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ORIGINAL RESEARCH ARTICLE

Clinical Outcomes of Continuation of Metformin Titration Instructions with Electronic Prescribing

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Abstract

Background Anecdotal evidence suggests that metformin titration instructions are not being updated and refill requests are approved without modification of the titration instructions such that the titration instructions is continued for patients newly initiated on metformin.

Methods This was a retrospective cohort analysis of adult patients who received newly initiated metformin pharmacotherapy. Patients were followed from their initial metformin purchase through two subsequent metformin refill purchases. Outcomes, including the 3-year incidence rate of patients with at least one set of continued titration instructions and proportions of patients with at least one gastrointestinal adverse effect (AE) and those with an elevated glucose measurement at follow-up, were assessed during the time period between patients' second and third metformin purchases. Analyses were performed comparing the exposure (i.e., patients with continued instructions) group to the control (i.e., patients *without* continued instructions) group.

Results The exposure group had a higher mean age and chronic disease score but lower metformin starting dose than the control group (all $p < 0.05$). The 3-year incidence rate of patients with at least one continuation of titration instructions was 60.3 % (95 % CI 58.3–62.3). Gastrointestinal AEs were rare with equivalent proportions of patients in each group experiencing an event ($p > 0.05$). Control patients (48.7 % of patients with a measurement) were more likely to have had poorly controlled glucose than exposure patients (35.7 % of patients with a measurement) ($p < 0.001$).

Conclusions A high rate of continuation of titration instructions for patients newly initiated on metformin was observed; however, such continuation did not negatively affect clinical outcomes.

Key Points

Anecdotal evidence suggests that metformin titration instructions are not being updated and refill requests are approved without modification of the titration instructions such that the titration instruction is continued for patients newly initiated on metformin.

We found a high rate of patients with at least one titration instruction continuation (3-year incident rate = 60.3 % [95 % CI 58.3–62.3]); however, such continuation did not negatively affect clinical outcomes.

Our analysis highlights a potential risk of electronic prescribing and likely patient non-adherence to directions printed on prescription labels.

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1 Background

The prevalence of type 2 diabetes mellitus (DM) continues to increase [1]. Metformin (Glucophage®), an oral biguanide, is first-line pharmacotherapy for the management of type 2 DM and is one of the most widely prescribed medications overall [2]. While metformin is effective, its adverse effects (AEs) include gastrointestinal disorders, which can lead to poor adherence and, subsequently, reduced glycemic control [3]. Upward dose titration is recommended when metformin therapy is initiated to decrease the potential for AEs and identify the minimum dose for adequate glycemic control [4]. For example, a patient's initial metformin prescription can have instructions that direct a patient to "Take one tablet by mouth twice daily for 1 week, increase to two tablets in the morning and one tablet in the evening, and then increase to two tablets twice daily". Patients often reach their target maintenance dose after 1 month [2].

After completing the dose titration phase, patients should receive a new prescription with updated instructions that reflect the maintenance dosing directions. However, with the increased use of electronic prescribing (e-prescribing) in the USA, there is a potential for unforeseen errors when providing new prescriptions [5]. Recent studies have drawn attention to some of the concerns associated with e-prescribing. These studies have focused on discrepancies in patient instructions that could potentially place individuals at risk for medication errors [6, 7].

Kaiser Permanente Colorado (KPCO) uses an electronic medical record (EMR) system for its information management and care delivery infrastructure. The EMR integrates inpatient, outpatient, and clinic medical records with appointments, registration, pharmacy, and billing information. Anecdotal evidence at KPCO suggested that metformin titration instructions were not being updated and refill requests may have been approved without modification of the titration instructions. So, instead of updated instructions directing a patient to take two tablets twice daily, titration instructions were perpetuated during e-prescribing with titration directions. Re-initiating titration may leave patients susceptible to decreased glycemic control but, conversely, less likely to report an AE. Little information exists on continued metformin titration instructions. The purpose of this analysis was to assess the incidence rate and effect of continued metformin titration instructions in a population of patients being initiated on metformin therapy.

2 Methods

2.1 Analytic Design and Setting

This was a retrospective cohort analysis of adult patients who received newly initiated metformin pharmacotherapy between 1 January 2011 and 31 December 2013. Patients were followed from their initial metformin purchase through two subsequent metformin refill purchases. Outcomes were assessed during the time period between patients' second and third metformin purchases, as this was hypothesized as the time period during which the effects of inappropriate titration were most likely to manifest [8].

This analysis was conducted at KPCO, an integrated healthcare delivery system with over 580,000 members and 27 ambulatory care clinics in Colorado at the time of the analysis. Kaiser Permanente Colorado utilizes an EMR that provides e-prescribing capabilities and captures coded and free-text medical, pharmacy, laboratory, emergency department (ED), hospitalization, membership, and death information internally from within the health system, as well as from other contracted and affiliated facilities. Kaiser Permanente Colorado owns and operates its pharmacies where its members can purchase subsidized prescription medications. Information on such purchases is captured in the electronic KPCO administrative pharmacy database.

The proposal for this analysis was reviewed by the KPCO Institutional Review Board and determined to not be Human Subjects Research, as defined by federal regulations and institutional policies, since it was conducted as a quality assurance project.

2.2 Patient Population

Patients included in this analysis: (1) had purchased a new 500-mg metformin prescription at a KPCO pharmacy between 1 January 2011 and 13 December 2013; (2) were ≥18 years of age on the purchase date (*index date*); (3) had no metformin purchase in the 180 days prior to index date (*pre-period*); (4) had at least two additional metformin purchases in the 180 days after the initial (*index*) purchase; (5) had continuous KPCO health plan membership with pharmacy benefit during the pre-period and through the third metformin purchase; and (6) had a type 2 DM or prediabetes diagnosis (ICD-9 codes available upon request) during the pre-period. Exposure patients (*titration continued* group) had titration instructions on the index purchase with the titration instructions repeated (i.e., continued) on at least the second metformin purchase. Control patients (*titration limited* group) had titration instructions on their

index purchase but the titration instructions were not continued on the second metformin purchase.

2.3 Outcomes

The primary outcome was the 3-year incidence rate (with 95 % confidence interval [CI]) of metformin prescription purchase with titration instructions continued on the subsequent metformin purchase. Secondary outcomes included assessments of the proportion of patients with at least one gastrointestinal AE, hyperglycemic glucose laboratory measurement, all-cause hospitalization, ED visit, and insulin/sulfonylurea purchase during follow-up.

2.4 Data Collection

The analysis cohort and patient characteristics and outcomes were identified through queries of KPCO's electronic administrative databases, including the EMR. Outcomes were assessed during the time period between patients' second and third metformin purchases. Outcome AEs included dyspepsia (ICD-9 code 536.8), diarrhea (ICD-9 code 787.91), nausea (ICD-9 code 787.02), vomiting (ICD-9 code 787.03), and nausea and vomiting (ICD-9 code 787.01) recorded during a telephone or medical office visit encounter. A hyperglycemic glucose laboratory measurement was defined as an A1c $\geq$7.0 %, a fasting blood glucose (FBG) $\geq$126 mg/dL, or a random glucose (RG) $\geq$200 mg/dL recorded in a medical office laboratory.

Information on co-morbidities diagnosed during telephone/medical office encounters during the pre-period included dementia, heart failure, hepatic disorders, hypertension, polycystic ovarian disease, and renal insufficiency (ICD-9 codes available upon request). Additionally, information on the index metformin provider, metformin dose, count of unique prescription purchases and elevated glucose measurements during the pre-period (i.e., the 180 days prior to the index purchase) was collected. Furthermore, a chronic disease score (CDS), a validated measure of a patient's burden of chronic illness, was calculated using ambulatory prescription medication purchases during the pre-period [9]. The CDS ranges from 0 to 36 with increasing values indicating a higher burden of chronic illness.

2.5 Data Analysis

Age was calculated as of the index date. Incident rate of titration instructions continuation was calculated by dividing the count of patients who purchased a new metformin prescription during the analysis period with continued titration instructions by the count of all patients with a new metformin prescription purchased during the analysis period. The glucose measurements used were those recorded during the pre-period and most proximal to, but before, the index date and after the second purchase, but before the third purchase date. Patients with no measurement available were excluded from this analysis.

All analyses were performed comparing the exposure to the control group. Patient characteristics and outcomes were reported as means ($\pm$standard deviations [SDs]) for interval-level variables and percentages for categorical variables. Wilcoxon rank-sum tests and t tests, as applicable, and chi-square tests of association or Fisher's exact tests, as applicable, were used to assess differences between groups for interval-level and categorical variables, respectively. Multivariate logistic regression analysis was performed for each outcome (except gastrointestinal AEs as the incidence was too low to perform adjustments). The titration limited group was the referent category and adjustment was made for all baseline patient characteristics with a p value <0.2 in the bivariate analyses (i.e., age, sex, pre-period elevated glucose laboratory measurement, chronic disease score, primary-care index metformin prescriber, index metformin dose, hepatic disorder, and hypertension).

3 Results

A total of 2416 patients were included with 1457 (60.3 %) and 959 (39.7 %) having and not having had titration instructions continued, respectively. The titration continuation group had a higher mean age and CDS but lower mean metformin starting dose than the titration limited group (all $p < 0.05$) (Table 1). In addition, the titration continuation group was less likely to have been prescribed metformin by a primary-care provider and to have had an elevated glucose measurement in the pre-period but more likely to have been diagnosed with hypertension (all $p < 0.05$).

The 3-year incidence rate of patients with at least one continuation of titration instructions was 60.3 % (95 % CI 58.3–62.3). Gastrointestinal disorder AEs, with equivalent proportions of patients in each group experiencing an event ($p = 0.766$) (Table 2). 981 (40.6 %) patients had a glucose measurement recorded between their second and third metformin purchases. Of these, titration-limited patients (48.7 % of patients with a measurement) were more likely to have had a hyperglycemic glucose laboratory measurement than titration-continuation patients (35.7 % of patients with a measurement) ($p < 0.001$). There were no differences between groups in the proportions of patients who experienced an all-cause hospitalization or ED visit (both $p > 0.05$). Titration-limited patients were more likely to have had an insulin/sulfonylurea purchase (19.4 % vs. 13.0 %, $p < 0.001$). In the multivariate

Table 1 Pre-period patient characteristics overall and by titration status

Characteristic	Overall cohort ($N = 2416$)	Titration continued ($n = 1457$)	Titration limited ($n = 959$)	p value
Mean age[a] (SD)	57.3 (12.7)	58.2 (12.8)	56.0 (12.4)	<0.001
Female (n, %)	1259, 52.1 %	779, 53.5 %	480, 50.1 %	0.100
Primary-care index metformin prescriber (n, %)	2129, 88.1 %	1255, 86.1 %	874, 91.1 %	<0.001
Mean chronic disease score (SD)	3.2 (3.0)	3.3 (2.9)	3.1 (3.1)	0.017
Mean count of unique Rx Medications purchased[b] (SD)	5.8 (4.0)	5.8 (3.9)	5.8 (4.2)	0.474
Mean index metformin dose (mg, SD)	1184 (743)	1082 (664)	1339 (850)	<0.001
Pre-period elevated glucose laboratory measurement[b,c] (n, %)	1718, 73.7 %[d]	947, 67.8 %[e]	771, 82.5 %[f]	<0.001
Ambulatory co-morbidity diagnosis[b] (n, %)				
Dementia	16, 0.7 %	12, 0.8 %	4, 0.4 %	0.308
Heart failure	24, 1.0 %	14, 1.0 %	10, 1.0 %	0.843
Hepatic disorder	70, 2.9 %	49, 3.4 %	21, 2.2 %	0.093
Hypertension	823, 34.1 %	522, 35.8 %	301, 31.4 %	0.024
Polycystic ovarian disease	0, 0.0 %	0, 0.0 %	0, 0.0 %	1.000
Renal insufficiency	192, 8.0 %	121, 8.3 %	71, 7.4 %	0.423

[a] At the time of index metformin purchase

[b] During the 180 days prior to index metformin purchase

[c] Recorded value most proximal to, but before, the index metformin purchase, A1c ≥6.5 %, fasting glucose PCLAB_MQ ≥126 mg/dL, or random glucose ≥200 mg/dL

[d] Percent is of the 2332 (96.5 %) patients who had at least one measurement

[e] Percent is of the 1397 (95.9 %) patients who had at least one measurement

[f] Percent is of the 935 (97.5 %) patients who had at least one measurement

Table 2 Unadjusted outcomes overall and by titration status

Outcome	Overall cohort ($N = 2416$)	Titration continued ($n = 1457$)	Titration limited ($n = 959$)	p value
Gastrointestinal adverse event (n, %)	2, 0.1 %	1, 0.1 %	1, 0.1 %	0.766
At least one hyperglycemic glucose laboratory measurement[a] (n, %)	405, 41.4 %[b]	198, 35.7 %[c]	207, 48.7 %[d]	<0.001
All-cause hospitalization (n, %)	37, 1.5 %	24, 1.7 %	13, 1.4 %	0.568
All-cause emergency department visit (n, %)	97, 4.0 %	58, 4.0 %	39, 4.1 %	0.916
Insulin/sulfonylurea purchase (n, %)	375, 15.5 %	189, 13.0 %	186, 19.4 %	<0.001

Recorded between the second and third metformin purchase dates

[a] Recorded most proximal to, but before, the third metformin purchase date, A1c ≥7.0 %, fasting glucose PCLAB_MQ ≥126 mg/dL, or random glucose ≥200 mg/dL

[b] Percent is of the 979 (40.7 %) patients who had at least one measurement

[c] Percent is of the 554 (38.0 %) patients who had at least one measurement

[d] Percent is of the 425 (44.3 %) patients who had at least one measurement

adjusted analysis, titration continuation patients had a 26 % reduction in the likelihood of at least one hyperglycemic glucose laboratory measurement (odds ratio [OR] 0.74, 95 % CI 0.56–0.98) and 24 % reduction in the likelihood of an insulin/sulfonylurea purchase (OR 0.76, 95 % CI 0.60–0.97) between their second and third metformin purchases (Table 3).

4 Discussion

This retrospective cohort analysis is the first, to our knowledge, to assess the effect of continuation of titration instructions during e-prescribing in patients newly initiated on metformin. We found that the majority (>60 %) of patients experienced continuation of titration instructions,

Table 3 Adjusted outcomes

Outcome	Odds ratio	95 % confidence interval	*p* value
At least one hyperglycemic glucose laboratory measurement[a]			0.039
Titration continued	0.74	0.56–0.98	
Titration limited	Referent	–	
All-cause hospitalization			0.563
Titration continued	1.24	0.60–2.53	
Titration limited	Referent	–	
All-cause emergency department visit			0.977
Titration continued	1.01	0.65–1.55	
Titration limited	Referent	–	
Insulin/sulfonylurea purchase			0.026
Titration continued	0.76	0.60–0.97	
Titration limited	Referent	–	

Recorded between the second and third metformin purchase dates

Adjusted for age, sex, pre-period elevated glucose laboratory measurement, chronic disease score, primary-care index metformin prescriber, index metformin dose, hepatic disorder, and hypertension

[a] Recorded most proximal to, but before, the third metformin purchase date, A1c ≥7.0 %, fasting glucose PCLAB_MQ ≥126 mg/dL, or random glucose ≥200 mg/dL. Analysis limited to patients with both a pre-period and outcome glucose/A1c measurement ($n = 945$)

suggesting that, while e-prescribing may allow for quicker and more convenient prescribing [10], such benefits can come with unintended consequences (e.g., refill request approvals by the prescriber without proper assessment of prescription details) [6, 7]. Nevertheless, we found that continuation of titration instructions did not negatively affect clinical outcomes, as patients with continuation of titration instructions were less likely to have had poorly controlled glucose and no more likely to have had a gastrointestinal AE compared to patients without continuation of titration instructions. The exposure group would be expected to have worse glycemic control, but fewer AEs, if they had re-initiated their titrations as directed on their prescription's instructions.

The reason for the lower proportion of patients with poorly controlled glucose in the exposure group during follow-up is difficult to pinpoint. The control group was initiated on a higher metformin dose, presumably to achieve more rapid glycemic control, but had worse glycemic control during the pre-period. In addition, the control group had a numerically lower rate of renal insufficiency such that they may have had better clearance of metformin. Since metformin is primarily cleared renally, any insufficiency could lead to accumulation of metformin and, perhaps, an increased risk of metformin-related AEs that hindered glycemic control [11, 12]. Furthermore, the control group may have had more severe DM/pre-diabetes as they were more likely to have received insulin or a sulfonylurea during follow-up. This is countered by the fact that the control patients were less likely to have been prescribed their index metformin by a specialist (e.g., an endocrinologist). This finding suggests that specialists were less likely to correct titration instructions for subsequent prescription fills.

While clinicians report perceived efficiencies in processing refills with e-prescribing [9], we identified no other studies of continuation of titration instructions with which to compare our findings. However, other investigators have attempted to rectify discrepancies in components of electronic prescriptions. Turchin and colleagues [13] modified the user interface in an EMR prescription ordering module to provide alerts to discrepancies. Theoretically, a functionality could be built into an EMR to alert prescribers to modify titration instructions once maintenance doses of certain medications have been achieved.

Our analysis had several limitations. We were unable to assess if patients actually re-initiated metformin titration. We only assessed if the titration instructions were continued. We were unable to assess if patients in the titration continued group were told by their prescribers to continue taking the target maintenance dose, regardless of the directions printed on their prescription labels. A dispensing pharmacist may have noticed the continuation of the titration instructions. However, the pharmacist would likely only have counseled the patient to see if she/he was at her/his maintenance dose and not otherwise altered the prescription. We were unable to measure the severity of our patients DM/pre-diabetes at baseline. Nevertheless, we did assess glycemic control at baseline as a proxy. Some patients may have tried and failed metformin prior to our 180-day pre-period. But in order to achieve the largest sample size possible, we included such patients as they were likely to experience the same effects as truly naïve metformin users. A limited number of prescriptions could have been initiated outside the KPCO e-prescribing system (e.g., during an inpatient stay/emergency room visit, transferred from a non-KPCO prescriber), but all prescriptions would have been renewed with e-prescribing. We did not assess metformin adherence such that those patients with an elevated glucose during follow-up may have been less adherent, regardless of the directions given. However, patients in our analysis had to have had at least two additional metformin purchases in the 180 days after index purchase indicating, at least, a modest level of adherence. This analysis was conducted in one health plan where titration instructions are printed on the prescription bottle and its results may not be generalizable to all health plans (e.g., where titration instructions are provided

verbally to a patient). However, we had a relatively large cohort of patients to assess the impact of continuation of metformin titration instructions and other health plans with e-prescribing may find similar results.

In conclusion, we found a high rate of continuation of titration instructions during e-prescribing for patients newly initiated on metformin. However, such continuation did not negatively affect clinical outcomes. Our analysis ultimately highlights a potential risk of e-prescribing and likely patient non-adherence to directions printed on prescription labels. While an alert in an EMR to modify instructions may attenuate the continuation of titration instructions, patient non-adherence to prescribers' directions may portend serious consequences in the long term. Future research should assess patient-reported adherence to the directions for use on prescription labels and evaluate ways to systematically alert prescribers to inappropriate refilling practices.

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Ethical standards This analysis was reviewed by the KPCO Institutional Review Board and determined to not be Human Subjects Research, as defined by US federal regulations and institutional policies, since it was conducted as a quality assurance project. Nevertheless, it was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Due to the retrospective nature of the analysis, informed consent of patients was not required or performed. However, details that might disclose the identity of any patient in the analysis have been omitted.

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