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Secondary metformin monotherapy failure in individuals with type 2 diabetes mellitus

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ABSTRACT

Introduction To assess secondary metformin monotherapy (MM) failure in a real-world type 2 diabetes mellitus (T2DM) cohort.

Research design and methods Using the IQVIA Electronic Medical Record (formerly GE Centricity) database, adults with T2DM who initiated MM between January 1, 2012 and June 30, 2016 and achieved glycemic control (hemoglobin A1c (HbA1c) <7% (53 mmol/mol); index date) were analyzed. Secondary MM failure was defined in two ways: loss of glycemic control (HbA1c ≥7% (53 mmol/mol)) and treatment change (addition or switch of antihyperglycemic agent). Multivariable logistic regression models assessed the association between secondary MM failure and sociodemographic and clinical factors.

Results The analysis included 4775 patients initiating MM. 32.9% and 19.2% experienced secondary MM failure at 24 months measured as loss of glycemic control and treatment change, respectively. Multivariable logistic regression found that women (OR=1.3, 95% CI 1.1 to 1.5) compared with men, lower Charlson Comorbidity Index (CCI) (OR=0.89, 95% CI 0.86 to 0.93), and lower baseline HbA1c (OR=0.93, 95% CI 0.88 to 0.98) were associated with increased likelihood of loss of glycemic control. Lower CCI was associated with increased likelihood of treatment change (OR=0.78, 95% CI 0.75 to 0.82).

Conclusions The observed frequency of secondary MM failure underscores the importance of the American Diabetes Association's recommendation for glycemic monitoring of at least every 6 months so that timely therapeutic adjustments can be made.

Significance of this study

What is already known about this subject?

- In the double-blind, randomized clinical trial ADOPT (A Diabetes Outcome Progression), in 4360 patients with type 2 diabetes mellitus, the cumulative prevalence of metformin monotherapy (MM) failure after 5 years of follow-up was 21%.
- Although a few studies have characterized secondary MM failure in the real world, they used data from a single healthcare system and thus their generalizability to the broader US population is limited.

What are the new findings?

- In a broad sample of US patients, nearly one-third (32.9%) of patients experienced secondary MM failure, defined as loss of glycemic control (hemoglobin A1c (HbA1c) ≥7% (53 mmol/mol)) and nearly one-fifth (19.2%) of patients experienced secondary MM failure, defined as treatment change, after 24 months. This indicates that a substantial proportion of individuals with type 2 diabetes who achieve glycemic targets on MM go on to lose glycemic control or change therapy in a relatively short period of time.
- Factors associated with increased risk of progression to HbA1c ≥7% (53 mmol/mol) were being a woman, having lower baseline HbA1c, and having lower Charlson Comorbidity Index (CCI). Only lower CCI was found to be associated with increased risk of treatment change.

How might these results change the focus of research or clinical practice?

- The observed frequency of secondary MM failure underscores the importance of the American Diabetes Association's recommendation for glycemic monitoring of at least every 6 months so that timely therapeutic adjustments can be made.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic and progressive disease characterized by elevated blood glucose levels. Estimates from national studies and surveillance registries in the USA estimate the prevalence of diabetes among adults age 18 and older is 13%, of which 21.4% are undiagnosed.[1] For most patients, the American Diabetes Association (ADA) standards of care state that 'An A1C goal for *many* non-pregnant adults of <7% (53 mmol/mol) is appropriate', although less stringent targets may be appropriate for some patients.[2] Half of patients with T2DM have suboptimal glycemic control.[3 4] Optimal glycemic control reduces the risk of hypoglycemia, cardiovascular disease, kidney disease, liver disease, obesity, and other microvascular complications.

Unless contraindicated, the ADA recommends metformin monotherapy (MM) as the first-line pharmacologic agent for T2DM

treatment.[5] Clinicians may consider second-line therapies on the basis of efficacy, hypoglycemia risk, weight change, side effects, and cost.[6] If MM treatment does not result in glycemic control at a maximal tolerated dose over 3–6 months, individuals may receive either treatment intensification on top of metformin or switch to another antihyperglycemic agent (AHA) if metformin is not tolerated.[5]

Secondary MM failure refers to loss of glycemic control after initial achievement of control on MM. Data assessing secondary MM failure are limited. In the double-blind, randomized clinical trial ADOPT (A Diabetes Outcome Progression), in 4360 patients with T2DM, the cumulative prevalence of MM failure after 5 years of follow-up was 21%. This study defined MM failure as fasting plasma glucose level >180 mg/dL.[7] Brown *et al*[8] assessed secondary MM failure (defined as hemoglobin A1c (HbA1c) ≥7.5% (58 mmol/mol)) using real-world data from patients in Kaiser Permanente Northwest (KPNW) Health Maintenance Organization (HMO) group; they found a mean secondary MM failure prevalence of 17% annually, and among those who failed the mean time to failure was 16.9 months. Nichols *et al*[9] also examined secondary MM failure in the KPNW population and found that 20.5% of patients who achieved HbA1c <8% (64 mmol/mol) within a year of MM reached an HbA1c ≥8% (64 mmol/mol) within a mean of 21.6 months. These findings suggest that MM durability in the real world may be lower than that previously reported in the ADOPT trial. However, it is difficult to generalize the findings from a randomized clinical trial (ADOPT) and a single healthcare system (KPNW) to a broader US patient population.

This study aimed to quantify and describe secondary MM failure within 2 years of initiating MM among a cohort of US patients with T2DM from a large, real-world electronic medical record (EMR) database.

RESEARCH DESIGN AND METHODS

Data source and study design

We conducted a retrospective cohort study among patients with T2DM in the IQVIA Electronic Medical Record database (formerly GE Centricity database); this database comprised data for more than 30 million US patients collected from over 30 000 healthcare providers across 49 states. The database includes deidentified information on patient demographics (age, gender, race, type of insurance coverage), comorbidities, prescription medications, laboratory assessments and orders, and diagnostic tests results. Exploratory analyses of the IQVIA EMR database demonstrated its ability to detect ambulatory medical conditions that aligned with the annual National Ambulatory Medical Care survey, a national survey of non-federal, office-based physicians administered by the US Centers for Disease Control and Prevention.[10] Furthermore, the IQVIA EMR database allows for indepth analysis of patterns of related comorbidities associated with T2DM across different demographic groups.[11]

This study included adults with T2DM (International Classification of Diseases (ICD)-9 codes: 250.x0, 250.x2; ICD-10 codes: E11) who initiated MM during the index assessment period (January 1, 2012–June 30, 2016) and achieved glycemic control (defined as HbA1c <7% (53 mmol/mol)) (figure 1). The index date was defined as the date of the first HbA1c result <7% (53 mmol/mol) within 1–6 months following the initiation date of MM. Patients were also required to be at least 18 years of age by the index date and have continuous data availability through baseline and follow-up periods. Patients were

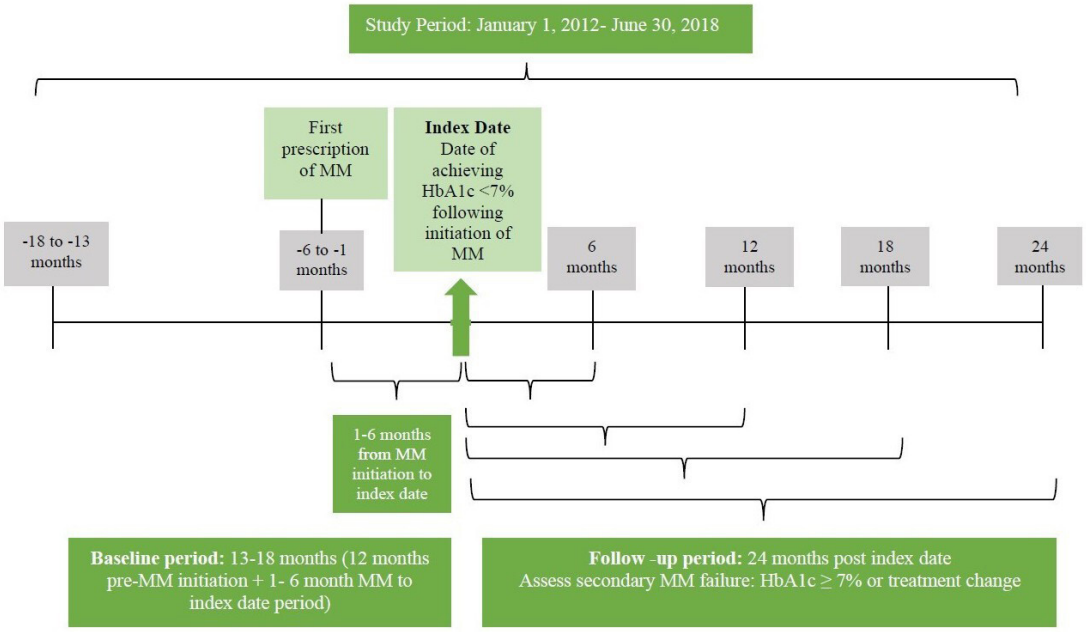

Figure 1 Study design. HbA1c, hemoglobin A1c; MM, metformin monotherapy.

also required to have continuous MM prescriptions without a treatment gap of more than 90 days between the MM initiation date and the index date. Patients were also required to have an HbA1c ≥6.5% (48 mmol/mol) in their history prior to MM initiation to further confirm T2DM diagnosis. Patients were excluded if they had a prescription for insulin or other AHAs during the 12 months prior to MM initiation or any time between the MM initiation date and the index date. Other exclusionary criteria consisted of diagnosis for type 1 diabetes, polycystic ovary syndrome, gestational diabetes, or other forms of secondary diabetes during the study period (online supplemental appendix 2 displays the cohort table and the diagnostic codes used).

Outcomes

The study evaluated secondary MM failure using two separate definitions: loss of glycemic control and/or treatment change. *Loss of glycemic control* was defined as an HbA1c ≥7% (53 mmol/mol) after the index date within the observation period, as depicted in figure 1. Sensitivity analyses assessed loss of control as HbA1c ≥7.5% (58 mmol/mol) and HbA1c ≥8% (64 mmol/mol) after the index date. Given the nature of this definition, only patients with an HbA1c available could be assessed for secondary MM failure by this definition. *Treatment change* was defined as the start of any other AHA prescription after the index date to either replace metformin or added to metformin for treatment intensification. All patients meeting the study inclusion/exclusion criteria, including those without available HbA1c measures, could be assessed for secondary MM failure by this definition. Secondary MM failure was estimated as part of an intent-to-treat analysis using the proportion of patients who experienced secondary MM failure by each definition separately at intervals of 0–6, 0–12, 0–18, and 0–24 months after the index date. For loss of glycemic control, proportions were based on all patients with HbA1c measures available in the relevant time periods, while for treatment change proportions were based on all patients in the study cohort (regardless of whether they had an HbA1c available). Sensitivity analyses were performed among (1) patients with index HbA1c <7.5% (58 mmol/mol) and (2) patients with two or more metformin prescriptions.

Statistical analysis

Descriptive statistics were reported for demographic and clinical characteristics as frequencies and percentages for categorical variables and as means and SD for continuous variables. The analysis generated separate multivariable logistic regression models for each definition of secondary MM failure to identify baseline characteristics associated with secondary MM failure at 24 months. Time until secondary MM failure was estimated with Kaplan-Meier (KM) curves for each definition of the outcome.

RESULTS

The database included 4775 patients with T2DM diagnoses who met all inclusion criteria. Table 1 summarizes the baseline and demographic characteristics of the cohort. More than half of the patients were younger than 65 years of age, with a mean age of 61.6 years (SD 11.9), and 53.4% were women. The majority of patients were white (75.2%), followed by black (10.7%), unknown race/ethnicity (11.1%), and Asian (2.3%). The largest proportion of patients resided in the South (37.4%), while 28.6% resided in the Northeast. The mean baseline HbA1c (in the 12-month period prior to metformin initiation) was 7.3% (56 mmol/mol) (SD 1.1), while the median baseline HbA1c was 6.9% (IQR 6.7–7.4). The mean/median index HbA1c value (during the 1–6 months following metformin initiation) was 6.3% (45 mmol/mol) (SD 0.4)/6.4 (IQR 6.1–6.6). Smoking was documented in 9.8% of the cohort. Microvascular complications included 7.6% and 3.8% of patients with nephropathy or neuropathy, respectively. Only 2.0%, 2.0%, 0.4%, and 0.2% of patients had a history of peripheral arterial/vascular disease, stroke, myocardial infarction, or congestive heart failure, respectively. The mean Charlson Comorbidity Index (CCI) score was 1.1 (SD 1.7).

Loss of glycemic control was assessed among study participants who had HbA1c measures available in the follow-up period (n=4591). Treatment change was computed using the entire study population (N=4775). Figure 2 summarizes the cumulative proportion of patients experiencing secondary MM failure as loss of glycemic control or treatment change over time. Among MM patients with an HbA1c measure available and an index HbA1c <7% (53 mmol/mol), 10.8%, 18.3%, 25.8%, and 32.9% experienced loss of glycemic control (HbA1c ≥7% (53 mmol/mol)) within 6, 12, 18, and 24 months, respectively. Sensitivity analyses that evaluated loss of glycemic control as progression to HbA1c ≥7.5% (58 mmol/mol) and ≥8% (64 mmol/mol) showed trends similar to the analysis for progression to HbA1c ≥7% (53 mmol/mol). More patients experienced secondary MM failure over time, yet the overall proportion was substantially smaller; 14.6% and 6.1% experienced secondary MM failure within 24 months when defined as a progression to HbA1c ≥7.5% (58 mmol/mol) or ≥8% (64 mmol/mol), respectively. Additional sensitivity analyses measuring secondary MM failure among patients with an index HbA1c <7.5% (58 mmol/mol) and in patients with two or more metformin prescriptions can be found in online supplemental appendix 1, and findings were in line with the results reported here.

Among patients classified as having secondary MM failure defined as treatment change, 7.0%, 11.2%, 15.3%, and 19.2% changed therapy at 6, 12, 18, and 24 months of follow-up, respectively.

Table 1 Demographic and clinical characteristics of patients experiencing secondary MM failure

Total	N=4775 (100%)
Age (years)	
<65	2603 (54.5)
65–75	1330 (27.8)
75+	842 (17.6)
Median (Q1, Q3)	63 (53, 71)
Mean (SD)	61.6 (11.9)
Gender	
Female	2549 (53.4)
Male	2226 (46.6)
Race	
White	3589 (75.2)
Black	510 (10.7)
Asian	108 (2.2)
Indian (American)	34 (0.7)
Native Hawaiian or Other Pacific Islander	3 (0.0)
Unknown	531 (11.1)
Region	
South	1785 (37.4)
Northeast	1367 (28.6)
West	911 (19.1)
Midwest	711 (14.9)
Unknown/missing	1 (0.0)
BMI (kg/m^2)	
Mean (SD)	33.8 (6.9)
Median (Q1, Q3)	33.0 (28.8, 37.7)
Baseline HbA1c	
Mean (SD)	7.3* (1.1)
Median (Q1, Q3)	6.9† (6.7, 7.4)
Index HbA1c	
Mean (SD)	6.3‡ (0.4)
Median (Q1, Q3)	6.4§ (6.1, 6.6)
Behavioral attributes	
Smoking	470 (9.8)
Comorbidities	
Microvascular complications	
Nephropathy	365 (7.6)
Neuropathy	179 (3.7)
Retinopathy	21 (0.4)
Macrovascular complications	
Arrhythmia	137 (2.9)
Stroke/transient ischemic attack	98 (2.0)
Peripheral arterial disease and peripheral vascular disease	94 (2.0)
Myocardial infarction	33 (0.7)
Angina	19 (0.4)
Congestive heart failure	12 (0.2)
Revascularization	6 (0.1)
Charlson Comorbidity Index score	
Mean (SD)	1.1 (1.7)
Median (Q1, Q3)	0 (0, 2)

*HbA1c 7.3% (56 mmol/mol)
†HbA1c 6.9% (52 mmol/mol).
‡HbA1c 6.3% (45 mmol/mol).
§HbA1c 6.4% (46 mmol/mol).
BMI, body mass index; HbA1c, hemoglobin A1c; MM, metformin monotherapy.

Figure 3 presents the ORs for factors associated with secondary MM failure from multivariable regression models. The analysis produced separate models for each definition: loss of glycemic control (HbA1c ≥7% (53 mmol/mol)) and treatment change (figure 3). In the regression model for loss of glycemic control (figure 3), women were more likely to progress to HbA1c ≥7% (53 mmol/mol) than men (OR 1.3, 95% CI 1.1 to 1.5), whereas patients with higher baseline HbA1c (OR=0.93, 95% CI 0.88 to 0.98) and more comorbidities (ie, CCI) (OR=0.89, 95% CI 0.86 to 0.93) were significantly less likely to experience MM failure. For the model that used treatment change as the outcome (figure 3), patients with higher CCI were significantly less likely to change treatment (OR=0.78, 95% CI 0.75 to 0.82). No other characteristics were associated with treatment change.

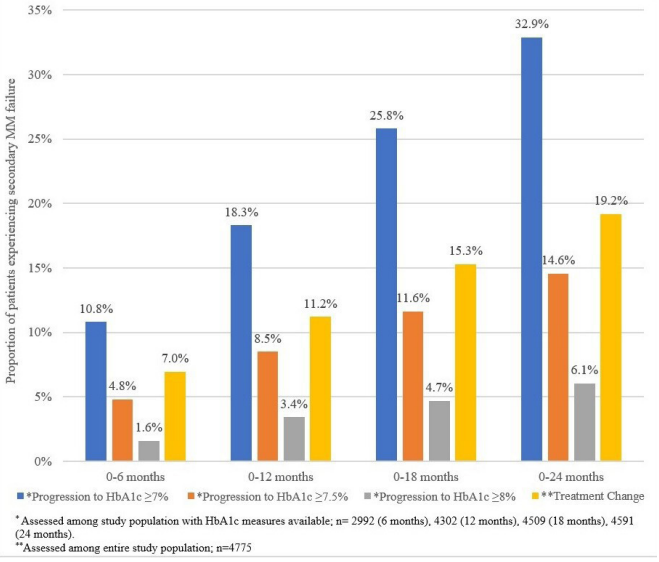

Figure 2 Proportion of patients with type 2 diabetes mellitus experiencing secondary MM failure, stratified by HbA1c thresholds and treatment change. HbA1c, hemoglobin A1c; MM, metformin monotherapy.

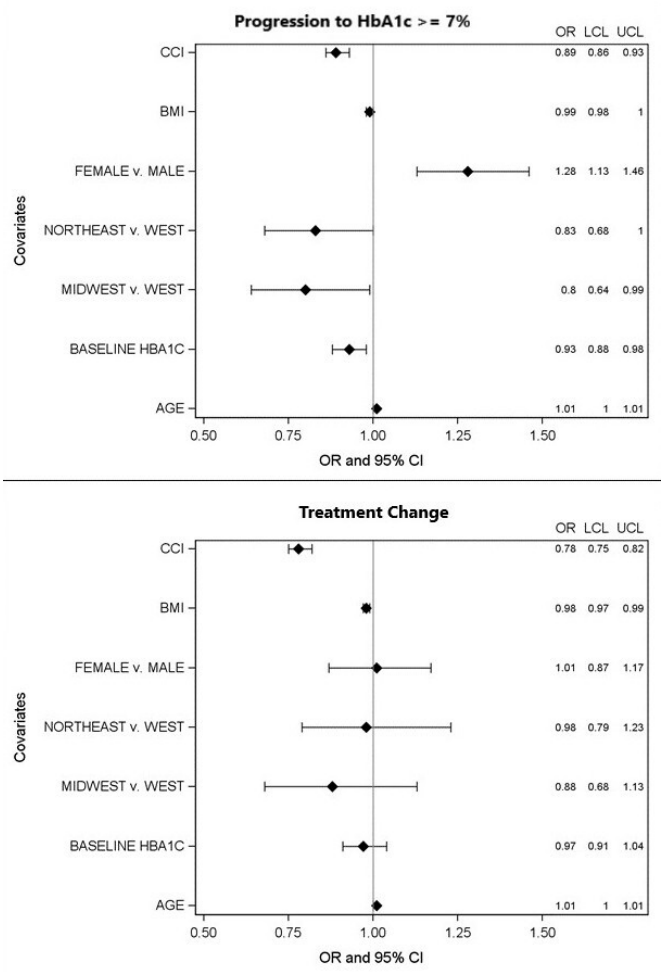

Figure 3 Odds Ratio (OR) for factors associated with secondary metformin monotherapy failure, defined as loss of glycemic control (progression to HbA1c ≥7%) or treatment change. Variables in the multivariable logistic regression models included age, baseline HbA1c, region (Midwest, Northeast, South, West), gender (female, male), BMI, CCI score, retinopathy, nephropathy, neuropathy, acute myocardial infarction, angina, arrhythmia, revascularization, heart failure, peripheral arterial/vascular disease, stroke/transient ischemic attack, alcohol, and smoking status. BMI, body mass index; CCI, Charlson Comorbidity Index; HbA1c, hemoglobin A1c; LCL, lower confidence limit; UCL, upper confidence limit.

Figure 4 depicts the KM curve for patients who progress to loss of glycemic control and treatment change. Around 2.7% of the patients experienced loss of glycemic control (HbA1c ≥7% (53 mmol/mol)) within 100 days of initiating MM. At 12 months, 17.09% of the patients included in the final cohort experienced HbA1c levels ≥7% (53 mmol/mol). At 24 months (730 days), 32.8% of the patients experienced loss of glycemic control (HbA1c ≥7% (53 mmol/mol)). However, the percentage of patients undergoing treatment change at the end of follow-up period was comparatively lower than the percentage of patients experiencing loss of glycemic control.

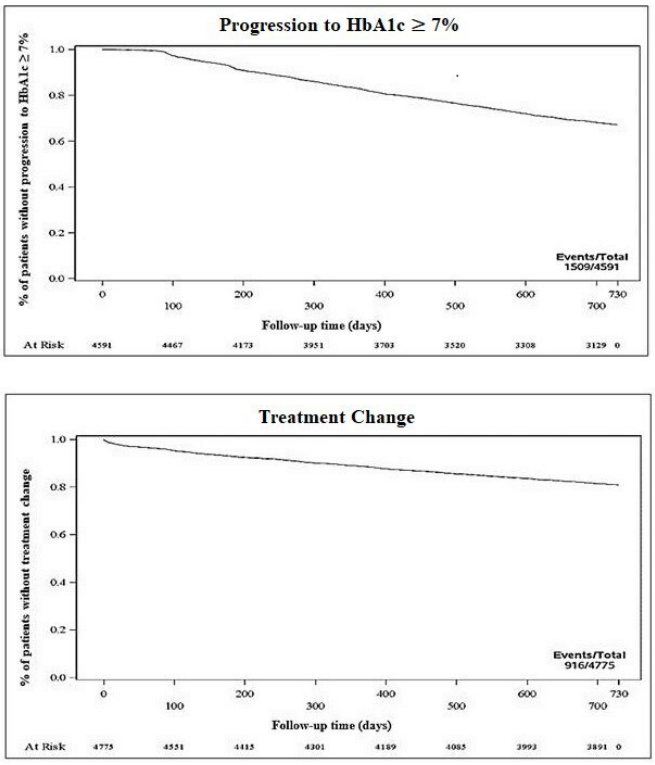

Figure 4 Kaplan-Meier curve for secondary metformin monotherapy failure by loss of glycemic control (progression to HbA1c ≥7%) or treatment change. HbA1c, hemoglobin A1c.

Approximately 4% of the patients changed their treatment within 100 days of initiating MM and 20% of the patients underwent treatment change within 24 months of initiating MM.

CONCLUSIONS

This retrospective analysis of a cohort from a real-world EMR database assessed secondary MM failure, defined as loss of glycemic control (HbA1c ≥7% (53 mmol/mol)) and/or treatment change, among individuals with T2DM. Nearly one-third (32.9%) of patients experienced secondary MM failure within 24 months by loss of glycemic control (HbA1c ≥7% (53 mmol/mol)). As secondary MM failure was redefined using higher thresholds for target HbA1c (≥7.5% (58 mmol/mol) and ≥8.0% (64 mmol/mol)), the prevalence of secondary MM failure was lower overall but consistently increased over time. Of the patients 19.2% experienced secondary MM failure by treatment change after 24 months. Factors associated with progression to HbA1c ≥7% (53 mmol/mol) were being a woman, having lower baseline HbA1c, and having lower CCI. Only lower CCI was found to be associated with treatment change.

As previously discussed, two real-world studies using KPNW patients reported an annual secondary MM failure rate of 17%,[8] loss of control (HbA1c ≥8% (64 mmol/mol)) rate of 20.5%, and treatment intensification rate of 25.9% over a mean time of 21.6 months

and 27.5 months, respectively.[9] The findings of this study are consistent with the Kaiser real-world studies on rates of loss of glycemic control, but in a larger US population. Further, in Kaiser's analysis, 5%, 9%, and 50% of patients progressed to HbA1c ≥8% (64 mmol/mol), stratified by baseline HbA1c of <6% (42 mmol/mol), 6%–6.9% (42–52 mmol/mol), and 7%–7.9% (53–63 mmol/mol), respectively.[9] While the present study did not stratify loss of glycemic control by baseline HbA1c, it did find 6.1% of patients progressed to an HbA1c ≥8% (64 mmol/mol) at 24 months (sensitivity analysis). For treatment change, the KM curves for the Kaiser cohort showed that ~5%–35% of patients changed therapies, stratified by lowest achieved HbA1c in the previous 12 months (<6% (42 mmol/mol), 6%–6.9% (42–52 mmol/mol), 7%–7.9%(53–63 mmol/mol)).[9] The findings of the present study fall about halfway between this range (19%). Using large, pharmacy claims databases based on a US population, Riedel *et al*[12] reported a secondary MM failure (HbA1c ≥7% (53 mmol/mol)) of 35.5% over 4 years, although the present study found that a similar proportion of patients failed by the same definition within 2 years. The ADA guidelines recommend performing HbA1c tests at least twice a year in patients who are meeting treatment goals.[13] Regular monitoring of HbA1c would allow for timely treatment adjustments and, if needed, intensification. The present study confirms the findings of the previous studies out of KPNW on a national level and shows that a substantial proportion of patients who achieve glycemic targets on MM go on to lose glycemic control or change therapy in a relatively short period of time. This underscores the importance of the ADA's recommendation for biannual glycemic testing in patients under glycemic control.

Although these findings share considerable similarity with prior research, there are some key differences. First, patients with greater comorbidity burden or higher HbA1c at baseline were less likely to experience secondary MM failure, defined either based on HbA1c level or treatment intensification at 24 months. This is also contrary to previous literature suggesting that the impact of comorbidity on glycemic control is insignificant.[14 15] It is possible these findings could reflect closer medical management or better adherence to MM in a population with more comorbid conditions, but it is impossible to fully examine the reasons behind this finding given the nature of a database study. Furthermore, Nichols *et al*[9] found that compared with having an HbA1c <7% (53 mmol/mol) at metformin initiation, an HbA1c >7% (53 mmol/mol) had 1.30–3.26 times greater risk of secondary MM failure by treatment change or loss of control. Interestingly, this study found the opposite to be true for the relationship between baseline HbA1c, or HbA1c prior to MM initiation, and secondary MM failure by loss of glycemic control and found no association between baseline HbA1c and secondary MM failure by treatment change. Second, Choe *et al*[16] had reported sex-based differences in glycemic control and recommended sex-specific approach for glycemic control management. In our study, women displayed significantly higher likelihood of secondary MM failure by loss of control (HbA1c≥7% (53 mmol/mol)) (OR=1.28). This association when measured as treatment intensification, although significant, was modest in comparison.

The current study has several limitations due to its retrospective, observational design. EMR data record information on prescribed medications and not dispensed medication or medication use; therefore, there is no way to confirm that patients were truly on MM. The analysis attempted to address this limitation through a sensitivity analysis, namely examining the primary objective in a subset of patients with two or more consecutive metformin prescriptions, and found similar results (online supplemental appendix 1). The EMR data also do not capture the reasons behind switching therapy or treatment intensification. Using treatment intensification as a proxy for secondary MM failure may introduce outcome misclassification bias; treatment change may be unrelated to secondary MM failure, and instead due to reasons including but not limited to adverse reactions to metformin, a lower individualized HbA1c goal, or a desire to change treatment due to non-glycemic benefits of another treatment (ie, weight loss, cardiovascular, and/or diabetic kidney disease benefits). However, this definition was included as a proxy measure for secondary MM failure due to more limited capture of HbA1c measures in EMR databases. Furthermore, although the ADA considers a target of HbA1c level <7% (53 mmol/mol) as optimal glycemic control for most patients,[2] a higher glycemic target may be appropriate for some patients and thus they may have been inappropriately classified as having failed treatment. We attempted to address this limitation by performing sensitivity analyses redefining loss of glycemic control as HbA1c ≥7.5% (58 mmol/mol) and ≥8% (64 mmol/mol). Intent-to-treat approach used to assess the HbA1c measurements may be susceptible to treatment-related attrition or exposure misclassification or both, namely non-adherence, switching, or augmentation. Finally, the HbA1c measurements were not always available for each follow-up time, thereby reducing the precision of estimates. The analysis, however, used relatively short intervals of 6, 12, 18, and 24 months of follow-up in order to minimize the bias. Lastly, the IQVIA EMR database is representative of 30 million US patients receiving ambulatory care from 30 000 healthcare providers across 49 states, and thus represents a larger, more diverse pool of patients with T2DM than previous analyses on secondary MM failure.[7–9] Nevertheless, it may not be generalizable to the entire US T2DM population.

In conclusion, this retrospective cohort study of real-world patients with type 2 diabetes documented that the likelihood of secondary MM failure increases over time regardless of HbA1c values used to define it.

Approximately one-third of the patients initiating MM progressed to HbA1c ≥7% (53 mmol/mol) and 19% either switched or intensified MM within 24 months. It is important that patients on MM receive glycemic monitoring at least every 6 months, as recommended by the ADA, to ensure loss of glycemic control is readily identified and proper therapeutic adjustments are made in a timely manner. Further studies assessing whether initial metformin combination therapy would result in more durable glycemic control would be valuable.

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Competing interests TW, LY, and SR are employees of Merck Sharp & Dohme, a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey, USA. KI was an employee of Merck Sharp & Dohme, a subsidiary of Merck & Co., Inc. at the time of study completion. LB is an employee of Ochsner Medical Center. TG was an employee of Complete HEOR Solutions, North Wales, Pennsylvania, USA, which was contracted to complete the study analysis on behalf of Merck & Co., Inc.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. Merck licensed the EMR data used in this study from IQVIA. Under its agreement with IQVIA, Merck does not have the permission to release the data to or share the data with any third party without explicit contractual consent between the third party and IQVIA. The study protocol contains the specifications of the database and details of patient selection. The study protocol is available upon request.

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Appendix 1: Additional Sensitivity Analyses

Cumulative proportions experiencing secondary MM failure at 6, 12, 18 and 24 months among A) patients with index [a]HbA1c <7.5% (58 mmol/mol) and B) patients with 2 or more metformin prescriptions

		6 months	12 months	18 months	24 months
A) Among patients with index [a]HbA1c <[b]7.5%	HbA1c ≥7.5%	6.3%	12.7%	17.5%	22.6%
	HbA1c ≥ 8%	3.2%	6.7%	8.8%	11.6%
	Treatment Change	5.8%	10.3%	14.0%	18.1%
B) Among patients with 2 or more metformin prescriptions only	HbA1c ≥7%	13.0%	20.1%	28.2%	36.0%
	HbA1c ≥7.5%	5.3%	8.6%	12.3%	15.8%
	HbA1c ≥ 8%	2.1%	3.7%	5.3%	7.0%
	Treatment Change	8.0%	12.9%	18.4%	22.7%

[a]HbA1c: Hemoglobin A1c; [b] HbA1c <7.5% (58 mmol/mol)

Appendix 2: Cohort table and diagnosis codes

Steps	Selection Criteria	HbA1c value < 7% (Base Case)	HbA1C value <7.5% (Sensitivity Analysis 1)
0	Patients with Type 2 diabetes mellitus diagnosis during the study period (Jan 01, 2012-June 30, 2018)	1,503,408	1,503,408
1	Patients without type 1 diabetes mellitus, polycystic ovary syndrome, gestational diabetes mellitus, or other forms of secondary diabetes during the study period	1,463,418	1,463,418
2	Patients treated with metformin monotherapy (MM) during period Jan 01, 2013 - May 31, 2016, the first date will be metformin date	556,294	556,294
3	No use of metformin, antihyperglycemic agents (AHAs) or insulin in 12 months prior to the first metformin date	289,329	289,329
4	Patients with index HbA1c value (as depicted in columns) in the 1-6 months following metformin date	68,948	83,285
5	Patients with no insulin or AHA between index date and metformin date	62,381	74,558
6	Patients with continuous MM prescription by checking continuous MM prescription (MM prescription within 90 days of preceding prescription) from metformin date to index date	15,611	19,219
7	At least 18 years of age on index date	15,544	19,141
8	Patients with continuous enrollment in the database during baseline period	11,738	14,408
9	Patients with continuous enrollment in the database during follow-up period (24 months)	7,098	8,715
10	Patients with baseline Hba1c value ≥6.5% at any point prior to metformin date	**4,775 (Base Cohort)**	**6,129 (Sensitivity Cohort 1)**
11	Patients with 2 or more continuous metformin prescriptions only	**1,942 (Sensitivity Cohort 2)**	NA

Pr Proprietary

ICD 9 and ICD 10 codes

	ICD 9	ICD 10
Type 2 diabetes mellitus	250.x0, 250.x2	E11
Type 1 diabetes mellitus	250.x1, 250.x3	E10.9
Complications of pregnancy	630-679	-
Secondary diabetes mellitus.	249.x	E08.x, E09.x
Gestational diabetes mellitus	648.8	024.4
Supervision of normal first pregnancy	V22, v22	-
Polycystic ovarian syndrome	256.4	E28.2

Comorbidities	Source	Code or criteria
Neuropathy	ICD-9 Diagnosis	356.9, 250.6, 358.1, 951.0, 951.1, 951.3, 354.0-355.9, 713.5, 357.2, 596.54, 337.0, 337.1, 564.5, 536.3, 458.0
Nephropathy	ICD-9 Diagnosis	5804, 58081, 58089, 5809, 5810, 5811, 5812, 5813, 58181, 58189, 5819, 5820, 5821, 5822, 5824, 58281, 58289, 5829, 5830, 5831, 5832, 5834, 5836, 5837, 58381, 58389, 5839, 5845, 5846, 5847, 5848, 5849, 585, 5851, 5852, 5853, 5854, 5855, 5856, 5859, 586, 587, 5880, 5881, 5888, 58881, 58889, 5889, 5890, 5891, 5899, 59000, 59001, 59010, 59011, 5902, 5903, 59080, 59081, 5909, 591, 5920, 5921, 5929, 5930, 5931, 5932, 5933, 5934, 5935, 5936, 5937, 59370, 59371, 59372, 59373, 59381, 59382, 59389, 5939, 7880, 7925, V1301, V420, V451, V560, V561, V562, V5631, V5632, V568, 0160, 01600, 01601, 01602, 01603, 01604, 01605, 01606, 2504, 25040, 25041 25042, 25043, 2741, 27410 27411, 27419, 403, 4030, 40300, 40301, 4031, 40310, 40311, 4039, 40390, 40391, 5800
Congestive heart failure	ICD-9 Diagnosis	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4, 425.5, 425.7, 425.8, 425.9, 428
Stroke/ Transient ischemic attacks	ICD-9 Diagnosis	430.x-435.x
Arrhythmia	ICD-9 Diagnosis	427.0 427.1 427.2 427.31 427.32 427.41 427.42 427.5 427.6 427.61 427.69 427.81 427.89 427.9
Peripheral arterial diseases	ICD-9 Diagnosis	093.0x, 437.3x, 440.0x-441.9x,443.1x-443.9x,447.1x,557.1x,557.9x, V43.4X
Diabetic Retinopathy	ICD-9 Diagnosis	250.5x
Acute Coronary Syndrome	ICD-9 Diagnosis	411.1
Acute Myocardial Infarction	ICD-9 Diagnosis	411.x, 410.x, 412.x
Angina	ICD-9 Diagnosis	413.9
Revascularization	CPT CODE	3722, 33520, 33515
Peripheral Vascular Disease	ICD-9 Diagnosis	0930, 4373, 440, 441, 4431, 4432, 4438, 4439, 4471, 5571, 5579, V434

List of AHA drugs

- Sulfonylureas
- Antidiabetic - Amino Acid Derivatives
- Biguanides
- Meglitinide analogues
- Alpha-Glucosidase Inhibitors
- Dipeptidyl Peptidase-4 (DPP-4) Inhibitors
- Dopamine Receptor Agonists – Antidiabetic
- Insulin sensitizing agents
- Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors
- Glucagon-like peptide-1 (GLP-1) receptor agonists
- Amylin analogues
- Antidiabetic combinations
- Bile acid sequestrants (colesevelam HCl)
- Insulin
  - Rapid Acting:
    o Insulin lispro (Humalog)
    o Insulin aspart (NovoRapid)
    o Insulin glulisin (Apidra)
  - Intermediate-acting:
    o Insulin isophane/NPH (Humulin I, Insulatard, Insuman Basal)
  - Long-acting:
    o Insulin glargine (Lantus)
    o Insulin detemir (Levemir)
    o Insulin degludec (Tresiba) Pre-mix:
    o Insulin aspart and protamine aspart (Novomix 30)
    o Insulin lispro and protamine lispro (Humalog Mix25, Humalog Mix50)
    o Insulin neutral and isophane (Humulin M3, Insuman Comb, Mixtard)