ORIGINAL RESEARCH

Variations in Metformin Prescribing for Type 2 Diabetes

Tiffany Goldberg, PharmD, Miranda E. Kroehl, MS, PhD, Kathleen Heist Suddarth, MD, and Katy E. Trinkley, PharmD

Background: **Reasons for suboptimal metformin prescribing are unclear, but may be due to perceived risk of lactic acidosis. The purpose of this study is to describe provider attitudes regarding metformin prescribing in various patient situations.**

Methods: **An anonymous, electronic survey was distributed electronically to 76 health care providers across the nation. The 14-item survey contained demographic questions and questions related to prescribing of metformin for T2DM in various patient situations, including suboptimal glycemic control, alcohol use, history of lactic acidosis, and varying degrees of severity for certain health conditions, including renal and hepatic dysfunction, chronic obstructive pulmonary disease, and heart failure.**

Results: **There were a total of 100 respondents. For suboptimal glycemic control, most providers (75%) would increase metformin from 1500 to 2000 mg daily; however, 25% would add an alternate agent, such as a sulfonylurea (18%) or dipeptidyl peptidase-4 inhibitor (7%). Although 51% of providers would stop metformin based on serum creatinine thresholds, the remainder would rely on glomerular filtration rate thresholds of <60 mL/min (15%), <30 mL/min (33%), or <15 mL/min (1%) to determine when to stop metformin. For heart failure, 45% of providers would continue metformin as currently prescribed regardless of severity. Most providers would adjust metformin for varying severity of hepatic dysfunction (74%) and alcohol abuse (40%).**

Conclusions: **Despite evidence supporting the cardiovascular benefits of metformin, provider attitudes toward prescribing metformin are suboptimal in certain patient situations and vary greatly by provider. (J Am Board Fam Med 2015;28:777–784.)**

Keywords: **Health Care Surveys, Lactic Acidosis, Metformin, Physician's Practice Patterns, Type 2 Diabetes Mellitus**

Metformin, is the only medication for type 2 diabetes (T2DM) that has demonstrated reproducible benefits on cardiovascular morbidity and mortality.[1] Thus, metformin is considered first-line treatment for T2DM per the American Diabetes Association's clinical practice guidelines.[2] In the UK Prospective Diabetes Study (UKPDS), cardiovascular morbidity and mortality benefits were demonstrated in patients with uncontrolled diabetes who were treated daily with metformin at doses of 1700 to 2550 mg.[1] At these doses, metformin reduced the risk of any diabetes-related end point, myocardial infarction, and all-cause mortality by 32% (P = .017), 39% (P = .010), and 36% (P = .011), respectively.[1] Despite these findings, manufacturer guidelines suggest that the minimum effective dose of metformin is 1500 mg/day.[3] In accordance with the manufacturer, other commonly used tertiary references also cite 1500 mg daily as the minimum effective dose of metformin.[4,5] Despite the clear benefits on glycemic control, morbidity, and mortality, metformin prescribing remains suboptimal.[6,7] It is estimated that metformin treatment is not initiated in nearly 50% of patients with T2DM.[8]

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From the Skaggs School of Pharmacy and Pharmaceutical Sciences, Department of Clinical Pharmacy (TG, KET), the School of Public Health (MEK), and the School of Medicine, Department of Medicine (KHS, KET), University of Colorado, Aurora.
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Corresponding author: Katy E. Trinkley, PharmD, BCACP, Department of Clinical Pharmacy, University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, Department of Medicine, School of Medicine, 12850 E. Montview Blvd, Mailstop C238, Aurora, CO 80045 (E-mail: katy.trinkley@ucdenver.edu).

Reasons for this suboptimal prescribing are not clearly defined in the literature, but they may be attributable to fear of precipitating lactic acidosis in patients with known risk factors. Potential risk factors for lactic acidosis include chronic kidney disease, hepatic dysfunction, heart failure, chronic obstructive pulmonary disease (COPD), alcohol abuse, and a history of lactic acidosis. Although there is little information on the exact risk of lactic acidosis with metformin, data suggest that the association is negligible; one study demonstrated an incidence of 4.3 per 100,000 patient-years.[9] Furthermore, previous studies demonstrated no increased risk of lactic acidosis with metformin use in the settings of heart failure and renal dysfunction.[10–12] Despite these data, the manufacturer recommends discontinuing metformin when serum creatinine exceeds 1.5 mg/dL for men and 1.4 mg/dL for women,[3] likely because of concerns for risk of lactic acidosis. This fear of increased lactic acidosis risk with metformin may stem from a preexisting medication, phenformin, which was associated with fatal cases of lactic acidosis in patients and has since been removed from the market.[13] However, there are few data to support similar concerns with metformin.

There is a need to gain an understanding of the current prescribing practices for metformin to optimize metformin prescribing for T2DM,[9] such that more patients with diabetes can benefit from metformin's unique cardiovascular morbidity and mortality effects. The purpose of this study was to gain a better understanding of metformin prescribing attitudes among health professionals in various clinical scenarios.

Methods

A 14-item survey was developed and modified based on feedback from a small focus group of primary care providers, consisting of 1 physician assistant and 4 physicians. During the focus group, cognitive testing of the survey was conducted in which the providers were asked to (1) complete the survey; (2) think aloud about how they constructed their answers; (3) discuss their interpretation of the meaning of each item; (4) report any difficulties in answering the questions; and (5) provide any other feedback. After incorporating the feedback from the pilot, the final survey included the same 14 items with the language modified for clarity. Four questions related to demographical information, including specific profession, duration of practice, practice site, and geographic location of practice. The remaining 10 questions related to prescribing attitudes in various clinical scenarios, including suboptimal glycemic control and presence of risk factors for lactic acidosis, including renal dysfunction, hepatic dysfunction, heart failure, COPD, alcoholism, history of lactic acidosis, and current lactic acidosis.

The survey was anonymous and distributed electronically using the online survey database Qualtrics. Survey participants were provided postcard consent before completing the survey, explaining that they were giving consent to participate by completing the survey. The survey was distributed to a convenience sample of people with ongoing professional relationships with the study investigators, and similar to the methodology of a prior study, recipients of the survey were asked to forward the survey to other clinician colleagues.[14] Survey respondents were providers who practiced in a setting in which they were involved in prescribing or recommending chronic drug therapy for T2DM, which was listed as inclusion criteria at the top of the electronic survey. To submit the survey, participants were required to complete all questions. This study was deemed exempt by the University of Colorado's institutional review board.

To determine whether there were characteristics associated with responses to the patient situations, the results from each situation were categorized into a binary outcome indicating whether the respondent reported they would take the recommended action or not. For scenarios where more than 1 answer was acceptable, respondents who selected any scenarios not within the suggested guidelines were considered as not following a recommended action. Individual logistic regression models were used to estimate the relationships between profession (physician vs pharmacist, n = 96), years practicing (n = 100), location (Midwest vs Mountain West, n = 97), and clinic type (academic vs all other, n = 100) for each patient situation. Given the small number of responses from the South region and midlevel practitioners, they were not included in the logistic regression models. To account for multiple comparisons, a false discovery rate adjustment was applied to the *P* values. All

analyses were conducted using SAS software (SAS Institute, Cary, NC).

Results

The survey was distributed nationwide to 76 providers who had ongoing professional relationships with the investigators. The survey was open from November 10, 2013, until January 17, 2014. A total of 101 surveys were completed as a result of survey respondents forwarding the survey to their clinician colleagues.

The majority of respondents (66%) were physicians who completed their residency training, 20% were pharmacists, and 10% were medical residents. The remaining 4% were divided evenly among nurse practitioners and physician assistants. Years of clinical experience were evenly distributed between <5 years to >15 years of experience. The majority of respondents practiced in the Mountain West region (68%) and in an academic clinic (61%). Demographic information, including details of geographic region, is described in Table 1.

Table 1. Demographic Characteristics of Survey Respondents (n = 100)

Demographic Information	Respondents (%)
Clinical profession	
Medical resident	10
Physician, completed residency training	67
Nurse practitioner	2
Physician assistant	2
Pharmacist	19
Years practicing in clinical profession	
<5 years	31
5–10 years	24
11–15 years	17
>15 years	28
Geographic location	
Midwest (IL, IN, IA, KS, MI, MN, MO, NE, ND, OH, OK, SD, WI)	29
South (AL, AR, FL, GA, KY, LA, MS, NC, SC, TN, TX, VA, WV)	3
Mountain West (AZ, CO, NV, NM, UT, WY)	68
Type of clinic	
Federally qualified healthcare clinic	17
Academic clinic	61
Private clinic	5
County hospital clinic	7
Veterans affairs clinic	3
Other	7

Provider attitudes regarding metformin prescribing in various clinical scenarios are described in Table 2. In patients with uncontrolled diabetes and an A1C of 8.3%, most providers (84%) chose to titrate metformin from 500 to 2000 mg daily, whereas 11% chose metformin 1500 mg daily as an appropriate regimen. Interestingly, in a similar patient with an A1C of 7.3%, 75% of providers would increase metformin from 1500 to 2000 mg daily, whereas 18% of providers chose to add a sulfonylurea.

Of providers, 50% followed the metformin manufacturer's recommendations to discontinue metformin use when serum creatinine is >1.5 mg/dL. While the other 50% of providers accepted glomerular filtration rate (GFR) as a better indicator of when to discontinue metformin use, there seems to be no consensus among providers on what the GFR cutoff should be. In patients taking metformin 1750 mg daily and with either hepatic dysfunction or heart failure, there was great variation in provider prescribing attitudes and no notable trends. For patients with COPD, however, 90% of providers did not alter the patient's metformin therapy. In patients with alcoholism, 59% of providers would not alter metformin dosing, but many providers would based on varying degrees of alcohol use. For patients with current or a history of lactic acidosis, provider attitudes were inconsistent.

There were no strong associations between any of the survey respondent characteristics and following the recommended practice in the patient situations. Results of the logistic regression analyses are shown in Table 3. Physicians were more likely than pharmacists to follow the suggested practices for 2 of the 10 situations presented, and those working in an academic setting were more likely than those working in any other setting to follow the suggested practices for 3 of the situations; however, statistical significance was lost after applying the false discovery rate adjustment.

Discussion

These findings suggest that attitudes toward metformin prescribing vary significantly among providers. There seems to be little consensus among providers in how to adjust metformin prescribing based on glycemic control or comorbidities. To

Table 2. Provider (n=100) Attitudes Toward Prescribing Metformin in Various Clinical Situations

	Provider Attitudes Toward Metformin Prescribing	Providers (%)
Patient situation 1: uncontrolled T2DM	A 50-year-old patient with controlled diabetes (A1C of 6.3%), is taking metformin 500 mg daily and tolerating it well. What would you do?	
	Keep 500 mg metformin/day	88
	Titrate metformin to a target dose of 1500 mg/day	5
	Titrate metformin to a target dose of 2000 mg/day	7
Patient situation 2: uncontrolled T2DM	If a 50-year-old patient with uncontrolled diabetes and an A1C of 8.3% is taking metformin 500 mg/day and tolerating it well, which of the following would you be most likely to do?	
	Titrate metformin to a target dose of 1500 mg/day	11
	Titrate metformin to a target dose of 2000 mg/day	84
	Add a sulfonylurea	3
	Add a dipeptidyl-peptidase-4 inhibitor	2
Patient situation 3: uncontrolled T2DM	If a 50-year-old patient with uncontrolled diabetes and an A1C of 7.3% is taking metformin 1500 mg/day and tolerating it well, which of the following would you be most likely to do?	
	Titrate metformin to a target dose of 2000 mg per day	75
	Add basal insulin	0
	Add a sulfonylurea	18
	Add a dipeptidyl-peptidase-4 (DPP-4) inhibitor	7
Patient situation 4: chronic kidney disease	For a 50-year-old male patient with chronic kidney disease and diabetes taking metformin 1750 mg/day, at what point would you stop the metformin?	
	When the serum creatinine is >1.5	51
	When the CKD-EPI eGFR is <60 mL/min	15
	When the CKD-EPI eGFR is <30 mL/min	33
	When the CKD-EPI eGFR is <15 mL/min or the patient is receiving dialysis	1
	I would not stop the metformin	0
Patient situation 5: hepatic dysfunction	For a patient with hepatic dysfunction and diabetes taking metformin 1750 mg/day, at what point would you stop metformin or decrease the dose? (Multiple answers are acceptable)	
	Elevated AST or ALT >3 times the upper limit of normal	49
	Elevated INR >1.5	35
	Elevated bilirubin >2	33
	Presence of cirrhosis	50
	Presence of cirrhosis with ascites	60
	Hepatic steatosis present on imaging	6
	I would not change the dose or stop metformin for any of these factors	27
Patient situation 6: heart failure	For a patient with heart failure and diabetes taking metformin 1750 mg/day, at what point would you stop the metformin or decrease the dose?	
	NYHA class I: symptoms only at activity levels that would limit normal individuals	1
	NYHA class II: symptoms with ordinary exertion	10
	NYHA class III: symptoms with less than ordinary exertion	32
	NYHA class IV: symptoms at rest	13
	I would not change the dose or stop metformin	44
Patient situation 7: chronic obstructive pulmonary disease	For a patient with COPD and diabetes taking metformin 1750 mg/day, at what point would you stop metformin or decrease the dose? (Multiple answers are acceptable)	
	Mild COPD (FEV_1 >80%)	0
	Moderate COPD (FEV_1 50% to 80%)	1
	Severe or very severe COPD (FEV_1 <50%)	6
	Needing oxygen chronically	10
	I would not change the dose or stop metformin	89

Continued

Table 2. Continued

	Provider Attitudes Toward Metformin Prescribing	Providers (%)
Patient situation 8: alcohol abuse	For a patient with alcoholism and diabetes taking metformin 1750 mg/day, at what point would you stop metformin or decrease the dose? (Multiple answers are acceptable)	
	If they are dependent on alcohol	28
	If they abuse alcohol	29
	If they consume fewer than 2 drinks/day for men and 1 drink/day for women/elderly	2
	If they consume >4 drinks/day or 14 drinks/week, regardless of sex or age	25
	I would not change the dose or stop metformin	60
Patient situation 9: history of lactic acidosis	For a 50-year-old patient with an A1C of 8.3% who is not currently taking any diabetes medications, has a remote history of lactic acidosis, and has no other risk factors for lactic acidosis, which one of the following would you do? (Multiple answers are acceptable)	
	Not start metformin	18
	Start metformin only	25
	Start metformin and monitor serum lactic acid	13
	Start metformin at a lower dose than I usually would	15
	Start metformin at a lower dose than I usually would and monitor serum lactic acid	26
	Start a sulfonylurea instead of metformin	29
	Start a diabetes medication other than a sulfonylurea or metformin	12
Patient situation 10: current lactic acidosis	For a 50-year-old patient with an A1C of 6.3%, who is only taking metformin 1750 mg/day for diabetes and who has a new diagnosis of lactic acidosis, which one of the following would you do acutely? The patient is not going to be admitted to the hospital, and their glycemia remains normal. (Multiple answers are acceptable)	
	Stop metformin only	54
	Stop metformin and switch to a sulfonylurea	30
	Stop metformin and switch to a diabetes medication other than a sulfonylurea or metformin	22
	Lower the metformin dose	2
	Lower the metformin dose and monitor serum lactic acid	8
	Continue metformin	0
	Continue metformin and monitor serum lactic acid	2

*Suggested answers are set in italics. For some questions, more than one answer was suggested, given that the available evidence does not suggest one correct answer.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration Equation; COPD, chronic obstructive pulmonary disease; eGFR, estimate glomerular filtration rate; FEV_1, forced expiratory volume in 1 second; INR, international normalized ratio; NYHA, New York Heart Association; T2DM, type 2 diabetes mellitus.

achieve cardiovascular morbidity and mortality benefits, the best available evidence suggests targeting metformin doses of 1700 to 2550 mg daily. However, 11% of providers still chose to titrate to metformin 1500 mg daily versus 2000 mg daily in an uncontrolled diabetic patient currently taking metformin 500 mg daily. This is likely because of the metformin manufacturer's recommendations for the minimum effective dose.[3] What is less clear from UKPDS is whether patients with controlled T2DM would benefit from escalating doses of metformin to the target range of 1700 to 2550 mg daily, given that subjects in UKPDS had uncontrolled T2DM. The survey results demonstrate that the majority of providers would not escalate metformin to the target range of 1700 to 2550 mg daily for patients with controlled T2DM.

While 50% of providers followed the metformin package insert recommendations to discontinue metformin when serum creatinine was >1.5 mg/dL for men, the remainder relied on GFR as a better indicator for discontinuing metformin use. Since there are no clear recommendations from the manufacturer regarding GFR cutoffs, providers seem to be split on when it is appropriate to discontinue

Table 3. Provider Characteristics and Associations with Prescribing Metformin in Various Clinical Situations

Provider Characteristics	Patient Scenario	Odds Ratio	95% CI	*P* Value	FDR-Adjusted *P* Value
Physicians* vs Pharmacists	1. Controlled T2DM	4.4	0.6–33.6	.1517	.4727
	2. Uncontrolled T2DM, metformin 500 mg/day	0.9	0.2–3.6	.9088	.9729
	3. Uncontrolled T2DM, metformin 1500 mg/day	1.5	0.5–4.6	.4614	.8057
	4. Chronic kidney disease	1.2	0.4–3.4	.7746	.9683
	5. Hepatic dysfunction	1.0	0.3–3.3	.9335	.9729
	6. Heart failure	2.5	0.8–7.5	.1138	.4270
	7. Chronic obstructive pulmonary disease	8.4	2.1–34	.0028	.1108
	8. Alcohol abuse	3.4	1.2–9.6	.0229	.2663
	9. History of lactic acidosis	1.4	0.5–4.4	.5353	.8236
	10. Current lactic acidosis	1.5	0.5–4.1	.4438	.8057
Years practicing	1. Controlled T2DM	1.7	0.7–4	.2527	.7221
	2. Uncontrolled T2DM, metformin 500 mg/day	0.6	0.4–1	.0399	.2663
	3. Uncontrolled T2DM, metformin 1500 mg/day	1.1	0.8–1.7	.4990	.8057
	4. Chronic kidney disease	0.7	0.5–1.1	.1174	.4270
	5. Hepatic dysfunction	1.0	0.7–1.5	.9878	.9878
	6. Heart failure	1.0	0.7–1.4	.9354	.9729
	7. Chronic obstructive pulmonary disease	1.0	0.6–1.8	.8681	.9729
	8. Alcohol abuse	1.1	0.8–1.5	.7582	.9683
	9. History of lactic acidosis	1.1	0.7–1.5	.7199	.9635
	10. Current lactic acidosis	1.3	0.9–1.8	.1166	.4270
Mountain West vs Midwest region	1. Controlled T2DM	1.6	0.3–10.2	.6152	.8789
	2. Uncontrolled T2DM, metformin 500 mg/day	1.7	0.5–5.3	.3562	.8057
	3. Uncontrolled T2DM, metformin 1500 mg/day	1.0	0.4–2.9	.9484	.9729
	4. Chronic kidney disease	2.4	0.9–6.6	.0978	.4270
	5. Hepatic dysfunction	0.7	0.3–1.8	.4404	.8057
	6. Heart failure	1.0	0.4–2.3	.9486	.9729
	7. Chronic obstructive pulmonary disease	2.6	0.7–9.9	.1536	.4727
	8. Alcohol abuse	0.9	0.4–2.3	.8698	.9729
	9. History of lactic acidosis	1.7	0.6–4.6	.2838	.7568
	10. Current lactic acidosis	0.7	0.3–1.7	.4651	.8057
Academic vs all other settings	1. Controlled T2DM	0.4	0–3.5	.3886	.8057
	2. Uncontrolled T2DM, metformin 500 mg/day	0.3	0.1–1.2	.0819	.4270
	3. Uncontrolled T2DM, metformin 1500 mg/day	0.8	0.3–2.2	.7227	.9635
	4. Chronic kidney disease	3.4	1.3–8.9	.0128	.2557
	5. Hepatic dysfunction	1.3	0.5–3.3	.5946	.8789
	6. Heart failure	2.5	1.1–5.8	.0351	.2663
	7. Chronic obstructive pulmonary disease	0.6	0.1–2.2	.4032	.8057
	8. Alcohol abuse	0.8	0.3–1.7	.5036	.8057
	9. History of lactic acidosis	1.5	0.6–3.7	.3557	.8057
	10. Current lactic acidosis	2.4	1.1–5.5	.0379	.2663

*Physicians include residents and those who have completed residency training.
CI, confidence interval; FDR, false discovery rate; T2DM, type 2 diabetes mellitus.

metformin use. There are several major guidelines outside the United States that indicate that GFR is a better measure of kidney function than serum creatinine and should be used to assess metformin use in patients with diabetes.[15] Although creatinine clearance (using the Cockcroft-Gault equation) is typically preferred for renal drug dose adjustments, metformin dose adjustments have not been evaluated in the same fashion as most other medications; thus GFR, which is a more accurate indicator of renal function, is preferred when dosing metformin.[2,13,16] While the majority of clinicians would stop metformin because of impaired renal function, it is unclear whether the reason is due to a per-

ceived risk of lactic acidosis or an alternate reason, perhaps such as fear of legal liability, the contraindication in the manufacturer's package insert, or unfamiliarity with the actual consequences of metformin use.

With regard to metformin use in patients with other comorbidities, such as hepatic dysfunction, heart failure, alcoholism, or history of lactic acidosis, responses indicate there is no consensus on when to adjust metformin therapy, but that the majority of clinicians would alter metformin therapy in varying stages or severities of these conditions. In contrast to renal dysfunction, metformin is not contraindicated in the setting of hepatic dysfunction, heart failure, alcoholism, or history of lactic acidosis; rather, these are considered warnings or precautions to metformin use.[3] Because these conditions are not contraindications, this may explain the greater variation in responses among providers in contrast to renal dysfunction, in which all clinicians would stop metformin at some degree of renal dysfunction. Nevertheless, the labeling of these comorbidities as warnings or precautions by the drug manufacturer may influence providers' decisions to prescribe metformin. Although many of these clinical situations are fairly common among patients, there are few studies indicating what should be done regarding metformin use in patients with these comorbidities.

Although not statistically significant after adjusting for multiple comparisons, providers practicing in academic clinics were more likely than those in nonacademic settings, and physicians were more likely than pharmacists, to follow the suggested prescribing practices for metformin in certain situations. Future research is needed to better understand these trends.

While this study demonstrated great variation in metformin prescribing, it is limited by the nature of the survey distribution, which was a convenience sample. Using a convenience sample limits the generalizability of the findings. Further, by requesting that respondents forward the survey to their clinician colleagues, we are unable to discern detailed characteristics of the population the survey was distributed to.

Despite the best available evidence suggesting little to no risk of lactic acidosis with metformin use, most clinicians would adjust metformin therapy in the setting of risk factors for lactic acidosis, including renal dysfunction, hepatic dysfunction, heart failure, alcoholism, and history of or current lactic acidosis. However, clinician thresholds for adjusting metformin prescribing are inconsistent. Further research is needed to better define and characterize risk factors for lactic acidosis with metformin use to help inform prescribing of metformin. Additional studies also are needed to better understand why attitudes toward prescribing metformin vary greatly and to allow for targeted interventions, which may be in the form of focused interviews or focus groups to answer these questions. A better understanding of the risk of lactic acidosis with metformin and reasons why prescribing attitudes vary are needed to improve appropriate prescribing of this important diabetes medication. Once more information is known about why providers are reluctant to prescribe metformin in certain clinical situations, implementation of targeted clinical decision support tools, such as electronic alerts within electronic health records, may assist in optimizing the use of this important medication. Further, aligning the manufacturer's recommendations of metformin prescribing with the best available evidence may also assist in optimizing prescribing. Optimizing metformin prescribing is critical to improving cardiovascular morbidity and mortality for the high-risk population of patients with T2DM.

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