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Metformin Use in Kidney Transplant Recipients in the United States: An Observational Study

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Key Words

Allograft survival · Diabetes · Kidney transplant · Metformin · Patient survival

Abstract

Background/Aims: Although metformin is contraindicated in patients with increased serum creatinine levels (≥1.5 mg/dl in men, ≥1.4 mg/dl in women) in the United States, its use has not been systematically examined in kidney transplant recipients. We aimed to determine the frequency of metformin use and its associations among kidney transplant recipients, and to assess allograft and patient survival associated with metformin use. ***Methods:*** In this retrospective cohort study, we linked Scientific Registry of Transplant Recipients data for all incident kidney transplants 2001–2012 and national pharmacy claims (n = 46,914). We compared recipients having one or more pharmacy claims for a metformin-containing product (n = 4,609) and recipients having one or more claims for a non-metformin glucose-lowering agent (n = 42,305). ***Results:*** On average, metformin claims were filled later after transplant and were associated with higher estimated glomerular filtration rates before the first claim. Median serum creatinine (mg/dl) levels before the first claim were lower in recipients with metformin claims than in those with non-metformin claims (1.3 [interquartile range 1.0–1.7] vs. 1.6 [1.2–2.5], respectively; $p < 0.0001$). Metformin was associated with lower adjusted hazards for living donor (0.55, 95% confidence interval 0.38–0.80; $p = 0.002$) and deceased donor (0.55, 0.44–0.70; $p < 0.0001$) allograft survival at 3 years posttransplant, and with lower mortality. ***Conclusions:*** Despite metformin being contraindicated in renal dysfunction, many kidney transplant recipients receive it, and it is not associated with worse patient or allograft survival.

Introduction

Diabetes is the leading cause of end-stage renal disease (ESRD) in the United States [1], and kidney transplant is the treatment of choice for ESRD patients with diabetes. Nondiabetic kidney transplant recipients are at risk for developing new onset diabetes after transplant (NODAT) [2]; this is a common complication associated with kidney transplant that can affect allograft and patient sur-

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vival [3]. To prevent the complications associated with diabetes, proper glycemic control is imperative.

Many pharmacologic agents are used to treat diabetes. Metformin is the first-line oral anti-glycemic agent used in the management of type 2 diabetes [4]. Metformin is excreted through the kidneys, and it can accumulate in patients with reduced renal function [5]. Metformin use is contraindicated in patients with renal dysfunction (serum creatinine ≥1.5 mg/dl in men or ≥1.4 mg/dl in women) because it can lead to lactic acidosis [4]. Concern about lactic acidosis has limited metformin use among patients with chronic kidney disease (CKD) [6]. However, Brown et al. showed that the prevalence of lactic acidosis among patients with type 2 diabetes was similar to that among metformin users, suggesting no increased risk [7]. Systematic reviews and case series have shown a low incidence of metformin-associated lactic acidosis [8, 9]. Salpeter et al. [10] conducted a comparative review and found that lactic acidosis was present in 4.3 cases per 100,000 patient-years among metformin users and in 5.4 cases among non-metformin users.

Kajbaf et al. [11] compared guidelines from around the world regarding metformin use in patients with CKD. While most of the guidelines agree on the serum creatinine threshold levels, the estimated glomerular filtration rate (eGFR) threshold values for avoidance of metformin vary. An eGFR threshold of 30 ml/min/1.73 m^2 was the most frequently recommended value. However, it has been suggested that current contraindications in metformin use should be revised [12].

Metformin is generally thought to be contraindicated in CKD patients, but its use may be considered after transplant when kidney function improves. The anti-glycemic effects of metformin are well established, along with its many other clinical benefits [13, 14]. The argument has even been made that metformin should be the first-line anti-glycemic agent used in transplant recipients [15]. However, the extent of metformin use among kidney transplant recipients in the United States is currently unknown. Our study aimed to determine the frequency of metformin use and its associations among kidney transplant recipients. We also assessed allograft and patient survival associated with metformin use.

Methods

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, waitlisted candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere [16]. The Health Resources and Services Administration, US Department of Health and Human Services, provide insights into the activities of the OPTN and SRTR contractors.

Study Population

Using the SRTR database, we constructed a cohort of kidney transplant recipients who underwent transplant between January 1, 2001, and October 4, 2012 (n = 184,649; online suppl. fig. S1; for all online suppl. material, see www.karger.com/doi/10.1159/000370034). Only the first transplant performed during this period was included. This cohort was linked to a national database of pharmacy fills aggregated by IMS Health (n = 143,972). The linkage was performed by the IMS Health staff using their patented algorithm; additionally, a final comparison was performed for the data elements sex, year of birth, and state of residence. Transplants with a direct mismatch of recipient year of birth or sex, or with insufficient matches by state of residence, were excluded from the cohort (n = 3,137). SRTR state of residence was preferentially defined as the state in which the transplant was performed; if this information was missing then the state at listing was used. When two different SRTR transplant records existed, we required that at least one state of residence match the state of residence in IMS Health records; when three different records existed, we required that at least two matched the IMS Health records (n = 140,835). The cohort was further restricted to recipients with at least one posttransplant fill of a diabetic medication in the IMS Health database (n = 46,914). Medications were categorized by the presence or absence of a metformin agent according to Lexi-Comp, an online drug information database [17]. Estimated GFR was calculated using the 4-variable Modification of Diet in Renal Disease equation [18].

Analysis

An initial comparison was made between patients with one or more metformin claims and patients with claims for non-metformin-containing diabetes medications. Tests of difference between categorical variables were performed using the Chi-square test, and tests of difference between continuous variables were performed using the Mann-Whitney and Wilcoxon test for nonparametric distributions. Unadjusted and adjusted survival curves were estimated using Cox proportional hazards models. Eight separate models were fit: 1- and 3-year patient and allograft survival for recipients of deceased and living donor kidneys. For the patient survival models, patients were followed up until death and 1 or 3 years posttransplant, whichever happened first; for the allograft survival models, patients were followed up until allograft failure, retransplant, death, loss to follow-up by center, and 1 or 3 years posttransplant, whichever happened first. To be included, patients were required to have at least 1 or 3 years of follow-up, unless any of the above-mentioned events occurred within this period. This methodology parallels the methodology that SRTR uses to produce its program-specific reports to evaluate the survival of all adult recipients (http://www.srtr.org/csr/current/Centers/201402_1401/all_csr_documentation.pdf).

The transplant date was treated as time zero, and patient and allograft survival were left-censored until the date of the first diabetic medication fill of any type. For all survival analyses, use of a

Table 1. Characteristics of the study cohort

Characteristics	One or more claims		p
	metformin	non-metformin	
n	4,609	42,305	
Sex			<0.0001
Women	2,122 (46.0)	15,633 (37.0)	
Men	2,487 (54.0)	26,672 (63.0)	
Age, years			<0.0001
18–34	285 (6.2)	2,385 (5.6)	
35–49	1,315 (28.5)	10,910 (25.8)	
50–64	2,304 (50.0)	21,214 (50.2)	
≥65	705 (15.3)	7,796 (18.4)	
Kidney donor type			<0.0001
Living	1,888 (41.0)	14,797 (35.0)	
Deceased	2,721 (59.0)	27,508 (65.0)	
Primary cause of kidney failure			<0.0001
Diabetes	1,340 (29.0)	22,763 (53.8)	
Hypertension	1,181 (25.6)	7,884 (18.6)	
Glomerulonephritis	854 (18.5)	4,375 (10.3)	
CKD	560 (12.2)	2,697 (6.4)	
Interstitial nephritis	160 (3.5)	887 (2.1)	
Neoplasms/tumor	22 (0.5)	149 (0.4)	
Secondary GN/vasculitis	123 (2.7)	731 (1.7)	
Allograft failure/CNI toxicity	20 (0.4)	360 (0.9)	
Other/unknown	349 (7.6)	2,459 (5.8)	
Time to first diabetic agent claim, median days (IQR)	289 (29–1,085)	63 (11–522)	<0.0001
Creatinine before first diabetic agent claim, median value (mg/dl, IQR)[1]	1.3 (1.0–1.7)	1.6 (1.2–2.5)	<0.0001
Women	1.1 (0.9–1.5)	1.4 (1.0–2.2)	<0.0001
Men	1.4 (1.1–1.8)	1.8 (1.3–2.8)	<0.0001
eGFR before first diabetic agent claim, median value (ml/min/1.73 m^2, IQR)[1]	59.1 (42.3–74.7)	45.9 (27–62.8)	<0.0001

Unless otherwise indicated, values are n (percent). [1] n = 2,533; creatinine value was missing for 5.4% of the cohort. CKD = Chronic kidney disease; CNI = calcineurin inhibitor; eGFR = estimated glomerular filtration rate; GN = glomerulonephritis; IQR = interquartile ratio.

metformin-containing medication was treated as a single-switch time-varying covariate. That is, metformin exposure began at the first metformin-containing fill and continued regardless of whether metformin use was observed in subsequent fills. For adjusted analyses, beta coefficients from the program-specific reports released in July 2012 were used to calculate the Xβ for each transplant. Because program-specific reports include all period prevalent kidney transplants in the United States, these beta estimates can be expected to be unbiased. Xβ was then entered as an offset term in the Cox models, and survival curves were estimated at the average Xβ value in the model cohort. The average Xβ value represents the average transplant recipient in the cohort with respect to all adjustment covariates; by extension, the survival estimates represent the effect of using metformin, compared with the effect of using a non-metformin agent, on this average recipient. Estimating the effect on the average transplant recipient helps control for the differences in underlying patient groups related to metformin use. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, N.C., USA).

Results

In the final dataset, 4,609 kidney transplant recipients had at least one claim for metformin or a metformin-containing product, and 42,305 recipients had at least one claim for a non-metformin diabetes medication. Recipients with metformin claims were more likely than those with non-metformin claims to be younger, to have ESRD not caused by diabetes, to be female, to have more days between transplant and first fill, and to have lower serum creatinine and higher eGFR before the first fill (all $p < 0.0001$) (table 1). However, although recipients with metformin claims had lower serum creatinine levels, the first serum creatinine level for a sizeable proportion of these recipients (37.6%) was higher than the level recommended by the US Food and Drug Administration (FDA)

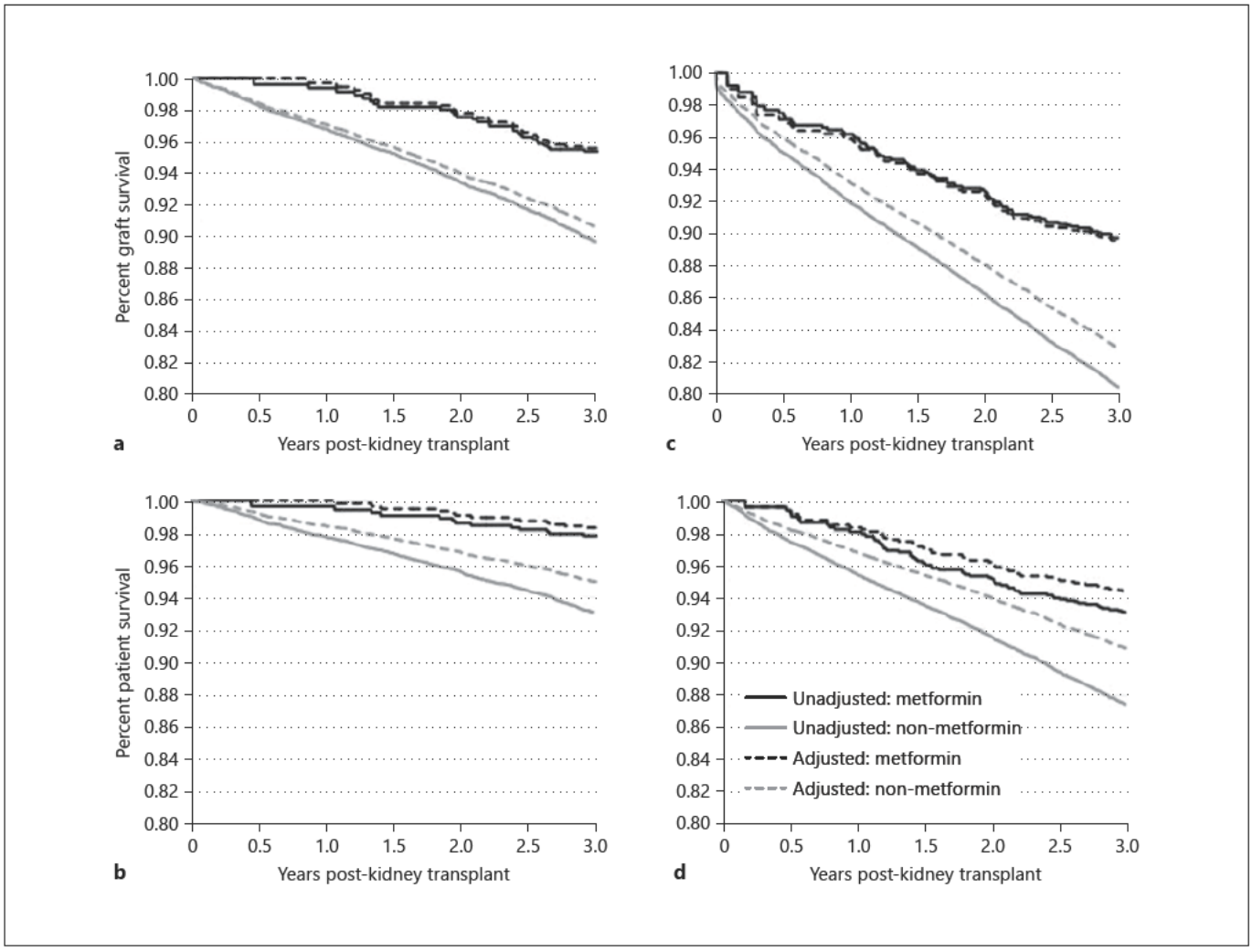

Fig. 1. Allograft survival (**a**) and patient survival (**b**) in living donor kidney recipients; allograft survival (**c**) and patient survival (**d**) in deceased donor kidney recipients. Time zero indicates date of transplant with survival left-censored until the date of the first diabetic medication fill of any type. Use of a metformin-containing medication was treated as a single time-varying covariate.

(table 2). A subset analysis limited to recipients with metformin and non-metformin claims in the first year post-transplant showed similar differences in creatinine and eGFR before first fill ($p < 0.0001$; data not shown).

The ratio of metformin to non-metformin users varied between transplant centers. The median ratio was 0.95 (range 0–1), but most centers had a ratio between 0 and 0.2. The size of the center did not appear to be associated with metformin use, although the few centers with ratios greater than 0.4 were of a small size (online suppl. fig. S2).

With and without adjustment, we found no patient or allograft survival disadvantage associated with metformin use for recipients of kidneys from living donors (fig. 1a and b) or deceased donors (fig. 1c and d). Rather,

Table 2. Kidney transplant recipients by metformin use and pre-fill creatinine level

Metformin use	Serum creatinine limit[1]		Total
	exceeded	did not exceed	
Yes	1,733 (37.6)	2,876 (62.4)	4,609 (9.8)
No	25,067 (59.3)	17,226 (40.7)	42,293 (90.2)
p			<0.0001

Unless otherwise indicated, values are n (percent). [1] US Food and Drug Administration limit, 1.4 mg/dl in women and 1.5 mg/dl in men.

Table 3. Association of metformin with and without adjustment for risk factors for allograft and patient survival

	Unadjusted model		Adjusted model	
	HR (95% CI)	p	HR (95% CI)	p
Allograft survival, living donor				
1-year[1]	0.23 (0.06–0.92)	0.04	0.23 (0.06–0.91)	0.04
3-year[2]	0.51 (0.35–0.75)	0.0005	0.55 (0.38–0.80)	0.002
Allograft survival, deceased donor				
1-year[3]	0.46 (0.28–0.77)	0.003	0.53 (0.32–0.89)	0.02
3-year[4]	0.49 (0.39–0.62)	<0.0001	0.55 (0.44–0.70)	<0.0001
Patient survival, living donor				
1-year[5]	0.16 (0.02–1.1)	0.07	0.17 (0.02–1.2)	0.08
3-year[6]	0.37 (0.21–0.64)	0.0004	0.40 (0.23–0.69)	0.001
Patient survival, deceased donor				
1-year[7]	0.48 (0.26–0.89)	0.02	0.55 (0.29–1.02)	0.06
3-year[8]	0.53 (0.41–0.70)	<0.0001	0.60 (0.46–0.79)	0.0003

Metformin-containing medication was treated as a single-switch time-varying covariate. CPRA = Calculated panel-reactive antibody; CVA = cerebrovascular accident; DSA = donation service area; HLA = human leukocyte antigen; PRA = panel-reactive antigen.

[1] Risk factors: donor age, donor race/ethnicity, donor relationship, HLA mismatches, peak PRA/CPRA, previous solid organ transplant, recipient age at transplant, recipient body mass index, recipient diagnosis, recipient hepatitis C serology, recipient insurance coverage, recipient race/ethnicity, recipient sex, time on renal replacement therapy.

[2] Risk factors: donor age, donor race/ethnicity, donor relationship, donor/recipient weight ratio, HLA mismatches, peak PRA/CPRA, previous solid organ transplant, recipient age at transplant, recipient body mass index, recipient diagnosis, recipient hepatitis C serology, recipient insurance coverage, recipient race/ethnicity, recipient sex, time on renal replacement therapy.

[3] Risk factors: cold ischemia time, donation after circulatory death, donor age, donor cause of death CVA/stroke, donor history of diabetes, donor history of hypertension, donor kidney was pumped, donor race/ethnicity, donor serum creatinine, donor/recipient weight ratio, expanded criteria donor, HLA mismatch, organ shipped outside recovery DSA, peak PRA/CPRA, previous solid organ transplant, recipient age at transplant, recipient body mass index, recipient diagnosis, recipient hepatitis C serology, recipient insurance coverage, recipient race/ethnicity, recipient sex, time on renal replacement therapy.

[4] Risk factors: cold ischemia time, donation after circulatory death, donor age, donor cause of death, donor history of diabetes, donor history of hypertension, donor kidney was pumped, donor race/ethnicity, donor serum creatinine, donor/recipient weight ratio, expanded criteria donor, HLA mismatches, organ shipped outside recovery DSA, peak PRA/CPRA, previous solid organ transplant, recipient age at transplant, recipient body mass index, recipient diagnosis, recipient hepatitis C serology, recipient insurance coverage, recipient race/ethnicity, recipient sex, time on renal replacement therapy.

[5] Risk factors: donor age, donor relationship, peak PRA/CPRA, previous solid organ transplant, recipient age at transplant, recipient diagnosis, recipient race/ethnicity, time on renal replacement therapy.

[6] Risk factors: donor age, donor race/ethnicity, donor relationship, HLA mismatches, peak PRA/CPRA, previous solid organ transplant, recipient age at transplant, recipient body mass index, recipient diagnosis, recipient hepatitis C serology, recipient insurance coverage, recipient race/ethnicity, recipient sex, time on renal replacement therapy.

[7] Risk factors: cold ischemia time, donation after circulatory death, donor age, donor history of diabetes, donor history of hypertension, donor kidney was pumped, donor race/ethnicity, donor serum creatinine, donor/recipient weight ratio, expanded criteria donor, HLA mismatches, organ shipped outside recovery DSA, peak PRA/CPRA, previous solid organ transplant, recipient age at transplant, recipient body mass index, recipient diagnosis, recipient hepatitis C serology, recipient insurance coverage, recipient race/ethnicity, recipient sex, time on renal replacement therapy.

[8] Risk factors: cold ischemia time, donation after circulatory death, donor age, donor history of diabetes, donor history of hypertension, donor kidney was pumped, donor race/ethnicity, donor serum creatinine, donor/recipient weight ratio, expanded criteria donor, HLA mismatches, organ shipped outside recover DSA, peak PRA/CPRA, previous solid organ transplant, recipient age at transplant, recipient body mass index, recipient diagnosis, recipient hepatitis C serology, recipient insurance coverage, recipient previous malignancy, recipient race/ethnicity, recipient sex, time on renal replacement therapy.

survival was superior for all outcomes for recipients who filled metformin claims compared with those who filled non-metformin agent claims (table 3). The association between metformin use and improved outcomes increased in significance but decreased in strength with longer follow-up time. Because the analysis was left-censored until the time of the first diabetic agent claim, not all members of the cohort contributed time to the 1-year survival estimates; this relatively lower n helps explain the lower p values and wider confidence intervals associated

with the 1-year estimates. A subset analysis limited to recipients with metformin and non-metformin claims in the first year posttransplant also showed no patient or allograft survival disadvantage associated with metformin use (data not shown).

Discussion

Metformin is widely prescribed to help maintain blood glucose levels. It is currently the preferred pharmacologic agent used to treat type 2 diabetes, if not contraindicated [19]. It has been shown to be safe and efficacious in patients with type 2 diabetes, and it may also reduce the risk of cardiovascular events [13]. Our study showed that 9.8% of kidney transplant recipients who filled at least one prescription for an antiglycemic agent also had at least one claim for metformin or a metformin-containing agent. Despite the FDA contraindications to metformin with regard to serum creatinine levels, levels for 37.6% of recipients in our sample who filled metformin claims were above the FDA-approved limit before the first fill. Additionally, our results showed no patient or allograft survival disadvantage associated with metformin use.

Concern about metformin use arose due to the development of the life-threatening lactic acidosis in nontransplant patients with serum creatinine levels above 1.4 mg/dl [6]. However, these reports were all linked to phenformin, another medication in the biguanide class, which was subsequently removed from the market. Phenformin's association with increased development of lactic acidosis cast doubts upon the entire biguanide class. Although phenformin and metformin belong to the same drug class, their pharmacologic properties differ in that metformin does not have a dynamic effect on lactic acid production. A fifteen-year (1980–1995) analysis of metformin users from Saskatchewan, Canada, found incidence of lactic acidosis of 9 per 100,000 patient-years [20]. This incidence is relatively higher than the estimates of 3 and 2.4 per 100,000 patient-years from Europe and Scandinavia, respectively, before metformin was approved in the United States; however, data suggest that lactic acidosis with metformin use is rare [12, 21]. Furthermore, pharmacokinetic studies performed in healthy subjects and in patients with renal insufficiency have shown reduced renal clearance of metformin in patients with reduced renal function, but sufficient evidence connecting metformin concentration levels to risk of lactic acidosis is lacking [12, 22]. Vasisht et al. [6] examined metformin use in 2104 patients with type 2 diabetes and CKD. In accordance with our results, they found that metformin use was frequent among patients whose eGFR value was less than 60 ml/min/1.73 m^2.

Despite generally adequate allograft function, kidney transplant recipients often have reduced renal function. In 2008, Kurian et al. [23] published a study examining the long-term safety and efficacy of metformin in 24 kidney transplant recipients; they demonstrated that metformin was safe for a mean duration of 16.4 months up to a maximum of 55 months. Although the study found no cases of lactic acidosis, eGFR decreased in all patients. Patients with preexisting diabetes experienced significant changes in eGFR [23].

Regardless of the potential risks associated with metformin use, its benefits are important to consider. The landmark UK Prospective Diabetes Study trial and follow-up trials illustrate the cardiovascular advantages of metformin, including significant reduction in risk of myocardial infarction and death from any cause [13, 14]. Since cardiovascular disease is a major contributor to patient death among kidney transplant recipients [24], and metformin use has been associated with significant risk reduction, metformin use could possibly reduce mortality in recipients with cardiovascular disease. Additionally, weight loss has been reported with metformin treatment [25]. While body mass index is considered during pretransplant evaluation, a notable 10% weight gain occurs during the first year posttransplant [3], making glycemic control difficult and negatively affecting body image. Additionally, unlike sulfonylureas, which stimulate the release of insulin, metformin has no effect on the release of insulin, thereby eliminating the risk of hypoglycemia [25]. Because NODAT is a common complication that occurs in approximately 15 to 30% of nondiabetic kidney transplant recipients [3], and at least 30% of recipients had preexisting diabetes in 2012, this is an important advantage of metformin.

Our study has limitations. Recipients who filled metformin and non-metformin claims differed in many respects. Most recipients with metformin claims were younger, received kidneys from living donors, and were started on metformin later; these recipients were likely healthier with stable allograft function and better glycemic control. Our adjustment methodology may be insufficient to control for the selection bias related to these recipients receiving metformin versus a non-metformin agent. Because recipients with metformin claims were likely healthier, more time may be needed for any detri-

mental effects to appear. Additionally, we used eGFR instead of direct GFR measurement, which can result in the overestimation of the actual kidney function. Measure of serum creatinine before first fill was as shown on a 6-month or yearly posttransplant follow-up form. This is an approximation of kidney function; it is possible, but unlikely, that kidney function may have improved before patients actually began using metformin. Because information on the most publicized outcome related to metformin, lactic acidosis, is not collected in the national registry, we were unable to compare the incidence of lactic acidosis between metformin and non-metformin users. In the future, patient-level data available from large integrated health care providers such as the Kaiser health care system or Veterans Affairs hospitals should be used to estimate the incidence of lactic acidosis in metformin and non-metformin users. Due to the study design, medication compliance cannot be determined. Despite these limitations, our study shows metformin to be a reasonable option for use in kidney transplant recipients with diabetes, since we found that there are no disadvantages of metformin with respect to graft or patient survival in the sample population.

To the best of our knowledge, this is the first large, systematic study to examine metformin use in kidney transplant recipients, specifically using SRTR data linked to pharmacy claims. These data allowed us to demonstrate patient and allograft survival in recipients using a particular medication. SRTR data could also be used to study medication safety and rare post-marketing adverse effects of medication beyond graft or patient outcomes, with a database of clinical events linked to the SRTR and IMS Health data. The ability to conduct safety analyses of any new or previously approved medications in solid organ transplant recipients has the potential to improve patient and allograft survival in the future.

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