Provider Decisions and Patient Outcomes After Premature Metformin Discontinuation

Jessica N. Bradley,[1] Krystal L. Edwards,[2] Jennifer T. Gunter,[1] Rick A. Weideman,[1] and Kevin C. Kelly[1]

ABSTRACT

The purpose of this study was to evaluate the effects of alternative antihyperglycemic therapy after discontinuation of metformin due to documented declining renal function. This retrospective, single-site study evaluated patients who had metformin discontinued between 1 January 1999 and 30 September 2013. Medical records were evaluated for documented adverse events, subsequent glycemic control, and costs associated with the alternative therapy. Patients served as their own controls. A total of 179 patients met study entry criteria, and their peak A1C was significantly higher within the year after metformin discontinuation (P <0.001). After the provider added new medications to control patients' blood glucose, their A1C by the end of the first year after discontinuing metformin was similar to their A1C while taking metformin. Significant weight gain accompanied the use of the medications added to replace metformin, with an average increase of 3.81 kg (P <0.001). Additionally, after discontinuing metformin, more patients experienced hypoglycemia with the addition of other medications to control their blood glucose (P <0.001). As expected, the cost of therapy was significantly higher (P <0.0001) after metformin was discontinued because metformin was generically available, whereas the replacement medications frequently were not. Providers should consider the expanded recommendations for the use of metformin in patients with mild to moderate stable renal dysfunction to help such patients avoid weight gain, hypoglycemia, loss of blood glucose control, and increased costs.

Type 2 diabetes affects ~25.9% of adults ≥65 years of age in the United States (1). Among veterans receiving care in the U.S. Department of Veterans Affairs health care system, approximately one in four patients have a diagnosis of diabetes (2). Approximately 40% of patients with diabetes develop chronic kidney disease (CKD), manifested by an impaired glomerular filtration rate (GFR) with or without albuminuria (3).

There are numerous published national and international clinical practice guidelines (4–11) for the management of type 2 diabetes that recommend metformin as an initial monotherapy agent if there are no contraindications to its use. Compared to other antihyperglycemic agents, metformin is less likely to cause hypoglycemia, is weight neutral (8,12), and has been linked to a reduction in mortality (8,13).

There are, however, some limitations to metformin use. The most com-mon adverse effect experienced with metformin therapy is transient gastrointestinal upset (14). In addition, metformin's package insert (15) contains a boxed warning for the rare but potentially fatal adverse event of lactic acidosis, which could occur in the setting of severe renal dysfunction.

[1]*North Texas Veterans Affairs Health Care System, Dallas, TX*

[2]*Texas Tech University Health Sciences Center School of Pharmacy, Dallas, TX*

Corresponding author: Kevin C. Kelly, kevin.kelly@va.gov

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Contraindications and precautions related to renal function are also described in the package labeling (15); metformin is contraindicated with a serum creatinine (SCr) ≥1.5 mg/dL in males and ≥1.4 mg/dL in females. These SCr limits were initially established based on the calculated ability to remove 3 g (greater than the maximum daily dose) of metformin within 24–48 hours. Although the actual clearance of the drug was calculated to occur at SCr values of 1.8–2 mg/dL, the lower cutoffs of 1.4–1.5 mg/dL were selected to ensure the safety of patients with declining renal function who may be lost to follow-up (16). The use of SCr does not take into account other factors that influence drug clearance such as age, race, or sex and is a poor substitute compared to estimated GFR (eGFR) calculations.

Although cases of lactic acidosis in patients taking metformin have been identified, there are usually other contributing patient factors such as cardiopulmonary resuscitation (17,18). Multiple recent trials (19–21) have provided no evidence that metformin therapy is associated with the risk of developing lactic acidosis, and much of the concern comes from previous experience with phenformin, which was a structurally similar biguanide agent that was removed from the U.S. market in 1978 after 300 fatal cases of lactic acidosis (22). Although metformin was approved in Europe in the early 1950s, its approval in the United States was delayed until 1994 because of concerns that lactic acidosis was a class effect.

Based on earlier data from Sweden, it was estimated at the time that the risk of lactic acidosis from phenformin was 10-fold higher than the risk from metformin; nonetheless, the approval of metformin by the U.S. Food and Drug Administration (FDA) was controversial. The FDA required a boxed warning for lactic acidosis, including the contraindications and precautions related to renal status (15,22). Additionally, the manufacturer committed to performing the large, randomized, controlled COSMIC Approach (Comparative Outcomes Study of Metformin Intervention Versus Conventional Approach) trial (20) to assess the safety of metformin compared to usual care. This study showed no differences in safety outcomes (severe adverse events, hospitalizations, and all-cause mortality) between 7,227 patients who received metformin and 1,505 patients who received usual care for 1 year, and there were no cases of lactic acidosis in either group. However, patients with any level of renal dysfunction were excluded from the study.

There have been requests in the United States to revise the prescribing label for metformin and exchange SCr cutoffs for eGFR-based dosing recommendations based on clinical practice guideline updates. Typically, the holder of the New Chemical Entity (NCE) provides data to the FDA to support any potential change in package labeling. Because metformin is a generic product, there is no incentive for the NCE holder to address a package insert update. A citizen petition to the FDA (23) was submitted in March 2013 and remains pending to date. Additionally, a recent systematic review (24) recommended changing dosage recommendations for patients with mild to moderate CKD based on the potential benefits of metformin and findings that it has little to no association with increased rates of lactic acidosis. The purpose of this retrospective study was to evaluate patients with diabetes at the Veterans Affairs North Texas Healthcare System (VANTHCS) who had metformin therapy discontinued because of an increase in SCr and to assess any consequences of terminating this useful antidiabetic medication. The selected alternative antihyperglycemic therapy, any adverse effects from the alternative therapy, subsequent glycemic control, and financial implications of the medication change were examined.

Design and Methods

A retrospective chart review of electronic medical records was performed, with a date range of 1 January 1999 through 30 September 2013, as approved by the VANTHCS institutional review board. This study was designed as a single-subject study, with each patient serving as his or her own control. Patients with type 2 diabetes were included if they were on metformin therapy for at least 3 months before its discontinuation for increased SCr (>1.5 mg/dL in males and >1.4 mg/dL in females). Patients were excluded if they were <18 years of age, if their metformin was discontinued for a reason other than declining renal function in CKD, if they were not followed for at least 6 months after metformin discontinuation, or if their chart had incomplete or undocumented data, including patients followed primarily by a non–Veterans Affairs physician. Patient outcomes were compared before and after discontinuation of metformin, with patient records followed for at least 6 months and up to 17 months after metformin discontinuation.

The primary endpoint was change in peak glycemic control at 1 year defined by A1C and was analyzed by a two-tailed, paired *t* test. Secondary endpoints were weight, monthly antihyperglycemic medication cost, hypoglycemic events, and alternative antihyperglycemic medication–related adverse drug events (ADEs). The secondary outcomes of weight and cost were analyzed using a two-tailed, paired *t* test. Hypoglycemic events were analyzed using a two-tailed McNemar's test. ADEs were collected as descriptive data only. Subgroup analyses of insulin-containing therapy versus alternative oral antihyperglycemic regimens were also performed.

Results

The initial patient cohort identified 584 patients with a discontinued

TABLE 1. Primary and Secondary Outcomes

Cohort (*n*)	Outcome (SD) on Metformin	Outcome (SD) on Alternative Regimen	*P*
Primary Outcome			
Whole cohort (179)	A1C: 7.7% (± 1.7%)	Peak A1C within 1-year follow-up: 8.3% (± 2.0%)	<0.001
Whole cohort (179)	A1C: 7.7% (± 1.7%)	A1C at 1-year follow-up: 7.6% (± 1.7%)	0.45
Patients on oral agents only (48)	A1C: 7.1% (± 1.3%)	A1C (on alternative oral regimen) at 1-year follow-up: 7.1% (± 1.4%)	0.96
Secondary Outcomes			
Whole cohort (179)	Weight: 98.1 kg (± 20.9 kg)	Weight at 1-year follow-up: 101.9 kg (± 21 kg)	<0.001
Patients on oral agents only (48)	Weight: 93.7 kg (± 13.9 kg)	Weight on alternative oral regimen at 1-year follow-up: 97.4 kg (± 15.6 kg)	<0.001
Whole cohort (179)	Monthly cost of metformin-containing therapy: $25.44 (± $26.49)	Monthly cost of alternative therapy at 1-year follow-up: $46.11 (± $44.26)	<0.001
Whole cohort (179)	Hypoglycemia: *n* = 10 (5.6%) (5 did not experience hypoglycemia on alternative regimen)	Hypoglycemia: *n* = 48 (26.8%) (5 also experienced hypoglycemia on metformin regimen)	<0.001

metformin prescription followed by a new prescription for an alternative antihyperglycemic agent. After application of inclusion and exclusion criteria, 179 patients were found to meet study criteria. The top reasons for exclusion included patient primarily followed by non-VA physician (*n* = 83), missing or lack of required data (*n* = 75), patient not followed for an appropriate time period surrounding metformin discontinuation (*n* = 46), metformin discontinuation due to suboptimal glycemic control (*n* = 34), and metformin discontinuation due to congestive heart failure (CHF) (*n* = 30). Of note, three patients were discontinued from metformin in the acute setting of lactic acidosis; in all cases, lactic acidosis was determined to have a cause other than metformin therapy, and SCr was within normal limits in all three cases.

Baseline characteristics of the study cohort were as follows: 98% male, average age 67.6 years (range 36–85 years), mean duration of metformin therapy before discontinuation 37 months (range 3–114 months), mean metformin daily dose 1,712 mg/day (range 500–3,000 mg/day), mean baseline SCr 1.73 mg/dL, and mean baseline A1C of 7.7% at the time of metformin discontinuation. All but 16 patients would have been candidates for continuation of metformin using the eGFR calculation. It was not clear why one patient received a metformin prescription that exceeded the maximum approved dosage.

The primary outcome revealed that patients discontinued from metformin reach a significantly higher peak A1C within the follow-up period (P <0.001) compared to their final A1C before discontinuation of metformin (Table 1). By the end of the 1-year follow-up period (range 6–17 months) after dose increases or the addition of new antihyperglycemic medication, glycemic control was restored, and there was no longer a significant difference between A1C values. There was also no difference in mean A1C at metformin discontinuation compared to mean A1C at the end for the subgroup of patients who were maintained on oral antihyperglycemic agents. Significant weight gain on an alternative regimen of an average 3.81 kg (P <0.001) was also noted. This remained true even for the subgroup of patients on alternative oral agents only at 1 year, who had an average weight gain of 3.7 kg (P <0.001). Cost of therapy was also significantly greater—nearly double—on alternative regimens (P <0.0001). The risk of hypoglycemic events was significantly higher on an alternative regimen than on a metformin-containing regimen (P <0.001). ADEs from alternative regimens are described in Table 2, with the most common being hypoglycemia and edema, which were experienced by 24 and 6.1% of patients, respectively.

Baseline antihyperglycemic regimens before metformin discontinuation and initial antihyperglycemic regimens chosen by providers after metformin discontinuation are detailed in Table 3. Of note, 84.4% of patients had dose increase(s) or additional antihyperglycemic agent(s) added at some point during the follow-up period. The majority of patients (73.2%) were on insulin therapy by the end of the follow-up period: 14 were on insulin therapy before metformin discontinuation, 54 were prescribed insulin as initial alternative therapy (± oral antihyperglycemics), and 63 were prescribed insulin later in the follow-up period. A minority of 48 patients (26.8%) remained on an oral antihyperglycemic regimen, with a thiazolidinedione (TZD) being the most common oral agent added (45.8%).

TABLE 2. ADEs on Alternative Therapy

ADE	*n* (%)
Hypoglycemia	43 (24)
Edema	11 (6.1)
Increase in liver function test values increase	3 (1.7)
Signs/symptoms of CHF	3 (1.7)
Diarrhea	2 (1.1)
Bloating	1 (0.6)
Leg stiffness	1 (0.6)
Decline in renal function	1 (0.6)
Skin reaction	1 (0.6)
Stomach cramps	1 (0.6)
Syncope	1 (0.6)
Vision changes	1 (0.6)

TABLE 3. Baseline Antihyperglycemic Therapy and Initial Alternative Antihyperglycemic Agent(s) Chosen by Provider at the Time of Metformin Discontinuation

	n (%)
Concomitant medication(s) with metformin	
Insulin	10 (5.6)
Sulfonylurea	116 (64.8)
TZD	4 (2.2)
Combination of multiple classes	26 (14.5)
None (metformin monotherapy)	23 (12.8)
Alternative antihyperglycemic agent(s) initiated after metformin discontinuation	
Insulin	40 (22.3)
Sulfonylurea	6 (3.4)
TZD	68 (38)
Dose increase of concomitant antihyperglycemic agent	10 (5.6)
Combination of multiple approaches above	27 (15.1)
None (continuation of concomitant antihyperglycemic therapy only)	28 (15.6)

Discussion

Based on the results of this retrospective study, discontinuing metformin results in weight gain, increase in medication costs, increase in risk for hypoglycemia, reversible worsening of glycemic control, and potential ADEs from alternative therapy. It is noted that, although discontinuing metformin initially resulted in deterioration of glycemic control, providers were able to use additional antihyperglycemic medications or increase the doses of current medications, and, at 1 year, glycemic control, was restored to the level seen before metformin discontinuation. However, this caused a transient increase in A1C, which can exacerbate the complications of diabetes and lead to patient and provider frustrations such as more frequent visits needed to titrate new medications.

In this study, 73.2% of patients were on insulin therapy 1 year after metformin discontinuation. The use of insulin may be one explanation for the significant amount of weight these patients gained after discontinuing metformin. Interestingly, patients who discontinued metformin and remained on oral antihyperglycemic agents only also gained a significant amount of weight, possibly as a result of metformin's association with weight neutrality or weight loss. Weight gain in this population increases the risk for further metabolic complications, including the promotion of greater insulin resistance and the potential for reduced compliance, especially with insulin-based therapies (25).

The increase in hypoglycemic events after metformin discontinuation also places patients at an increased risk for further complications, including mortality (26). Both insulin and some alternative oral agents carry this risk.

The increased monthly medication cost found after metformin discontinuation has the potential to affect both patients and the health system. Within the VA health care system, most veterans are charged a copayment for each medication, and at least 15% of the patients in this study required more than one medication to attain similar glycemic control after metformin discontinuation. An additional medication often would require a veteran to pay an additional copayment of up to $8 for a 30-day supply.

Finally, the patients' quality of life is likely to be affected from glycemic control deterioration requiring dose adjustments or additional medications, weight gain, ADEs such as hypoglycemia and edema from alternative therapy, and increased cost.

The risk of lactic acidosis in patients on metformin with mild to moderate renal impairment has not been demonstrated in studies (22,27). Available evidence (16,18–19) suggests that metformin can be used with benefit because of its low risk of adverse events in this population, as long as sensible dosing and mon-

itoring are implemented. The eGFR offers a more reliable estimate of renal function than SCr, and recent clinical guideline updates support the use of metformin in patients with mild to moderate stable renal dysfunction with eGFR-based dosing.

In a study by Rachmani et al. (28), patients with a relative contraindication to the use of metformin were randomized to continue metformin or have it discontinued. These patients had either chronic obstructive pulmonary disease, CHF, abnormal liver function, acute coronary syndrome, or renal dysfunction. Patients whose metformin was discontinued experienced an average weight gain of 1.8 kg during the first year and additional weight gain of 1.8 kg during the next 3 years (P <0.001). Patients who remained on metformin experienced only a minor weight gain of 0.9 kg over the 4-year period. There were no cases of lactic acidosis in either group. Patients' glycemic control significantly deteriorated over time if they discontinued metformin.

There are many similarities between the study by Rachmani et al. and ours, including the weight gain that patients experienced when taken off metformin and placed on other hypoglycemic medications. Additionally, our study demonstrated a loss of glycemic control, although this loss was not as durable as in the Rachmani study, perhaps because of a strong emphasis on controlling diabetes within the VA health care system. Although these two studies were similar, there were important differences, including additional evaluation in our study of the adverse events that may occur in patients who are required to start other hypoglycemic agents in lieu of metformin. Additionally, the cost of alternative medication to attain glycemic control was not evaluated by Rachmani et al. Finally, the focus on patients with renal dysfunction in the current study emphasizes one of the most common reasons for metformin discontinuation.

TABLE 4. VISN 17–Accepted eGFR-Based Dosing Recommendations*

eGFR (mL/min/1.73 m^2)	Action
≥60	No renal contraindication to metformin
	Monitor renal function annually
45–59	Continue metformin use
	Increase monitoring of renal function (every 3–6 months)
30–44	Prescribe metformin with caution
	Use lower dose (half-maximal dose)
	Closely monitor renal function (every 3 months)
	Do not start new patients on metformin
<30	Discontinue metformin
Additional caution is required in patients at risk for acute kidney injury or with anticipated significant fluctuations in renal status based on history, other comorbidities, or potentially interacting medications.	

**eGFR calculated using the formula eGFR = 175 × [SCr] – 1.154 × [age] – 0.203 × [0.742] if female × [1.210] if black. Adapted from Inzucchi et al. (8).*

At the VANTHCS, the Veterans Integrated Service Network (VISN) 17 Pharmacy and Therapeutics Committee approved the eGFR-based dosing recommendations detailed in Table 4. These recommendations were adapted from the American Diabetes Association/European Association for the Study of Diabetes position statement on the topic (8). VISN 17 recommends that providers document acknowledgment of diminished but stable renal function and specific plans for long-term patient monitoring. Of note, the VISN 17 approval of eGFR-based dosing does not override the FDA-approved labeling, and providers may continue to adhere to the metformin dosing restrictions based on SCr, as described in the package insert. We expect this recommendation to increase the number of patients who are candidates for metformin.

Limitations

This study was a retrospective design; thus, there is potential for missing data such as providers not documenting ADEs or hypoglycemic events. Also, retrospective studies carry the potential for confounding variables; patients may have had documented or undocumented factors such as lifestyle changes that affected one or more of the outcomes assessed.

Additionally, although electronic records in the VA health care system provide an abundance of data, there is not a suitable method for assessing patient compliance to medication therapy in a retrospective study. The scope of this study also did not include an assessment of individual patients' A1C goals or whether those goals were met on metformin-containing therapy versus alternative therapy.

Because this study was conducted at a VA facility, its results may not be applicable to a private institution. VA providers are restricted to formulary agents, and the majority of included patients were older males. Additionally, the cost data for the agents added to replace metformin were based on costs at the time of switching, and many of these medications are now available in generic form.

Our study did not collect data on patients' race. We calculated the eGFR assuming all patients were non-black, which likely underestimated subjects' renal function. Finally, although 16 patients would not have been able to continue met-

formin based on eGFR calculations at the time of their discontinuation, it is possible that adjustment of medications and increasing fluid intake could have resulted in an eGFR >30 mL/min, which may have made them candidates to continue metformin at a subsequent visit.

Conclusion

The results of this study promote the use of metformin in patients with type 2 diabetes in the setting of stable CKD to minimize worsening of glycemic control and risk of hypoglycemic events and avoid increased medication cost and potential ADEs from other antihyperglycemic therapies. To our knowledge, this is the first study that has evaluated the consequences of discontinuation of metformin in patients who could have continued if eGFR-based dosing were used. Providers should be educated about and implement current clinical practice guidelines and consider dosing metformin based on eGFR, rather than following the recommendations of the package insert, which state that providers should discontinue metformin when a patient's SCr reaches the defined threshold in the setting of chronic but stable renal dysfunction.

Duality of Interest

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

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