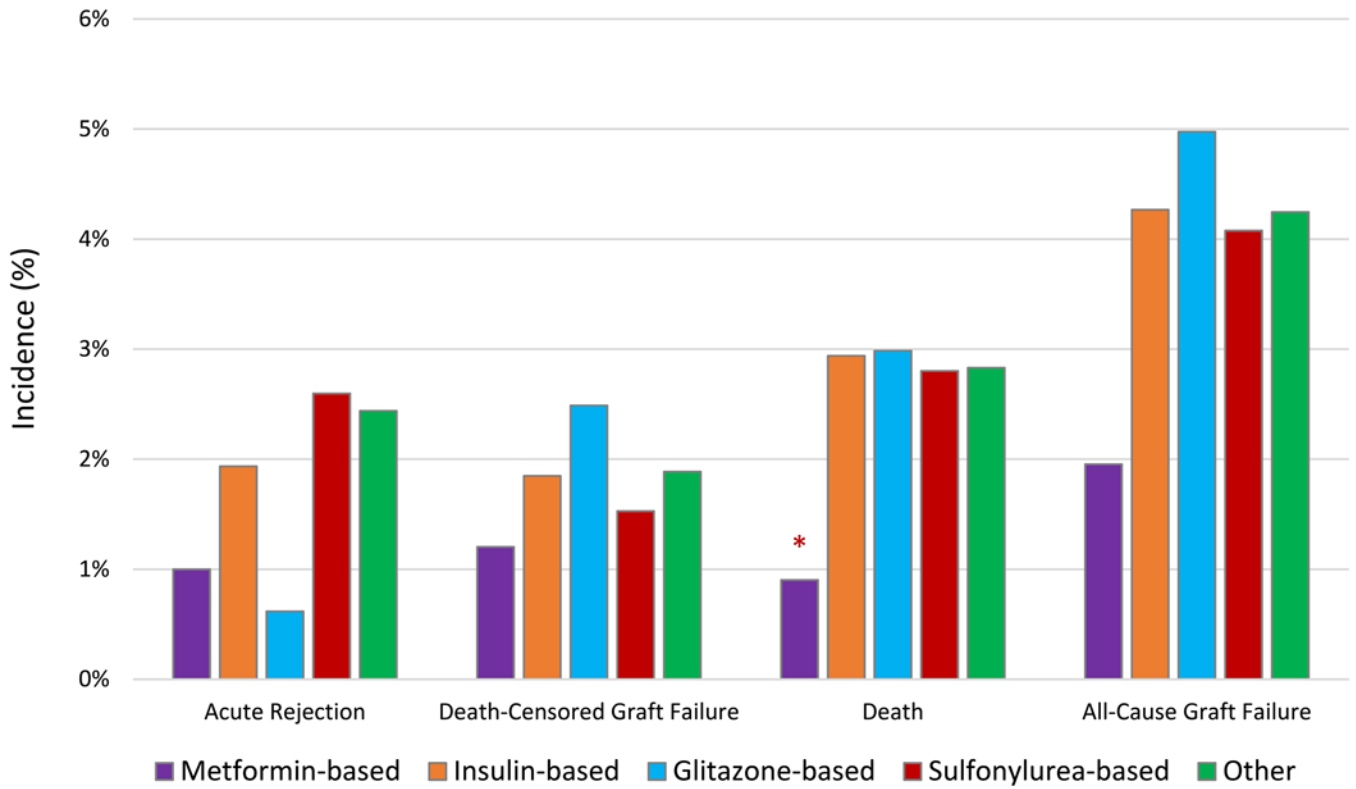
Figure 3.
Acute rejection, graft failure, and death after the first transplant anniversary, according to diabetes treatment in first year posttransplant.P-values: * p<0.05for differences in >1 to 2yr outcomes for those in a given diabetes treatment group compared with insulin reference.
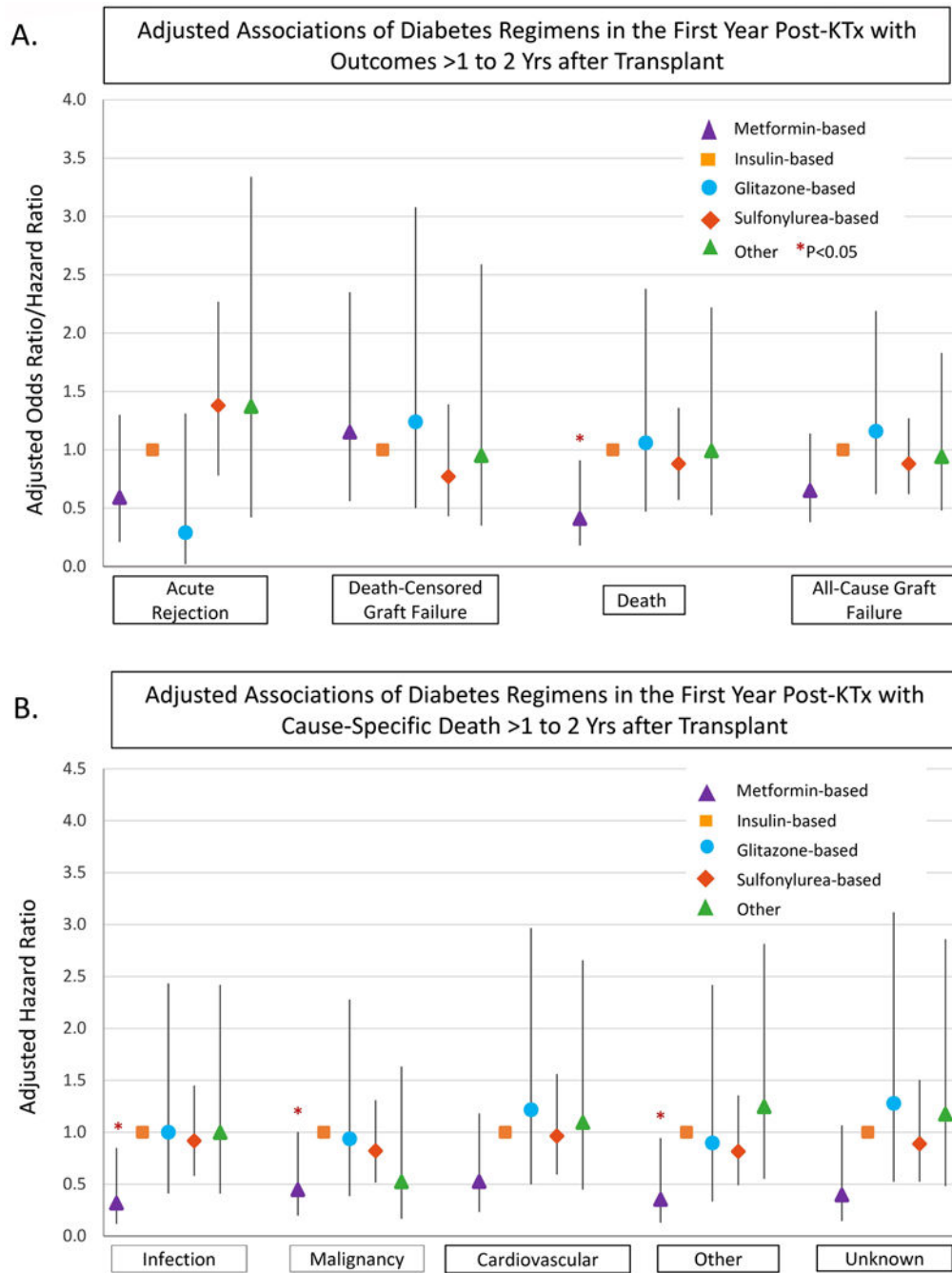
Figure 4.
Adjusted associations of diabetes treatment in first year post kidney transplant with subsequent acute rejection, graft failure and death. Adjusted for recipient, donor, and transplant clinical factors as listed in Table 1. ACGF, all-cause graft failure; DCGF, death-censored graft failure; KTx, kidney transplant

Table 1

Distributions of clinical traits in the study sample according to diabetes treatment in first year posttransplant. Frequency distributions are compared with insulin-based as the reference. Adjusted odds ratios compare metformin-based versus all other diabetes treatments.

|	Diabetes Treatment in First Year after Transplant					Propensity for Metformin Use
	Metformin-based (N=665)	Insulin-based (N=12281)	Glitazone-based (N=201)	Sulfonylurea-based (N=785)	Other (N=212)	
	%	%	%	%	%	Adjusted Odds Ratio (95% CI)
Recipient Factors						
Age, yrs.				*	*	
10 to 18	0.2	0.1	0.0	0.0	0.0	2.28 (0.10–22.04)
19 to 30	0.5	0.4	0.0	0.4	0.5	Reference
31 to 45	8.1	8.6	7.5	7.0	4.7	1.13 (0.39–4.76)
46 to 60	39.8	42.5	40.8	36.4	35.8	1.17 (0.42–4.88)
>60	51.4	48.4	51.7	56.2	59.0	1.29 (0.47–5.38)
Female	40.3 [†]	33.4	28.9	29.9	34.4	1.27 (1.07–1.50) [*]
Recipient Race			*	*	†	
White	45.0	43.8	41.8	43.7	49.5	1.09 (0.89–1.34)
Black	27.2	30.9	31.8	33.4	26.9	Reference
Hispanic	19.1	18.0	12.9	14.3	11.3	1.20 (0.94–1.53)
Other	8.7	7.3	13.4	8.8	12.7	1.26 (0.92–1.71)
Body mass index, kg/m^2				*		
<18.5	0.8	0.7	0.0	0.8	1.4	1.13 (0.39–2.60)
18.5 to 25	14.7	14.2	13.9	16.8	16.5	Reference
>25 to 30	31.3	32.5	36.3	35.0	33.0	0.91 (0.75–1.10)
>30	32.6	32.0	27.4	30.2	31.6	1.00 (0.83–1.22)
Missing	1.5	2.4	3.5	3.1	1.4	0.62 (0.30–1.12)
Cause of ESRD	‡		‡	‡	‡	
Diabetes Type 2	75.3	79.8	67.7	62.2	63.2	Reference
Glomerulonephritis	6.9	3.8	6.5	10.4	9.0	1.60 (1.14–2.18) [*]
Hypertension	17.0	15.9	22.9	26.0	24.5	1.08 (0.86–1.34)
Polycystic kidney disease	3.0	1.9	5.0	2.2	2.4	1.54 (0.93–2.42)
Other	2.4	3.2	5.0	6.0	5.7	0.81 (0.45–1.35)
ESRD duration, mos.	*				*	
None (pre-emptive)	15.8	11.4	14.9	12.5	19.3	1.13 (0.88–1.44)
>0 to 24	31.7	29.9	27.9	28.0	32.1	Reference
25 to 60	35.0	38.7	38.8	35.8	28.8	0.94 (0.76–1.16)
>60	17.1	19.2	17.9	22.8	19.3	0.88 (0.67–1.14)
Missing	0.3	0.8	0.5	0.9	0.5	0.36 (0.06–1.15)

	Diabetes Treatment in First Year after Transplant					Propensity for Metformin Use
	Metformin-based (N=665)	Insulin-based (N=12281)	Glitazone-based (N=201)	Sulfonylurea-based (N=785)	Other (N=212)	
	%	%	%	%	%	Adjusted Odds Ratio (95% CI)
Recipient comorbidities						
Coronary disease/angina	12.3	11.4	10.9	12.1	9.9	1.17 (0.91–1.49)
COPD	0.9	1.6	1.0	3.1 *	1.9	0.49 (0.19–1.02)
Hypertension	86.0 *	82.5	84.6	84.2	84.0	1.24 (0.98–1.58)
Cerebral vascular disease	3.9	4.2	3.5	3.8	4.2	0.93 (0.60–1.38)
Peripheral vascular disease	9.3	10.5	6.0	9.3	9.9	0.90 (0.68–1.18)
Highest Level of Education				*		
High School or lower	46.9	48.7	45.8	44.6	40.6	0.97 (0.82–1.15)
College/Graduate School	45.7	44.7	48.8	47.1	50.9	Reference
Unknown	7.4	6.7	5.5	8.3	8.5	1.26 (0.91–1.73)
Recipient physical capacity			*		*	
No Limit	68.0	64.1	74.6	68.2	72.6	Reference
Limited	10.2	10.6	9.5	9.0	9.4	0.97 (0.74–1.26)
Unknown	21.8	25.3	15.9	22.8	17.9	0.88 (0.72–1.08)
Employment Status						
Working	22.1	22.2	23.4	23.6	21.2	Reference
Not Working	71.9	70.6	68.2	69.2	72.6	1.08 (0.87–1.33)
Unknown	6.0	7.2	8.5	7.3	6.1	0.93 (0.63–1.34)
Insurance Type						
Private	31.0	30.1	37.8	29.9	36.3	Reference
Public	69.0	69.8	62.2	69.9	63.7	1.08 (0.88–1.31)
Transplant Factors						
Previous transplant	1.4	2.4	2.5	2.4	4.7	0.54 (0.25–1.06)
PRA level (most recent)					*	
< 10	71.1	74.1	79.1	75.8	68.4	Reference
10 to 79	17.7	14.7	11.4	14.1	15.1	1.14 (0.91–1.41)
80	3.5	3.3	4.0	2.9	3.3	0.93 (0.58–1.42)
Missing	7.7	7.9	5.5	7.1	13.2	0.90 (0.66–1.21)
HLA mismatches						
Zero A, B, and DR	6.9	6.8	6.5	6.6	7.5	0.94 (0.67–1.28)
Zero DR	9.8	10.9	9.0	11.2	12.3	0.81 (0.62–1.05)
Other	83.3	82.2	84.6	82.2	80.2	Reference
Donor Type	‡					
Living	35.9	30.1	26.9	28.9	36.3	0.95 (0.77–1.17)
Standard Criteria Deceased	42.9	43.4	44.8	41.5	38.7	Reference
Expanded Criteria Deceased	9.6	15.9	18.9	18.6	16.5	0.64 (0.48–0.84) *

	Diabetes Treatment in First Year after Transplant					Propensity for Metformin Use
	Metformin-based (N=665)	Insulin-based (N=12281)	Glitazone-based (N=201)	Sulfonylurea-based (N=785)	Other (N=212)	
	%	%	%	%	%	Adjusted Odds Ratio (95% CI)
Donation after Cardiac Death	11.6	10.6	9.5	11.0	8.5	1.32 (1.00–1.72) *
Discharge eGFR level	‡					
60	30.2	19.6	17.9	20.4	23.6	1.35 (1.11–1.64) *
30 to 59	36.8	34.1	30.3	32.7	30.7	Reference
15 to 29	15.5	20.6	23.4	19.0	21.2	0.69 (0.54–0.88) *
< 15	17.4	25.7	28.4	27.9	24.5	0.60 (0.47–0.77)‡
Year of transplant	†		‡		*	
2007–2009	23.8	30.7	55.7	32.5	21.7	Reference
2010–2012	52.3	50.2	33.8	49.9	55.2	1.37 (1.13–1.67) *
2013–2015	23.9	19.1	10.4	17.6	23.1	1.69 (1.34–2.13)‡

P-values:

*
p<0.05–0.002

†
p=0.001–0.0001

‡
p<0.0001

for differences of distributions of clinical traits among patients in a given diabetes treatment group compared with insulin-based reference. COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HLA, human leukocyte antigen; PRA, panel reactive antibody. "Other race" includes Asian, Native American, Pacific Islander and multi-racial.