Metformin Use in Practice: Compliance With Guidelines for Patients With Diabetes and Preserved Renal Function

Gregory J. Salber,[1] Yu-Bo Wang,[2] John T. Lynch,[3] Karen M. Pasquale,[3] Thiruchandurai V. Rajan,[4] Richard G. Stevens,[5] James J. Grady,[2] and Anne M. Kenny[1]

IN BRIEF Several contraindications limit the use of metformin, most notably the risk of lactic acidosis. This article reports on an examination of a population of patients with diabetes with preserved renal function to evaluate provider compliance with guidelines on metformin use and to identify factors that contributed when practice diverged from recommendations. It found that metformin was withheld from approximately one-third of these patients because of *1*) an existent contraindication to metformin, *2*) patient behavior or preference, or *3*) provider preference or bias based on patient or personal factors. Although providers generally follow current recommendations for the use of metformin, deviations from guidelines in practice are common.

Metformin is among the oldest and most well studied oral antihyperglycemic agents. Its efficacy has been demonstrated both in the primary prevention of disease (1) and secondary prevention of diabetes-related morbidity and mortality (2). Because of metformin's proven efficacy, low cost, and minimal side effect profile, it is largely recommended as the first-line, initial monotherapy and as part of any combination therapy (including with insulin) for the treatment and prevention of type 2 diabetes (3).

When applying metformin's use in clinical practice, providers must weigh both patient-specific contraindications and personal preferences. Metformin has several adverse effects that may make it less palatable to patients and carries risks that providers must consider before prescribing it. Chief among these risks is the development of metformin-associated lactic acidosis. Concern about lactic acidosis with the use of agents in the biguanide drug class has persisted since the early days of their use. The U.K. Prospective Diabetes Study demonstrated metformin's efficacy in practice, and retrospective analysis found that the incidence of lactic acidosis with metformin was significantly less than with phenformin (2,4). Despite these findings, concern about metformin-associated lactic acidosis persisted among clinicians and strongly influenced the definition of contraindications to metformin use.

The majority of metformin's contraindications stem from conditions that may potentiate or directly cause lactic acidosis (5). The most prominent and widely recognized contraindication is renal dysfunction (creatinine of 1.4/1.5 mg/dL or an estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) because metformin is largely metabolized by the kidneys, and renal dysfunction is itself an independent risk factor for acidosis. It is also recommended that metformin be used with caution in conditions such as congestive heart failure (CHF), hepatic failure, alcohol abuse, chronic obstructive pulmonary disease, and intravenous contrast use (6). These conditions either promote the for-

[1]*Center on Aging, University of Connecticut Health Center, Farmington, CT*

[2]*Connecticut Institute for Clinical and Translational Science, University of Connecticut Health Center, Farmington, CT*

[3]*Connecticut Center for Primary Care, Farmington, CT*

[4]*Pathology and Laboratory Medicine, University of Connecticut Health Center, Farmington, CT*

[5]*Community Medicine, University of Connecticut Health Center, Farmington, CT*

Corresponding author: Anne Kenny, kenny@uchc.edu

https://doi.org/10.2337/cd15-0045

mation of lactate via tissue hypoxia, interfere with lactate's metabolism, or promote decreased clearance of metformin, and all are thought to potentiate metformin-induced lactic acidosis. Caution is also advised for initiation of therapy in patients >80 years of age given the risks of unrecognized renal dysfunction. Additionally, metformin has been linked to decreased levels of vitamin B12 (7). Care is also advised with the concurrent use of furosemide, nifedipine, and other cationic drugs that have a proven or theoretical effect of increasing plasma metformin levels (6).

Clinical practice often differs from guidelines, however, and several studies have attempted to catalog the incidence with which metformin has been improperly used in various clinical settings (8–10). These studies have yielded surprising results: between 21.4 and 73% of patients had at least one contraindication or condition for which caution was advised in the use of metformin (8–10). One such study (8) found that 24.5% of patients receiving metformin had preexisting contraindications to its use, and 87% of patients already taking metformin continued to take it despite developing a new contraindication (8). In one study (10), the most common contraindications observed were age, renal function, and concurrent cationic drug use. In all of the studies, the development of lactic acidosis was found to be exceedingly rare or did not occur at all. These studies were observational, so confounding factors affecting the outcome could not be excluded. Additionally, the majority of cases reported on inpatient stays, with less examination of metformin use in the outpatient setting (8,9).

Despite the marked use of metformin in cases in which it is contraindicated, the development of lactic acidosis remains rare (11). Large reviews have concluded that the incidence of metformin-induced lactic acidosis is no higher than that with other antihyperglycemic medications (12). These findings have led experts to conclude that the major risk factor for developing metformin-induced lactic acidosis is not metformin, but rather diabetes itself (13,14). Others have identified no increase in lactic acidosis with metformin use compared to the use of other antihyperglycemic agents in patients with heart failure (15). Thus, the traditional view of metformin's safety profile has evolved as its role in type 2 diabetes management has grown ,and evidence supporting its safety has accumulated. How the changing view of metformin's safety plays out in real-world clinical practice has yet to be examined.

The aim of this study was to shed more light on the use of metformin in practice. We specifically focused on patients who, either through personal preference or provider choice, were not taking metformin despite having adequate renal status. We sought to determine which factors beyond renal failure were important in decisions to keep patients off metformin and to compare how metformin's use in practice correlates with existing guidelines in light of lessening concerns regarding the safety of this agent. To our knowledge, a large outpatient study has not been performed previously. Notably, earlier cross-sectional studies examining provider compliance with guidelines predate many of the recent calls for revisions to recommendations for metformin's use.

Design and Methods

Research Design

This was an observational, cross-sectional, epidemiological study that included patients ≥18 years of age with type 2 diabetes in primary care settings. This project assembled data from health record sources as outlined below. Patient identities were masked throughout the study in a limited dataset format in accordance with the Health Insurance Portability and Accountability Act.

Study Sample and Data Collection

Data for this study were derived from the Building Infrastructure for Comparative Effectiveness Protocols (BICEP) study, which included 19,570 type 2 diabetes patients obtained from electronic health records (EHRs) of 307 primary care practitioners. The records included practice management system demographics, administrative claims, EHR clinical problem lists, office measures, notes, laboratory results, and medication histories. Type 2 diabetes was defined using a method similar to that defined by Nichols et al. (16) and DeSai t al. (17), triangulating type 2 diabetes from EHR problem lists, type 2 diabetes claims diagnoses, A1C >6.5%, and diabetes medications. Patients with type 1 diabetes, gestational diabetes, or polycystic disease and children <18 years of age were excluded.

Observation Period

A patient-specific study baseline was defined as the first type 2 diabetes encounter for each patient fully recorded in the EHR with a complete medication history after September 2009 and before the last data pull on 12 March 2012.

Study Measures

Dependent Variables

The primary endpoint was the use of metformin in those with a normal eGFR.

Independent Variables

Independent variables included demographics (i.e., age, sex, race, ethnicity, marital status, history of smoking, and primary language spoken), health system variables (i.e., primary insurance, provider specialty, provider age, and number of diabetes cases for provider), office measures (i.e., height, weight, BMI, and blood pressure), laboratory metrics (i.e., eGFR, A1C, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, anion gap, alanine aminotransferase, aspartate aminotransferase, microalbumin, serum albumin, and serum creati-

TABLE 1. Descriptive Data for All Patients With an eGFR >60 mL/min

Demographic	*n*	Off Metformin (%)	*P*
Women	1,516	34.68	<0.0001
Men	1,637	29.37	
Black	221	30.07	0.3209
White	2,932	31.84	
A1C (%)			
5.6–6.4	1,756	44.52	<0.0001
6.5–7.5	1,003	26.18	
7.6–9.0	230	17.79	
>9.0	164	18.72	
Comorbidities (*n*)			
1–5	215	27.46	<0.0001
6–10	985	29.37	
11–15	1,169	31.44	
16–20	579	36.34	
≥21	205	41.75	
Provider age (years)			
>40	2,714	31.35	0.0495
≤40	439	34.08	
>55	1,450	30.93	0.1156
≤55	1,703	32.40	
Provider specialty: family medicine	1,356	30.90	0.1252
Provider specialty: internal medicine	1,797	32.34	

Medication	*n*	Off Metformin (%)	*P*
Insulin	536	33.09	0.1924
No insulin	2,617	31.44	
Other diabetes medications (PO)	810	17.39	<0.0001
No other diabetes medications (PO)	2,343	44.32	
ACE or ARB	1,632	28.82	<0.0001
No ACE or ARB	885	35.13	
Loop diuretic	250	38.34	<0.0001
No loop diuretic	2,267	30.11	
Thiazide	821	30.10	0.3549
No thiazide	1,696	31.10	
K-sparing diuretic	104	37.82	0.0099
No K-sparing diuretic	2,413	30.52	
Statin	1,762	29.19	<0.0001
No statin	755	35.20	
Nonstatin cholesterol drug	409	25.12	<0.0001
No nonstatin cholesterol drug	2,108	32.16	
Beta blocker	925	33.99	<0.0001
No beta blocker	1,592	29.15	

Comorbid Condition	*n*	Off Metformin (%)	*P*
CHF	177	41.55	<0.0001
No CHF	2,976	31.27	
Hypertension	2,570	31.19	0.0139
No hypertension	583	34.23	
Hepatic disease	166	30.02	0.3796
No hepatic disease	2,897	31.15	
Drug or alcohol abuse	297	9.42	0.7221
No drug or alcohol abuse	655	9.65	

K, potassium; PO, orally.

TABLE 2. Descriptive Data for Patients With an eGFR >60 mL/min Who Were Not Taking Metformin or Insulin

Demographic	*n*	%	Medication	*n*	%	Comorbid Condition	*n*	%
Black	234	6.42	Other diabetes medications (PO)	1,143	31.38	CHF	272	7.47
White	3,409	93.58	No other diabetes medications (PO)	2,500	68.62	No CHF	3,371	92.53
A1C (%)			ACE or ARB	1,936	64.84	Hypertension	3,096	84.98
5.6–6.4	2,330	63.78	No ACE or ARB	1,050	35.16	No hypertension	547	15.02
6.5–7.5	1,157	31.67	Loop diuretic	369	12.36	Hepatic disease	166	4.56
7.6–9.0	126	3.45	No loop diuretic	2,617	87.64	No hepatic disease	3,477	95.44
>9.0	40	1.09	Thiazide	1,094	36.64	Drug or alcohol abuse	337	9.25
Comorbidities (n)			No thiazide	1,892	63.36	No drug or alcohol abuse	3,306	90.75
1–5	208	5.71	K-sparing diuretic	155	5.19			
6–10	1,063	29.18	No K-sparing diuretic	2,831	94.81			
11–15	1,335	36.65	Statin	2,112	70.73			
16–20	746	20.48	No statin	874	29.27			
≥21	291	7.99	Nonstatin cholesterol drug	515	17.25			
Provider age (years)			No nonstatin cholesterol drug	2,471	82.75			
>40	3,169	86.99	Beta blocker	1,210	40.52			
≤40	474	13.01	No beta blocker	1,776	59.48			
>55	1,699	46.64						
≤55	1,944	53.36						
Provider specialty: family medicine	1,526	41.89						
Provider specialty: internal medicine	2,117	58.11						

K, potassium; PO, orally.

nine), major diagnoses (i.e., hypertension, heart failure, renal failure, liver disease, history of drug or alcohol abuse, asthma or chronic obstructive lung disease, and comorbidity count), and selected medications (including 11 classes of diabetes medications, 6 classes of cholesterol-lowering agents, antiarrhythmics, 5 classes of diuretics, ACE inhibitors, angiotensin receptor blockers [ARBs], and beta blockers).

The major diagnoses and the comorbidity count were defined using the Hierarchical Condition Category (HCC) model, which provides a disease-specific, validated methodology for risk stratification (18). We used the CMS CY 2011 HCC Risk Adjustment Model to create 184 "Condition Category" variables (19).

Age was aggregated into eight age-groups. Medications were aggregated into groups using Generic Product Identifier six-digit codes. BMI was calculated using height and weight and then aggregated into underweight, normal weight, overweight, obese, and unknown. Office measures and laboratory metrics were also aggregated into logical groups. Baseline laboratory values were transformed into binary variables, distinguishing an abnormal result from a normal or missing result.

Statistical Analysis

Descriptive analysis was done to compare those with a normal eGFR on and off metformin (Table 1) and those with a normal eGFR on and off metformin and not receiving insulin (Table 2). Due to multiple comparisons, *P* values were defined as significant if <0.01. In both tables, χ^2 tests were used to compare the proportions of metformin usage in each group, and those with significant associations were used in the statistical model. Among those with a normal eGFR, we used logistic regression to model the binary outcome of metformin use (yes vs. no) to estimate odds ratios (ORs) and 95% CIs for age, comorbidity count, prescriber's age (dichotomized as ≤40 or >40 years), A1C

TABLE 3. Multiple Logistic Model (Probability Modeled Is "Not on Metformin") for All Patients With an eGFR >60 mL/min

		Analysis of Maximum Likelihood Estimates				
Parameter	df	Estimate	SE	Wald χ^2	Probability > χ^2	OR
Intercept	1	–2.3858	0.1618	217.4070	<0.0001	—
Age	1	0.0262	0.00226	134.0024	<0.0001	1.027
A1C 6.5–7.5% (baseline 5.6–6.4%)	1	0.0785	0.0517	2.3115	0.1284	0.504
A1C 7.6–9.0% (baseline 5.6–6.4%)	1	–0.4241	0.0740	32.8334	<0.0001	0.305
A1C >9.0% (baseline 5.6–6.4%)	1	–0.4179	0.0922	20.5454	<0.0001	0.307
Comorbidities ≤11	1	–0.0804	0.0275	8.5527	0.0035	0.851
ACE or ARB	1	–0.0969	0.0277	12.2464	0.0005	0.824
Nonstatin cholesterol medication	1	–0.1169	0.0339	11.8944	0.0006	0.792
Other diabetes medications	1	–0.5563	0.0278	401.1475	<0.0001	0.329
Provider age ≤40 years	1	0.0803	0.0375	4.5790	0.0324	1.174
Statin	1	–0.1716	0.0290	34.9271	<0.0001	0.709
Insulin	1	0.3970	0.0403	97.2182	<0.0001	2.212
CHF	1	0.1324	0.0587	5.0869	0.0241	1.303

SE, standard error.

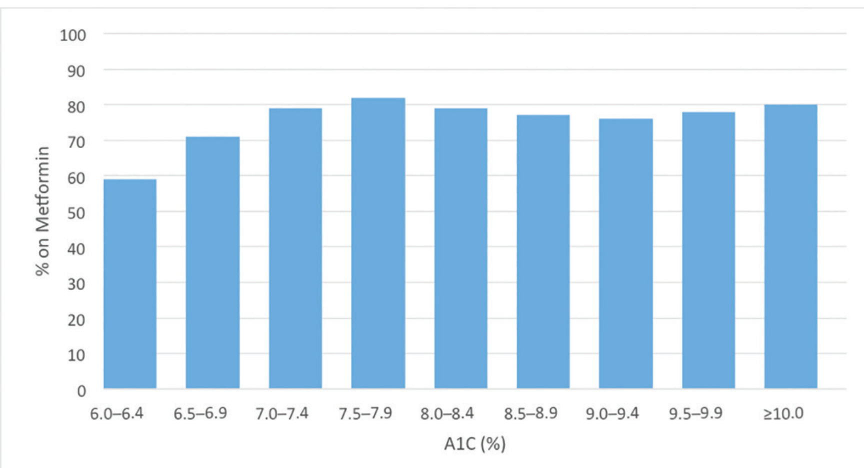


FIGURE 1. The percentage of individuals receiving metformin based on A1C level.

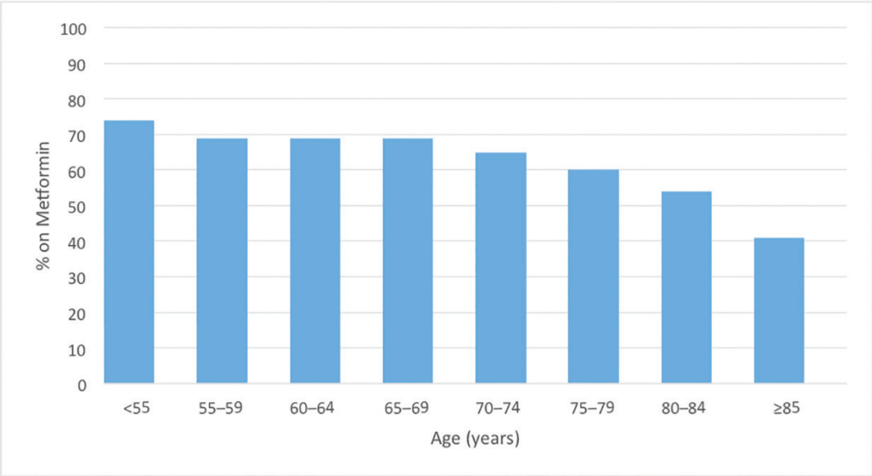
status, heart failure status, and use of antihypertensive and diabetes drugs (Table 3). All analyses were conducted using SAS® (SAS Institute, Inc.; Cary, NC).

Results

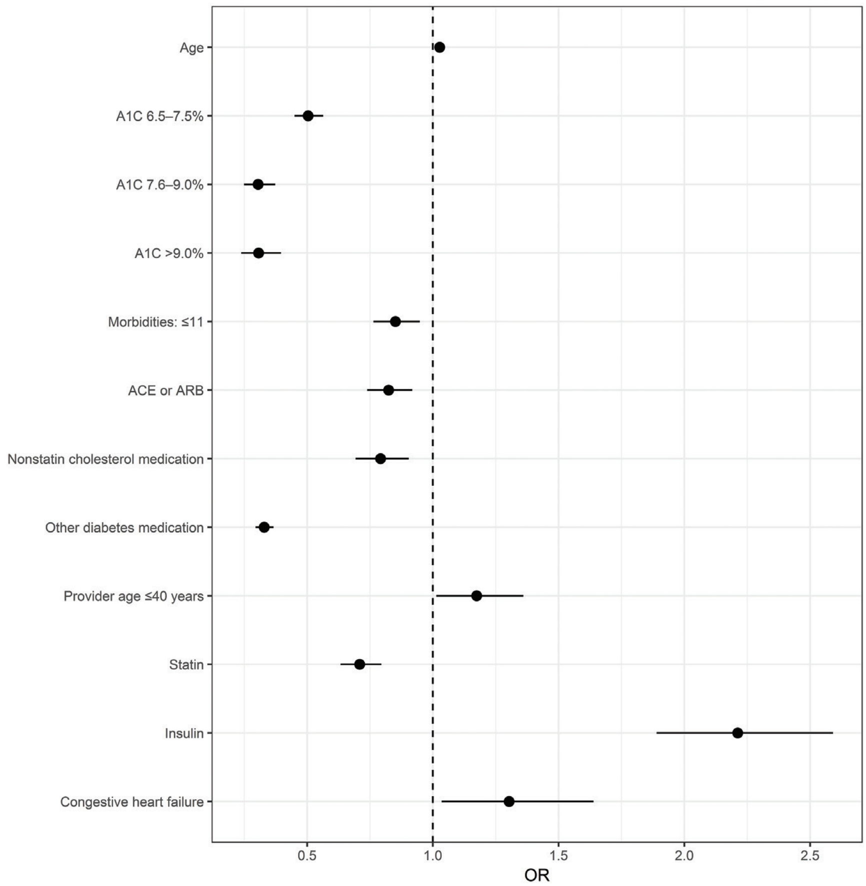
When comparing demographic data for patients with an eGFR >60 mL/min for their metformin status, several variables appear to be associated (Table 1). Women were significantly less likely than men to be on metformin. Worsening A1C was associated with an increased probability of metformin use (Figure 1); a significant increment of metformin use was observed when A1C increased (χ^2 test P <0.0001) Those <70 years of age had similar rates of metformin use; those ≥70 years of age appeared to have lower rates of use (Figure 2). As number of comorbid conditions increased, patients were less likely to be on metformin (Figure 3). Providers ≤40 years of age were less likely to prescribe their patients metformin; however, this relationship was not maintained when providers were stratified by age 55 years. There was no difference between prescription rates among provider specialties.

Among specific comorbid conditions, only patients with CHF had a significant difference in metformin prescription rate; those with CHF were much less likely to receive a prescription for metformin. No differences were observed between patients with hypertension, hepatic disease, or significant drug or alcohol use.

There was no significant difference in prescription rates for patients who were on insulin. Patients who were also prescribed an ACE inhibitor, an ARB, a statin, or a nonstatin cholesterol agent were all significantly more likely to also be prescribed



■ **FIGURE 2**. The percentage of individuals receiving metformin based on age.



■ **FIGURE 3**. ORs of receiving metformin for outcome measures, including age, number of comorbidities, provider age, A1C level, history of CHF, and use of medications, including ACE or ARB, statin, nonstatin cholesterol medication, other diabetes medications, and insulin.

metformin. Patients who were prescribed any type of beta blocker, any potassium-sparing diuretic, or a loop diuretic were all less likely to receive a prescription for metformin.

Multivariate logistic regression (Table 3 and Figure 3) provided the ORs of a specific variable predicting a patient's metformin status when simultaneously considering other potent variables. In the fitted model, increasing patient age, having a provider ≤40 years of age, having CHF, and being treated with insulin were strong predictors that a patient would not be on metformin. In contrast, having ≤11 comorbidities, having a higher A1C, and being on an ACE or ARB, statin, nonstatin cholesterol medication, or other diabetes medication were all strong predictors that a patient would be treated with metformin.

Discussion

Diabetes is a complex, chronic illness requiring continuous medical care with multifactorial risk-reduction strategies beyond glycemic control. Because of the role lifestyle plays in the acquisition of insulin resistance and the chronic and progressive nature of glucose intolerance, type 2 diabetes is rarely seen in isolation; it is often accompanied by a significant burden of comorbid disease such as hypertension, hyperlipidemia, heart disease, vascular disease, and neuropathy, all of which have independent chronic therapy requirements.

It is unfortunate happenstance that many of the conditions caused by diabetes are themselves direct contraindications to its treatment. Providers must carefully balance a patient's diabetes care needs with those of their other conditions. Thus, there are three general scenarios in which metformin would not be an optimal therapy choice for patients with diabetes: *1*) there is an existent contraindication to metformin's use, *2*) patient behavior or preference may play a role in alternate agent selection, or *3*) providers may have a preference or personal bias from experience or other factors. Indeed, these three scenarios may be common in clinical practice; of the eligible patients in this study who did not meet exclusionary criteria for metformin use, 33.9% were, nonetheless, not on metformin.

Contraindications

The most prominent and frequently encountered contraindication to metformin use in the outpatient setting is renal failure, and rates of its inappropriate use in this setting are well documented in the literature (8,9). Patients with renal failure were excluded from our analysis. Of the remaining contraindications examined in our study, only CHF was associated with differences in prescription patterns. Patients with CHF were significantly less likely to be prescribed metformin, in proper accordance with guidelines. This trend was also reflected in prescription of other medications; patients on beta blockers, loop diuretics, and potassium-sparing diuretics—agents that are largely used in the treatment of CHF—were significantly less likely to receive metformin. Providers may correctly recognize that CHF is a contraindication to metformin, or some other factor may be at work (15,20). However, there appeared to be no difference in metformin use in patients with either hepatic failure or alcohol abuse. These conditions may be overlooked by providers as a risk for metformin-induced lactic acidosis, or other factors may be weighed in the decision to continue therapy against guidelines.

Patient Preference

Patient preference may also play a role in the selection of therapies other than metformin. It is well documented that lifestyle modification is an effective component in both the prevention and management of type 2 diabetes (21,22). Extrapolating information from the 3,153 subjects presented in Table 1, the majority did not take insulin or other diabetes medications, and 31 and 44%, respectively, also did not take metformin. We do not have direct evidence about patient preferences, but our data suggest a few potential explanations. It may be that a large segment of the population may choose to manage diabetes through lifestyle modification alone. Those who had poor glycemic control but were on no medical therapy may represent a patient population that is averse to treatment, given that noncompliance rates for diabetes medical therapy have been shown to be very high (23).

Metformin has several known adverse effects that may make it less palatable for patients. The most common is gastrointestinal upset, occurring in 10.4–19.3% of patients, usually in the first few weeks of therapy. Although it appears that few patients discontinue therapy early in the course of treatment, a significant portion of patients continue to experience these effects at 6 months (24). Thus, the group on other diabetes oral agents may have switched to an alternative therapy to avoid intolerable side effects.

Finally, a segment of the population with poor glycemic control was on metformin and other oral agents, but not insulin. In fact, being on another oral antihyperglycemic agent was a strong predictor of also having a prescription for metformin. This finding likely represents the population who wish to remain on the therapy even in the setting of poor control. Such prescription patterns often stem from the common patient preference to avoid insulin (25).

Provider Preference

Guidelines must always be applied in the context of the individual patient. Clinical experience or personal bias may lead to a provider to offer an alternative agent when deemed necessary. Our study demonstrated that decreased metformin use was associated with older age of patients and with those who had a higher burden of disease, as evidenced by their number of comorbidities. The majority of clinical trials for diabetes control have excluded elderly and frail patients with multiple comorbidities. The elderly represent a heterogeneous population, and with less defined guidelines for optimal therapy, providers are granted more leeway in treatment decisions for these patients (26).

Worsening glycemic control was also associated with higher rates of metformin use. For patients with an A1C >8.0%, it as equally likely that they would or would not be prescribed metformin. This result indicates that providers are following the established practice of including metformin in combination with oral therapy and in combination with insulin therapy. Insulin use, however, was associated with a decreased frequency of metformin use.

The American Diabetes Association recommends that patients with diabetes who are >40 years of age and have ≥1 cardiovascular risk factor (i.e., family history of coronary artery disease, hypertension, smoking, dyslipidemia, or albuminuria) receive a statin medication (27). Multiple trials have demonstrated improved cardiovascular outcomes in patients with diabetes who are treated with statins (28). Our study demonstrates that providers prescribing and patients receiving metformin for glycemic control when their eGFR is >60 mL/min are also more likely to be prescribing/receiving medications to control cardiovascular risk. We do not have information about whether this is the result of provider or patient preferences, but it does represent an area in need of further inquiry. Modifications to behavior of both providers and patients can be further explored to improve health outcomes. Evolving continuing medical education strategies have found practices such as office detailing (a practice in which a representative is sent to an office to provide one-on-one educational discussion with the physician) to improve provider behavior (29). More extensive analysis of EHRs may guide us in an approach to improve provider and patient behaviors to promote better health.

Treatment disparities are commonly observed across all fields of treatment. In our study, there appeared to be no differences by race in performance indicators, although the minority populations observed were quite small compared to national averages (30). There was, however, a significant difference in the prescription rate of women with preserved renal function. At this time, the reasons for this difference are unknown, and there appear to be no reported specific diabetes management disparities between sexes reported in the literature.

This study highlights several issues regarding provider compliance with guidelines for the use of metformin. However, several questions are left unresolved and would benefit from further examination. This study was limited by its observational nature, so confounding factors affecting its outcomes cannot be excluded. We were unable to directly assess patient preferences for treatment, so we relied on indirect measures to suggest preferences. Our sampled population also had a very low minority prevalence, limiting its generalization to the population at large.

Acknowledgments

The original BICEP project was supported by grant number R24HS019474 from the Agency for Healthcare Research and Quality. The continuing research reported here received no additional funding. The authors thank Lisa Godin for her expert assistance with manuscript preparation.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

References

1. DPP Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403

2. U.K. Prospective Diabetes Study Group. Effect of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854–865

3. Rodbard HW, Jellinger PS, Davidson JA, et al. Statement by an American Association of Clinical Endocrinologists/ American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. Endocr Pract 2009;15:540–559

4. Stang MR, Wysowski DK, Butler-Jones D. Incidence of lactic acidosis in metformin users. Diabetes Care 1999;22:925–927

5. Scarpello J, Howlett H. Metformin therapy and clinical uses. Diabetes Vasc Dis Res 2008;5:157–167

6. U.S. Food and Drug Administration. Glucophage [Internet]. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2000/21202lbl.pdf. Accessed 4 May 2017.

7. de Jager J, Kooy A, Lehert P, et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. BMJ 2010;20:340:c2181

8. Emslie-Smith AM, Boyle DI, Evans JM, Sullivan F, Morris AD; DARTS/ MEMO Collaboration. Contraindications to metformin therapy in patients with type 2 diabetes: a population-based study of adherence to prescribing guidelines. Diabet Med 2001;18:483–488

9. Rakovac I, Jeitler K, Gfrerer RJ, et al. Patients with type 2 diabetes treated with metformin: prevalence of contraindications and their correlation with discontinuation. Diabet Med 2005;22:662–664

10. Sulkin TV, Bosman D, Krentz AJ. Contraindications to metformin therapy in patients with NIDDM. Diabetes Care 1997;20:925–928

11. Rojas LB, Gomes MB. Metformin: an old but still the best treatment for type 2 diabetes. Diabetol Metab Syndr 2013;5:6

12. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev 2010;20:CD002967

13. Tahrani AA, Varghese GI, Scarpello JH, Hanna FWF. Metformin, heart failure and lactic acidosis: is metformin absolutely contraindicated? BMJ 2007;355:508–512

14. Misbin RI. The phantom of lactic acidosis due to metformin in patients with diabetes. Diabetes Care 2004;27:1791–1793

15. Eurich DT, Weir DL, Majumdar SR, et al. Comparative safety and effectiveness of metformin in patients with diabetes mellitus and heart failure: systematic review of observational studies involving 34,000 patients. Circ Heart Fail 2013;6:395–402

16. Nichols G, Desai J, Lafata J, et al. Construction of a multisite DataLink using electronic health records for the identification, surveillance, prevention, and management of diabetes mellitus: the SUPREME-DM project. Prev Chronic Dis 2012;9:E110

17. DeSai J, Wu P, Nichols G, Lieu T, O'Connor P. Diabetes and asthma case identification, validation, and representativeness when using electronic health data to construct registries for comparative effectiveness and epidemiologic research. Med Care 2012;50(Suppl.):S30–S35

18. Mosley DG, Peterson E, Martin DC. Do hierarchical condition category model scores predict hospitalization risk in newly enrolled Medicare Advantage participants as well as probability of repeated admission scores? J Am Geriatr Soc 2009;57:2306–2310

19. Pope G, Kautter J, Ingber M, Freeman S, Newhart C. Evaluation of the CMS-HCC risk adjustment model: final report. RTI Project Number 0209853. Available from http://www.nber.org/risk-adjustment/2011/Evaluation2011/ Evaluation_Risk_Adj_Model_2011.pdf. Acccessed 8 May 2017

20. Papanas N, Maltezos E, Mikhailidis DP. Metformin and heart failure: never say never again. Expert Opin Pharmacother 2012;13:1–8

21. Knowler WC, Barrett-Connor E, Fowler SE, et al.; DPP Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403

22. Sigal RJ, Kenny GP, Wasserman DH, Castaneda-Sceppa C. Physical activity/ exercise and type 2 diabetes. Diabetes Care 2004;27:2518–2539

23. Cramer JA, Benedict A, Muszbek N, Keskinaslan A, Khan ZM. The significance of compliance and persistence in the treatment of diabetes, hypertension and dyslipidaemia: a review. Int J Clin Pract 2008;62:76–87

24. Schwartz S, Fonseca V, Berner B, Cramer M, Chiang YK, Lewin A. Efficacy, tolerability, and safety of a novel once-daily extended-release metformin in patients with type 2 diabetes. Diabetes Care 2006;29:759–764

25. Peyrot M, Rubin RR, Lauritzen T, et al.; International DAWN Advisory Panel. Resistance to insulin therapy among patients and providers: results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study. Diabetes Care 2005;28:2673–2679

26. Dardano A, Penno G, Del Prato S, Miccoli R. Optimal therapy of type 2 diabetes: a controversial challenge. Aging (Albany NY) 2014;6:187–206

27. American Diabetes Association. Standards of medical care in diabetes—2014. Diabetes Care 2014;37(Suppl. 1):S14–S80

28. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2013;1:CD004816

29. Mazmanian PE, Davis DA, Galbraith R; American College of Chest Physicians Health and Science Policy Committee. Continuing medical education effect on clinical outcomes: effectiveness of continuing medical education: American College of Chest Physicians Evidence-Based Educational Guidelines. Chest 2009;135 (Suppl. 3):49S–55S

30. Chou AF, Brown AF, Jensen RE, Shih S, Pawlson G, Scholle SH. Gender and racial disparities in the management of diabetes mellitus among Medicare patients. Womens Health Issues 2007;17:150–161