



Metformin use in kidney transplant recipients throughout the United States

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Introduction

- Diabetes is the leading cause of end-stage renal disease (ESRD); moreover, nondiabetic patients can develop diabetes posttransplant.
- Metformin is an oral antihyperglycemic medication indicated for the management of type 2 diabetes.
- Metformin use is contraindicated in patients with renal dysfunction (serum creatinine \geq 1.5 mg/dL, men; \geq 1.4 mg/dL women) due to increased risk of lactic acidosis.
- Frequency of metformin use and its associations with allograft and patient survival in kidney transplant recipients are not known.

Methods

- Pharmacy claims from IMS Health were linked to Scientific Registry of Transplant Recipients (SRT) kidney transplant recipient data.
- Two separate cohorts were constructed: recipients with at least one claim posttransplant for a diabetic but non-metformin containing medication (n=42,293); recipients with at least one claim posttransplant for a diabetic and metformin-containing medication (n=4609).
- One- and three-year patient and allograft survival by donor type was calculated.
- Patient and allograft survival were left-censored from transplant until the date of the first diabetic medication fill. Use of a metformin-containing medication was treated as a single time-varying covariate.
- For adjusted analyses, beta coefficients from the SRT posttransplant kidney survival PSRs were used.

Results

- Table 1 shows differences in characteristics of the study population by use of metformin-containing diabetic agents.
- A considerable portion of metformin users had a serum creatinine above the FDA recommendation (Table 2).
- Recipients who filled metformin had superior survival rates for all outcomes compared to those who filled a non-metformin containing diabetic agent (Table 3).
- We found no patient or allograft survival disadvantage associated with metformin use for recipients of kidneys from living or deceased donors in either unadjusted or adjusted analyses (Figure 1).

Table 1: Differences in patient characteristics by use of metformin-containing diabetic agents (n=46,914)

Characteristics of the study cohort	One or More Claims		P
	Metformin	Non-Metformin	
n	4609	42,305	
Sex			<0.0001
Women	2122 (46.0)	15,633 (37.0)	
Men	2487 (54.0)	26,672 (63.0)	
Age, yrs			<0.0001
18-34	285 (6.2)	2385 (5.6)	
35-49	1315 (28.5)	10,910 (25.8)	
50-64	2304 (50.0)	21,214 (50.2)	
\geq 65	705 (15.3)	7796 (18.4)	
Kidney donor type			<0.0001
Living	1888 (41.0)	14,797 (35.0)	
Deceased	2721 (59.0)	27,508 (65.0)	
Primary cause of kidney failure			<0.0001
Diabetes	1340 (29.0)	22,763 (53.8)	
Hypertension	1181 (25.6)	7884 (18.6)	
Glomerulonephritis	854 (18.5)	4375 (10.3)	
CKD	560 (12.2)	2697 (6.4)	
Interstitial nephritis	160 (3.5)	887 (2.1)	
Nephroses/nephrosis	22 (0.5)	149 (0.4)	
Secondary GN/vacuolitis	123 (2.7)	731 (1.7)	
Allograft failure/CNI toxicity	20 (0.4)	360 (0.9)	
Other/unknown	849 (18.4)	2459 (5.8)	
Time to first diabetic agent claim, median days (IQR)	289 (29-1085)	63 (11-522)	<0.0001
Creatinine before first diabetic agent claim, median value, mg/dL (IQR)	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)	59.1 (42.3-74.7)	45.9 (27-62.8)	<0.0001

Note: Unless otherwise indicated, values are n (percent).
 CKD, chronic kidney disease; CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; GN, glomerulonephritis; IQR, interquartile ratio.

Figure 1: Allograft and Patient Survival in Kidney Transplant Recipients by Donor Type

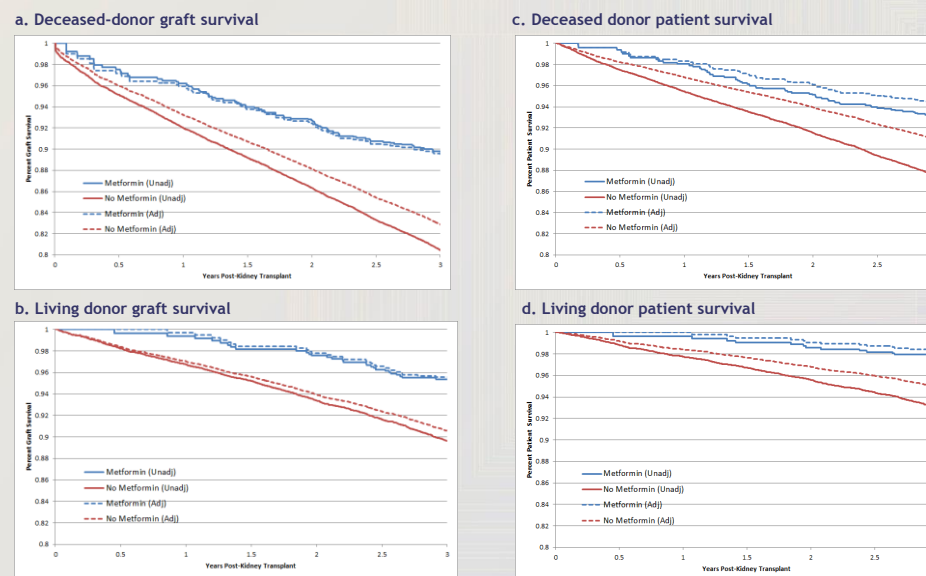


Table 2: Recipients by metformin use and pre-fill creatinine level

Metformin Use	Serum Creatinine Limit ¹		Total
	Exceeded	Did Not Exceed	
Yes	1733 (37.6)	2876 (62.4)	4609 (9.8)
No	25,067 (59.3)	17,226 (40.7)	42,293 (90.2)
P			<0.0001

Note: Unless otherwise indicated, values are n (percent).

¹US 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)	0.003

BMI, body mass index; CPRA, calculated panel-reactive antibody; CVA, cerebrovascular accident; DSA, donation service area; HLA, human leukocyte antigen; PRA, panel-reactive antigen; RRT, renal replacement therapy.
¹ Risk factors: donor age, race/ethnicity, relationship; HLA mismatches; peak PRA/CPRA; previous solid organ transplant; recipient age at transplant, BMI, diagnosis, hepatitis C serology, insurance coverage, race/ethnicity, sex, time on RRT.
² Risk factors: donor age, race/ethnicity, relationship; donor/recipient weight ratio; HLA mismatches; peak PRA/CPRA; previous solid organ transplant; recipient age at transplant, BMI, diagnosis, hepatitis C serology, insurance coverage, race/ethnicity, sex, time on RRT.
³ Risk factors: cold ischemia time; donation after circulatory death; donor age, cause of death CVA/stroke, history of diabetes, history of hypertension, kidney was pumped, race/ethnicity, 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, BMI, diagnosis, hepatitis C serology, insurance coverage, race/ethnicity, time on RRT.
⁴ Risk factors: cold ischemia time; donation after circulatory death; donor age, cause of death, history of diabetes, history of hypertension, kidney was pumped, race/ethnicity, 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, BMI, diagnosis, hepatitis C serology, insurance coverage, race/ethnicity, sex, time on RRT.
⁵ Risk factors: donor age, relationship; peak PRA/CPRA; previous solid organ transplant; recipient age at transplant, diagnosis, race/ethnicity, time on RRT.
⁶ Risk factors: donor age, race/ethnicity, relationship; HLA mismatches; peak PRA/CPRA; previous solid organ transplant; recipient age at transplant, BMI, diagnosis, hepatitis C serology, insurance coverage, race/ethnicity, sex, time on RRT.
⁷ Risk factors: cold ischemia time; donation after circulatory death; donor age, history of diabetes, history of hypertension, kidney was pumped, race/ethnicity, 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, BMI, diagnosis, hepatitis C serology, insurance coverage, previous malignancy, race/ethnicity, recipient sex, time on RRT.
⁸ Risk factors: cold ischemia time; donation after circulatory death; donor age, history of diabetes, history of hypertension, kidney was pumped, race/ethnicity, 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, BMI, diagnosis, hepatitis C serology, insurance coverage, previous malignancy, race/ethnicity, recipient sex, time on RRT.

Conclusions

- Metformin use is estimated at 10% of the diabetic kidney transplant population.
- Metformin use was associated with younger age, lower creatinine levels, living donor kidney transplant, and primary cause of kidney disease other than diabetes.
- Furthermore, in appropriate patients, use of metformin was not associated with worse patient or graft survival. However, confounding by indication is likely.