Changing Trends in Type 2 Diabetes Mellitus Treatment Intensification, 2002-2010

Rozalina G. McCoy, MD; Yuanhui Zhang, PhD; Jeph Herrin, PhD; Brian T. Denton, PhD; Jennifer E. Mason, PhD; Victor M. Montori, MD; Steven A. Smith, MD; Nilay D. Shah, PhD

Diabetes is one of the most prevalent and costly chronic diseases; it affects more than 12% of the US adult population[1] and accounts for nearly 13% of total healthcare expenditures.[2] Poor glycemic control is associated with worse quality of life and increased risk of diabetes-related complications.[3-9] Because of the high burden of illness—in addition to rising costs to individuals, society, and healthcare systems[2]—improving the quality of diabetes care has emerged as a priority for patients, healthcare providers, payers, and government organizations.

Individuals with hyperglycemia not adequately controlled by lifestyle modifications alone are generally started on metformin, the first-line agent in the management of type 2 diabetes mellitus (T2DM).[10,11] Due to the progressive course of diabetes, most patients ultimately require the addition of other glucose-lowering medications,[12] and failure to intensify treatment in a timely manner has been linked to poor glycemic control and greater risk of diabetes-related complications.[13-15] Treatment intensification may be delayed due to a variety of patient-related factors, such as concern for polypharmacy, burden of treatment, nonadherence, and financial challenges. Similarly, provider-related factors may stem from competing clinical demands, lack of awareness or education, and inadequate encounter times. Such clinical inertia is common and contributes to poor glycemic control.[13-17] Recently, the percent of diabetes patients in the United States who meet glycemic targets has improved,[18] potentially as a result of increased focus on public reporting of diabetes performance metrics and prioritization of glycemic control.[19]

Public availability of performance data and performance-based reimbursement may have affected provider practice and led to increased rates of treatment intensification.[19] Two seminal studies, published in 2003[20] and 2006,[21] revealing the inadequacies of diabetes care and delayed treatment intensification also may have led clinicians to increase their focus on achieving and maintaining glycemic targets. However, little is known about recent trends in treatment intensification in clinical practice.

ABSTRACT

Objectives: Glycemic control can lower the risk of diabetes-related complications, and delayed treatment intensification can impede optimal diabetes care. This study examines trends in hyperglycemia treatment intensification between 2002 and 2010.

Study Design: Retrospective secondary data analysis of a large national administrative data set of privately insured individuals across the United States.

Methods: Adults 18 years or older with diabetes, initiated on metformin monotherapy between 2002 and 2007, were studied, stratified by date of first metformin prescription (2002-2003, 2004-2005, 2006-2007). Time to treatment intensification between 2002 and 2010, defined by the addition of ≥1 agents to metformin, was estimated using Kaplan-Meier and Cox proportional hazards regression analysis.

Results: There were 75,069 treatment-naïve adults with diabetes first initiated on metformin between 2002 and 2007; mean age was 60 years (SD = 11.5), 49.7% were women, and 63.1% were non-Hispanic white. Diabetes therapy was intensified in 26,169 individuals (34.6%). Treatment intensification became increasingly more likely with time for the 2004-2005 cohort (hazard ratio [HR], 1.07; 95% CI, 1.04-1.10) and for the 2006-2007 cohort (HR, 1.11; 95% CI, 1.07-1.14) compared with the 2002-2003 cohort (P <.001), after adjustment for significant confounders including sex, income level, education level, and comorbidity burden. Sulfonylureas were the most commonly used agents, though their use declined over time; thiazolidinedione use decreased; and incretin use increased (all P <.001).

Conclusions: There was a significant increase in diabetes treatment intensification between 2002 and 2010. Choice of second-line agents changed as well, with decreasing prevalence of thiazolidinedione and sulfonylurea use and rising prevalence of incretin use.

Am J Manag Care. 2015;21(5):e288-e296

Moreover, the choice of second-line agents used to intensify diabetes therapy probably changed as a result of greater availability and marketing of new pharmacotherapies. Several recent studies showed changing trends in the use of glucose-lowering therapies,[22,23] but they were not designed to assess treatment intensification practices, as they did not distinguish between monotherapy and combination therapy, or specify whether certain drugs were used as first-, second-, or third-line therapies.

Take-Away Points

This study examines trends in treatment intensification among privately insured adults of all ages in the era of greater focus on quality improvement and performance measurement for diabetes.

- In a geographically and demographically diverse population, time to treatment intensification decreased consistently between 2002 and 2010.
- This study specifically addresses the selection of second-line agents as add-on therapy to metformin in routine clinical practice. The use of incretin agents and insulin increased significantly over the past decade, while the use of thiazolidinediones has decreased.
- Sulfonylureas remained the most commonly prescribed class of second-line agents used to treat type 2 diabetes mellitus.

We used data from a large nationally representative data set of privately insured individuals to identify and characterize the temporal changes in treatment intensification rates, and medications used as second-line therapies, between 2002 and 2010.

METHODS AND RESEARCH DESIGN

Design and Data Set

We conducted a retrospective secondary data analysis of adults 18 years and older with T2DM included in Optum Labs Data Warehouse, an administrative claim database of enrollees from commercial US health plans. This database includes medical and pharmacy benefit coverage for more than 96 million individuals in all 50 states and of all ages and ethnic/racial groups. Medical claims include diagnosis and procedure codes, site of service codes, provider specialty codes, and health plan and patient costs. Pharmacy claims include information on medications dispensed, prescription quantity, and date of issue. Study data were accessed using techniques compliant with the Health Insurance Portability and Accountability Act of 1996. Because this study involved analysis of preexisting, de-identified data, it was exempt from institutional review board approval.

Study Population

Individuals with T2DM were identified on the basis of Healthcare Effectiveness Data and Information Set criteria.[24] In order to restrict data analysis to treatment-naïve individuals newly initiated on metformin monotherapy, we included only those people who had a period of 6 or more months preceding enrollment without a claim for any diabetes medications. Patients who received a prescription for another antihyperglycemic agent within 30 days following the first metformin prescription were excluded, as they were likely started a priori on combination therapy rather than metformin monotherapy. Cohort entry point was defined by the issue date of the first metformin prescription, and patients were allocated to 1 of 3 cohorts based on the years when this occurred (2002-2003, 2004-2005, and 2006-2007).

Assessment of Treatment Intensification

Our primary outcome was the number of days to treatment intensification after first initiation of metformin monotherapy. Treatment intensification was defined as a new prescription for ≥1 antihyperglycemic agent(s) in addition to metformin, or replacement of metformin by insulin (insulin prescription filled within 90 days of the preceding metformin coverage date). Second-line agents were grouped into 1 of 5 categories (**eAppendix**, available at **www.ajmc.com**), and combination tablets and insulins were considered as consisting of both classes.

Censoring occurred when patients were disenrolled from the health plan (defined as no pharmacy claims for ≥6 months), when they discontinued metformin (unless replaced by insulin), or on December 31, 2010. Medication discontinuation was identified by a lack of refills 90 days beyond the last day covered by the preceding fill. There was no difference in the relative proportion of patients censored due to metformin discontinuation, metformin replacement by another non-insulin hypoglycemic agent, or health plan disenrollment between the 3 cohorts. Based on all available information, we assumed that censoring was non-informative.

Independent Variables

Diagnoses were determined using *International Classification of Diseases, Ninth Revision, Clinical Modification* codes. Administrative claims were used to derive the Charlson comorbidity (CC) index and count for 1 calendar year prior to initiation of metformin. The CC index is a widely used measure of disease burden that weighs comorbid conditions by the strength of their association with 1-year mortality,[25] and it has been previously validat-

ed for use in diabetes.[26,27] Socioeconomic characteristics included age, gender, race/ethnicity, highest education level achieved, and median household income at the census block level based on the residence of the individual.

Statistical Analysis

Patient characteristics were compared among cohorts using χ^2 tests for categorical variables, and ANOVA for continuous variables (age).

We graphed the Kaplan-Meier curves for the 3 cohorts, and used a log-rank test to test for differences in unadjusted time to intensification curves for the 3 cohorts.[28] Proportional hazards assumptions were checked by testing a nonzero slope in a generalized linear regression of the scaled Schoenfeld residuals on functions of time for the cohort variable.[28,29] Preliminary analysis rejected the assumption that hazards were proportional across the 3 cohorts, so we assessed a range of parametric specifications for time-to-event models according to model performance, selecting a Gompertz model[30] as most appropriate.

We then estimated a single model to determine the association between cohort and the risk of future treatment intensification while adjusting for patients' age at the time of metformin initiation, gender, race/ethnicity, income level, education level, CC count, and concomitant statin treatment. Patient's age at the time of metformin initiation was modeled as a continuous variable; other covariates were modeled as categorical variables. Missing data were imputed using ordered and multiple logit models that included age, sex, CC count, statin use, and cohort.[31] We report coefficients as hazard ratios, and the *P* values for the hypothesis that the hazard ratio was different from zero. For categorical covariates, we also report the Wald test *P* value for the hypothesis that the set of hazard ratios for that covariate were jointly equal to zero.

To assess patterns of second-line treatments according to year of metformin initiation, we summarized the frequency of use of each drug class for each study cohort. We used χ^2 tests to test for differences in rates of each agent across cohorts, and report the *P* values.

All analyses were conducted using SAS 9.3 (SAS Institute, Cary, North Carolina) and Stata 13.1 (Stata Corp, College Station, Texas). Probability values <.05 were considered to be statistically significant.

RESULTS

Patient Characteristics

Between 2002 and 2007, 75,069 treatment-naïve adults with T2DM were initiated on metformin monotherapy; their baseline demographic and comorbidity characteristics are summarized in Table 1. Median duration of follow-up until treatment intensification or censoring was comparable between the 3 cohorts: 1.7 years (interquartile range [IQR], 0.8, 3.3), 1.7 years (IQR, 0.8, 3.2), and 1.6 years (IQR, 0.8, 2.8) for the 2002-2003, 2004-2005, and 2006-2007 cohorts, respectively. Average age at the time of metformin initiation was 60.0 (SD = 11.5) years, and there was a significant trend toward younger age at metformin initiation over time (*P* <.001). Nearly a third of patients had 1 or more chronic medical illnesses in addition to diabetes, with an overall mean CC index of 1.5 (SD = 1.4) (Table 1). Chronic disease burden increased over time, with mean CC index rising from 1.4 (SD = 1.3) in the 2002-2003 cohort to 1.5 (SD = 1.4) in the 2004-2005 cohort, and 1.6 (SD = 1.5) in the 2006-2007 cohort (*P* <.001). The number of patients with no chronic illness aside from diabetes declined from 70.1% in the 2002-2003 cohort, to 65.7% in the 2004-2005 cohort, to 62.7% in the 2006-2007 cohort (*P* <.001). The prevalence of concomitant statin therapy was 42% across all years, and increased in successive cohorts: 34.2% in the 2002-2003 cohort, 40.3% in the 2004-2005 cohort, and 46.8% in the 2006-2007 cohort (*P* <.001).

Choice of Second-Line Therapy

There was a persistent and significant change in the class of second-line agents used to intensify glucose-lowering therapy over each cohort of new metformin starters (Table 2). Sulfonylureas and meglitinides were the most commonly used second-line agents, but their use decreased from 48.9% in the 2002-2003 cohort, to 43% in the 2004-2005 cohort, to 42.3% in the 2006-2007 cohort (*P* <.001). Two drug classes saw profound changes in prescription patterns: thiazolidinediones and incretins. The use of incretins rose for each successive cohort, from 4.2% in the 2002-2003 cohort, to 12.7% in the 2004-2005 cohort, to 26.7% in the 2006-2007 cohort (*P* <.001). Conversely, thiazolidinedione use decreased slightly between the 2002-2003 and 2004-2005 cohorts, from 43.5% to 40.9%, but then fell sharply to 26.2% in the 2006-2007 cohort (*P* <.001). Insulin use as a second-line agent increased from 3.2% in the 2002-2003 and 2004-2005 cohorts to 4.5% in the 2006-2007 cohort (*P* <.001).

Treatment Intensification

The likelihood of treatment intensification was significantly higher in each successive cohort of patients on metformin monotherapy (Table 3 and Figure). Overall, compared with the 2002-2003 cohort, the hazard ratio for intensification was 1.07 (95% CI, 1.04-1.10; *P* <.001) in the 2004-2005 cohort, and was 1.11 (95% CI, 1.07-1.13; *P* <.001)

Table 1. Study Population Demographics

	Overall	2002-2003	2004-2005	2006-2007	*P*[a]
Patients: N	75,069	16,783	23,577	34,709	
Age, years: mean (SD)	60.0 (11.5)	60.8 (11.3)	60.5 (11.7)	59.3 (11.4)	<.001
Female: N (%)	37,346 (49.7)	8417 (50.2)	11,979 (50.8)	16,950 (48.8)	<.001
Race/ethnicity: N (%)					<.001
White	47,381 (63.1)	10,779 (64.2)	15,269 (64.8)	21,333 (61.5)	
Black	6587 (8.8)	1378 (8.2)	2117 (9.0)	3092 (8.9)	
Hispanic	5369 (7.2)	1166 (6.9)	1679 (7.1)	2524 (7.3)	
Asian	1974 (2.6)	448 (2.7)	590 (2.5)	936 (2.7)	
Missing	13,758 (18.3)	3012 (17.9)	3922 (16.6)	6824 (19.7)	
Education level: N (%)					<.001
<High school	1570 (2.1)	331 (2.0)	525 (2.2)	714 (2.1)	
High school	25,857 (34.4)	5842 (34.8)	8323 (35.3)	11,692 (33.7)	
College	29,220 (38.9)	6565 (39.1)	9272 (39.3)	13,386 (38.6)	
Post graduate	7293 (9.7)	1629 (9.7)	2373 (10.1)	3291 (9.5)	
Missing	11,129 (14.8)	2416 (14.4)	3084 (13.1)	5629 (16.2)	
Income level: N (%)					<.001
<$15,000	1147 (1.5)	281 (1.7)	371 (1.6)	495 (1.4)	
$15,000-$39,999	11,162 (14.9)	2613 (15.6)	3612 (15.3)	4937 (14.2)	
$40,000-$75,000	27,363 (36.5)	6114 (36.4)	8840 (37.5)	12,409 (35.8)	
>$75,000	21,515 (28.7)	4713 (28.1)	6809 (28.9)	9993 (28.8)	
Missing	13,882 (18.5)	3062 (18.2)	3945 (16.7)	6875 (19.8)	
Statin therapy: N (%)	31,513 (42.0)	5742 (34.2)	9510 (40.3)	16,261 (46.8)	<.001
Comorbidities: N (%)					
MI	2096 (2.8)	413 (2.5)	645 (2.7)	1038 (3.0)	.002
CHF	2917 (3.9)	541 (3.2)	906 (3.8)	1470 (4.2)	<.001
PVD	3367 (4.5)	547 (3.3)	1028 (4.4)	1792 (5.2)	<.001
Stroke	3652 (4.9)	585 (3.5)	1168 (5.0)	1899 (5.5)	<.001
Lung disease	13,150 (17.5)	2515 (15.0)	4042 (17.1)	6593 (19.0)	.02
Peptic ulcer disease	1068 (1.4)	201 (1.2)	352 (1.5)	515 (1.5)	<.001
Liver disease	5054 (6.7)	829 (4.9)	1517 (6.4)	2708 (7.8)	<.001
Kidney disease	772 (1.0)	118 (0.7)	225 (1.0)	429 (1.2)	<.001
Rheumatic disease	1654 (2.2)	295 (1.8)	515 (2.2)	844 (2.4)	<.001
Cancer	3979 (5.3)	778 (4.6)	1224 (5.2)	1977 (5.7)	<.001
CC index: mean (SD)[b]	1.5 (1.4)	1.4 (1.3)	1.5 (1.4)	1.6 (1.5)	<.001
CC count: N (%)[c]					
0	48,994 (65.3)	11,760 (70.1)	15,487 (65.7)	21,747 (62.7)	<.001
1	17,458 (23.3)	3607 (21.5)	5411 (23.0)	8440 (24.3)	<.001
2	5628 (7.5)	968 (5.8)	1785 (7.6)	2875 (8.3)	<.001
≥3	2989 (4.0)	448 (2.7)	894 (3.8)	1647 (4.7)	<.001

CC indicates Charlson comorbidity; CHF, congestive heart failure; MI, myocardial infarction; PVD, peripheral vascular disease.
All patient characteristics are from time of cohort entry (eg, initiation of metformin monotherapy).
[a] *P* values based on χ^2 tests of independence for categorical variables, ANOVA for continuous variables.
[b] "Diabetes" and "diabetes with chronic disease" were included in the calculation of the Charlson comorbidity index.
[c] "Diabetes" and "diabetes with chronic disease" were excluded from the Charlson comorbidity count.

in the 2006-2007 cohort. The log-rank test showed statistically significant differences in the cumulative probability of treatment intensification between any 2 cohorts for the whole observation period (*P* <.001). This trend remained highly significant after adjustment for potential confounders of treatment intensification, specifically patient age, sex, race/ethnicity, education and median household income, comorbidity burden, and statin therapy.

DISCUSSION

Clinical inertia and failure to escalate glucose-lowering therapy in the management of diabetes contributes to deterioration of glycemic control[13-17] and increased risk of diabetes-related complications.[3-9] Population-level studies, particularly the 2003 assessment of chronic disease care in

Table 2. Patterns of Second-Line Glucose-Lowering Agent Use by Cohort

	Overall	2002-2003	2004-2005	2006-2007	*P*
Patients: N	26,169	6687	8841	10,641	
Sulfonylurea: N (%)	12,110 (44.18)	3409 (48.85)	3967 (42.97)	4734 (42.26)	<.001
Thiazolidinedione: N (%)	9753 (35.58)	3035 (43.49)	3780 (40.94)	2938 (26.23)	<.001
Incretins: N (%)	4449 (16.23)	290 (4.16)	1169 (12.66)	2990 (26.69)	<.001
Insulin: N (%)	1025 (3.74)	224 (3.21)	292 (3.16)	509 (4.54)	<.001
Other: N (%)	75 (0.27)	20 (0.29)	25 (0.27)	30 (0.27)	.97

Sulfonylurea class includes both sulfonylureas and meglitinides. Patients started on more than 1 drug at the same time (eg, within 30 days of each other) are included in both categories.
P values are based on χ^2 tests of independence of agent over cohort.

the United States, revealed deficiencies in the quality of diabetes care[20]; the importance of treatment intensification in achieving high-quality diabetes care was subsequently highlighted in 2006.[21] Both studies were thought to have affected and improved clinical practice, and the 2-year cohorts in our study were designed to follow these important secular trends. While recent studies showed improved population-level glycemic control over time,[18] less was known about concurrent trends in diabetes treatment intensification practices. This study, conducted in a large, national, and racially diverse cohort of adults with T2DM, found that the likelihood of treatment intensification rose significantly and consistently over the past decade, albeit in small increments.

Our study confirmed prior observations regarding several important confounders of treatment intensification. These include socioeconomic status (assessed in our study using median education level and household income of the region where the patient lives), age, sex, and comorbidity. Because administrative data do not include laboratory values such as A1C, we could not establish with certainty the degree to which observed differences in treatment intensification are due to differences in glycemic control versus disparities in healthcare access and disease management practices. Still, these important observations highlight the need for further study of enduring disparities in healthcare.

Consistent with studies in different populations, we found that the patients with greater disease burden were more likely to have their treatment intensified.[32,33] This stands in stark contrast to current guidelines that recommend a more cautious and less intensive therapeutic approach to managing patients with multiple comorbidities.[10] A possible reason for this is that patients with multiple chronic diseases have closer contact with the healthcare system, allowing more opportunities for treatment intensification. Nonetheless, whether treatment intensification in this patient population ultimately improves clinical outcomes or quality of life is uncertain.

The choice of second-line agents used in clinical practice to intensify metformin monotherapy changed significantly over the course of the study. These trends are consistent with recently published epidemiologic data about the overall use of antidiabetes drugs (not specifically as second-line agents).[22,23,34] While metformin is regarded by most as the first-line agent in the treatment of T2DM due to its efficacy, safety, and affordability, there is no consensus and insufficient empirical evidence supporting the use of one second-line agent over another.[10,35-37] Our study, in contrast to others, focused specifically on choice of second-line agents as add-on therapy to metformin. We found that while sulfonylureas continue to be the most common choice for second-line therapy, their use decreased as they lost a percentage of their market share to newer agents that are better marketed and potentially have a lesser side effect profile.[38-41]

We also saw a dramatic decline in thiazolidinedione use, and an even greater rise in incretin use. Thiazolidinediones have become progressively unpopular since rosiglitazone was linked to increased risk of cardiovascular events, and pioglitazone to risk of fractures and bladder cancer.[42-45] Incretin agents were the newest class of diabetes medications included in our study, and they carry little risk of hypoglycemia and weight gain.[38,39,41] However, there is uncertainty regarding the optimal timing of their initiation, specifically whether they are better used as second-line agents when metformin is no longer sufficient or as third-line agents in addition to metformin and another glucose-lowering drug such as a sulfonylurea.[10,35,46] How this change in clinical practice will influence patient outcomes remains to be seen, but emerging evidence suggests that incretins as second-line agents are not superior to sulfonylureas. Indeed, their use is associated with shorter time to serious diabetes complications, shorter time of insulin-independence, and significantly higher cost.[47]

Limitations

Although secondary analysis of administrative data enables real-world longitudinal assessments of disease

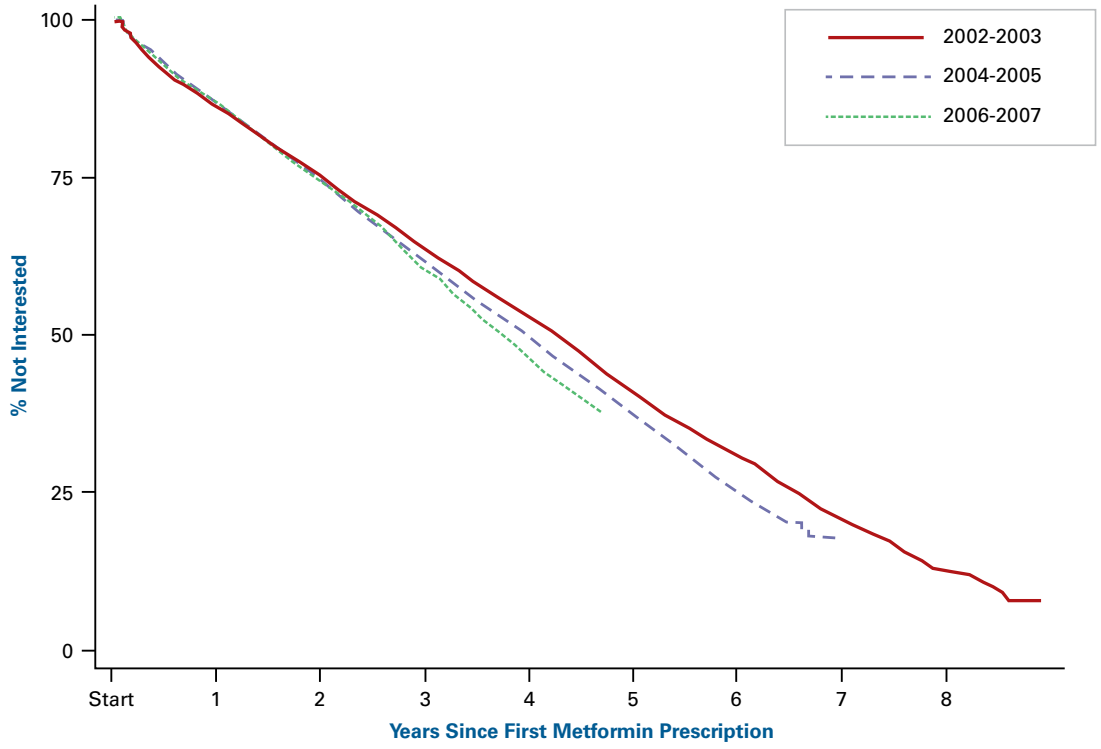
Table 3. Effect of the Year That Metformin Was First Initiated on the Risk of Future Treatment Intensification

	Hazard Ratio	95% Confidence Interval	*P*	Wald Test *P* Value
Year of metformin initiation				<.001
2002-2003	Ref			
2004-2005	1.07	1.04-1.10	<.001	
2006-2007	1.11	1.07-1.14	<.001	
Age at metformin initiation	0.99	0.99-0.99	<.001	
Sex				
Male	Ref			
Female	0.85	0.82-0.87	<.001	
Race/ethnicity				.26
White	Ref			
Black	0.97	0.93-1.02	.30	
Hispanic	1.03	0.98-1.07	.26	
Asian	0.96	0.89-1.03	.27	
Education level				.02
<High school	Ref			
High school	0.98	0.90-1.07	.62	
College	0.97	0.89-1.06	.45	
Post graduate	0.91	0.83-1.00	.049	
Income level				<.001
<$15,000	Ref			
$15,000 - $39,999	0.99	0.89-1.11	.93	
$40,000 - $75,000	0.98	0.89-1.10	.83	
>$75,000	0.94	0.84-1.05	.25	
Statin therapy				
No	Ref			
Yes	0.91	0.88-0.93	<.001	
CC count				.003
0	Ref			
1	1.01	0.98-1.04	.70	
2	1.02	0.97-1.07	.40	
≥3	1.14	1.06-1.21	<.001	

CC indicates Charlson comorbidity; ref, reference.
Patients' age at the time of metformin initiation is a continuous variable, and all other covariates are categorical variables. Higher hazard ratio is indicative of greater likelihood of treatment intensification.
Calculations were controlled for patients' age at the time of metformin initiation, gender, ethnicity, income level, education level, Charlson comorbidity count, and concomitant treatment with a statin, using the Cox proportional hazard model.

management and progression, this methodology has important limitations that are apparent in our study. Because only data from the period of health plan enrollment are available, potential therapies and interventions prior to enrollment are unknown. Another limitation of our study is the censoring for patients who discontinued metformin, as such censoring may be informative rather than outcome-neutral. Patients who discontinue all medications may be at low risk of intensification because of excellent glycemic control, or may be nonadherent and therefore at high risk. An analysis that accounted for all competing risks, including medication changes to a variety of different regimen or no regimen, is problematic when the proportional hazards assumption is not met, as found in our study. Patients were also censored upon disenrollment from the health plan. There are several potential reasons for plan disenrollment, ranging from change of job and insurance provider to death. While

Figure. Cumulative Probability of Treatment Intensification After First Initiation of Metformin Monotherapy



Note the progressively steeper slopes of the cumulative probability of treatment intensification in each successive cohort of individuals. Differences between cohorts remained highly significant after adjustment for potential covariates of patients' age at the time of metformin initiation, gender, race/ethnicity, income level, education level, Charlson comorbidity count, and statin therapy.

it is possible that the different reasons for disenrollment may be differentially associated with likelihood of treatment intensification, this was controlled for by including a measure of comorbidity in our analyses.

The type of pharmacy benefit—specifically differences in coinsurance and annual caps on pharmacy benefit—may have contributed to patient adherence as well as provider treatment intensification practices. While all patients in our study had private medical insurance with a pharmacy benefit, the effect of individual plan variability on treatment intensification and second-line medication choice could not be determined. Similarly, people covered primarily by public health insurance programs are not included, such that our study population is not fully representative of the general population, with greater representation of younger individuals of higher socioeconomic status. However, these are also strengths of our study, as we focused on a population often excluded from research using public insurance or specific health system data.

CONCLUSIONS

Our study extends and reinforces earlier findings by Fu and colleagues, who showed that the likelihood of treatment intensification among patients with T2DM on metformin monotherapy increased between 1997 and 2008.[48] However, the study by Fu and colleagues was restricted by its reliance on electronic health records (EHRs) to define the target population and measure treatment intensification,[48] such that medication changes made outside systems using these EHRs could not be captured, and data on both treatment initiation and discontinuation may therefore be incomplete. Although the data set used by Fu and colleagues included EHRs from a large number of healthcare providers, it is unclear whether data were collected on the patient or practice level, whereby patients who changed practices may have been counted twice (if moved to another participating practice) or missed (if moved to a nonparticipating practice). Moreover, this study was conducted in the early era of EHR implementation, and patients receiving care in practices that had access to EHRs may not be representative of the general population.[49] By using administrative data, we were able to ensure a more comprehensive measure of treatment intensification. Because our data set is patient- rather than provider-centered, patients were not lost if they switched

providers or pharmacies. Finally, our study took into consideration confounders of treatment intensification such as race/ethnicity, education level, and socioeconomic status, which were not assessed in prior studies.

In the current era of quality improvement and performance measurement, we observed a steadily increasing rate of diabetes treatment intensification. However, it remains unclear if such intensification resulted in better long-term outcomes for patients, or to what degree it increased the burden of disease, affected quality of life and patient capacity, or impeded adherence.

Author Affiliations: Division of Endocrinology, Diabetes, Metabolism, & Nutrition, Department of Medicine (RGM, VMM, SAS), and Knowledge and Evaluation Research Unit (VMM, NDS), and Division of Health Care Policy & Research, Department of Health Sciences Research (VMM, SAS, NDS), Mayo Clinic, Rochester, MN; Graduate Program in Operations Research, North Carolina State University (YZ), Raleigh, NC; Division of Cardiology, Yale School of Medicine, Yale University (JH), New Haven, CT; Health Research & Educational Trust (JH), Chicago, IL; Department of Industrial & Operations Engineering, University of Michigan (BTD), Ann Arbor, MI; Department of Public Health Sciences, University of Virginia (JEM), Charlottesville, VA.

Source of Funding: Funding for this work was provided by the National Science Foundation grant number CMMI 0969885 (BTD), Agency for Healthcare Research and Quality research grants R21HS017628 and R18HS018339 (NDS), and National Center for Advancing Translational Sciences research grant UL1RR024150 (NDS). The authors of the manuscript are responsible for the entirety of its content. Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the National Science Foundation or any other funding agency.

Author Disclosures: The authors report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design (BTD, JEM, VMM, RGM, NDS, SAS, YZ); acquisition of data (NDS); analysis and interpretation of data (BTD, JH, JEM, VMM, RGM, NDS, SAS, YZ); drafting of the manuscript (BTD, VMM, RGM); critical revision of the manuscript for important intellectual content (JH, JEM, VMM, RGM, NDS, SAS, YZ); statistical analysis (BTD, JH, YZ); obtaining funding (BTD); administrative, technical, or logistic support (NDS); and supervision (BTD, VMM).

Address correspondence to: Nilay D. Shah, PhD, Division of Health Care Policy & Research, Department of Health Sciences Research, Mayo Clinic, 200 First St SW, Rochester, MN 55905. E-mail: shah.nilay@mayo.edu.

REFERENCES

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014. Atlanta, GA: US Department of Health and Human Services; 2014.

2. American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. *Diabetes Care.* 2013;36(4):1033-1046.

3. Riddle MC, Ambrosius WT, Brillon DJ, et al; Action to Control Cardiovascular Risk in Diabetes Investigators. Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. *Diabetes Care* 2010;33(5):983-990.

4. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med.* 2008;358(6):580-591.

5. McBrien KA, Manns BJ, Chui B, et al. Health care costs in people with diabetes and their association with glycemic control and kidney function. *Diabetes Care.* 2013;36(5):1172-1180.

6. Zhang CY, Sun AJ, Zhang SN, et al. Effects of intensive glucose control on incidence of cardiovascular events in patients with type 2 diabetes: a meta-analysis. *Ann Med.* 2010;42(4):305-315.

7. Zhang P, Brown MB, Bilik D, Ackermann RT, Li R, Herman WH. Health utility scores for people with type 2 diabetes in U.S. managed care health plans: results from Translating Research Into Action for Diabetes (TRIAD). *Diabetes Care.* 2012;35(11):2250-2256.

8. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ.* 2000;321(7258):405-412.

9. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med.* 2008;359(15):1577-1589.

10. American Diabetes Association. Standards of medical care in diabetes—2015. *Diabetes Care.* 2015;38(suppl 1):S1-S90.

11. Redmon B, Caccamo D, Flavin P, et al. Diagnosis and management of type 2 diabetes mellitus in adults. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2014 Jul: 85.

12. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS 49) Group. *JAMA.* 1999;281(21):2005-2012.

13. Schmittdiel JA, Uratsu CS, Karter AJ, et al. Why don't diabetes patients achieve recommended risk factor targets? poor adherence versus lack of treatment intensification. *J Gen Intern Med.* 2008;23(5):588-594.

14. Sidorenkov G, Voorham J, Haaijer-Ruskamp FM, de Zeeuw D, Denig P. Association between performance measures and glycemic control among patients with diabetes in a community-wide primary care cohort. *Med Care.* 2013;51(2):172-179.

15. Sidorenkov G, Voorham J, de Zeeuw D, Haaijer-Ruskamp FM, Denig P. Do treatment quality indicators predict cardiovascular outcomes in patients with diabetes? *PLoS One.* 2013;8(10):e78821.

16. Khunti K, Wolden ML, Thorsted BL, Andersen M, Davies MJ. Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. *Diabetes Care.* 2013;36(11):3411-3417.

17. Grant RW, Cagliero E, Dubey AK, et al. Clinical inertia in the management of type 2 diabetes metabolic risk factors. *Diabet Med.* 2004;21(2):150-155.

18. Stark Casagrande S, Fradkin JE, Saydah SH, Rust KF, Cowie CC. The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988–2010. *Diabetes Care.* 2013;36(8):2271-2279.

19. Kerr EA, Lucatorto MA, Holleman R, Hogan MM, Klamerus ML, Hofer TP; VA Diabetes Enhancement Research Initiative (QUERI) Workgroup on Clinical Action Measures. Monitoring performance for blood pressure management among patients with diabetes mellitus: too much of a good thing? *Arch Intern Med.* 2012;172(12):938-945.

20. McGlynn EA, Asch SM, Adams J, et al. The quality of health care delivered to adults in the United States. *N Engl J Med.* 2003;348(26):2635-2645.

21. Rodondi N, Peng T, Karter AJ, et al. Therapy modifications in response to poorly controlled hypertension, dyslipidemia, and diabetes mellitus. *Ann Intern Med.* 2006;144(7):475-484.

22. Turner LW, Nartey D, Stafford RS, Singh S, Alexander GC. Ambulatory treatment of type 2 diabetes in the U.S., 1997-2012. *Diabetes Care.* 2014;37(4):985-992.

23. Hampp C, Borders-Hemphill V, Moeny DG, Wysowski DK. Use of antidiabetic drugs in the U.S., 2003-2012. *Diabetes Care.* 2014;37(5):1367-1374.

24. National Committee for Quality Assurance (NCQA). HEDIS 2009, vol. 2: technical update. Washington, DC: NCQA; 2008.

25. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol.* 1994;47(11):1245-1251.

26. McEwen LN, Kim C, Karter AJ, et al. Risk factors for mortality among patients with diabetes: the Translating Research Into Action for Diabetes (TRIAD) Study. *Diabetes Care.* 2007;30(7):1736-1741.

27. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol.* 1992;45(6):613-619.

28. Zwiener I, Blettner M, Hommel G. Survival analysis: part 15 of a series on evaluation of scientific publications. *Dtsch Arztebl Int.* 2011;108(10):163-169.

29. Gharibvand L, Jeske DR, Solomon L. Evaluation of a Hospice Care Referral Program Using Cox Proportional Hazards Model. 2008 Annual Conference Proceedings of the Western Users of SAS® Software (WUSS); 2008; Universal City, California. http://www.lexjansen.com/

wuss/2008/anl/anl06.pdf. Accessed April 25, 2015.

30. Lee ET, Wang JW. *Statistical Methods for Survival Data Analysis*. 3rd ed. Hoboken, NJ: J. Wiley & Sons; 2003.

31. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. New York, NY: J. Wiley & Sons, 1987.

32. Vitry AI, Roughead EE, Preiss AK, et al. Influence of comorbidities on therapeutic progression of diabetes treatment in Australian veterans: a cohort study. *PLoS One.* 2010;5(11):e14024.

33. Voorham J, Haaijer-Ruskamp FM, Wolffenbuttel BH, de Zeeuw D, Stolk RP, Denig P. Differential effects of comorbidity on antihypertensive and glucose-regulating treatment in diabetes mellitus--a cohort study. *PLoS One.* 2012;7(6):e38707.

34. Alexander GC, Sehgal NL, Moloney RM, Stafford RS. National trends in treatment of type 2 diabetes mellitus, 1994-2007. *Arch Intern Med.* 2008;168(19):2088-2094.

35. Garber AJ, Abrahamson MJ, Barzilay JI, et al. AACE/ACE comprehensive diabetes management algorithm 2015. *Endocr Pract.* 2015; 21(4):438-447.

36. Riethof M, Flavin PL, Lindvall B, et al. *Diagnosis and Management of Type 2 Diabetes Mellitus in Adults.* Bloomington, MN: Institute for Clinical Systems Improvement; 2012.

37. Bennett WL, Maruthur NM, Singh S, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations [published correction appears in *Ann Intern Med.* 2011;155(1):67-68]. *Ann Intern Med.* 2011;154(9):602-613. Review.

38. Bennett WL, Wilson LM, Bolen S, et al. Oral Diabetes Medications for Adults With Type 2 Diabetes: An Update. Rockville, MD: Agency for Healthcare Research and Quality (US); 2011.

39. Shyangdan DS, Royle P, Clar C, Sharma P, Waugh N, Snaith A. Glucagon-like peptide analogues for type 2 diabetes mellitus. *Cochrane Database System Rev.* 2011(10):CD006423.

40. Liu SC, Tu YK, Chien MN, Chien KL. Effect of antidiabetic agents added to metformin on glycaemic control, hypoglycaemia and weight change in patients with type 2 diabetes: a network meta-analysis. *Diabetes Obes Metab.* 2012;14(9):810-820.

41. Karagiannis T, Paschos P, Paletas K, Matthews DR, Tsapas A. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. *BMJ.* 2012;
344:e1369.

42. Niyomnaitham S, Page A, La Caze A, Whitfield K, Smith AJ. Utilisation trends of rosiglitazone and pioglitazone in Australia before and after safety warnings. *BMC Health Serv Res.* 2014;14:151.

43. Starner CI, Schafer JA, Heaton AH, Gleason PP. Rosiglitazone and pioglitazone utilization from January 2007 through May 2008 associated with five risk-warning events. *J Manag Care Pharm.* 2008;14(6): 523-531.

44. Cohen A, Rabbani A, Shah N, Alexander GC. Changes in glitazone use among office-based physicians in the U.S., 2003-2009. *Diabetes Care.* 2010;33(4):823-825.

45. Ruiter R, Visser LE, van Herk-Sukel MP, et al. Prescribing of rosiglitazone and pioglitazone following safety signals: analysis of trends in dispensing patterns in the Netherlands from 1998 to 2008. *Drug Saf.* 2012;35(6):471-480.

46. Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2012;156(3):218-231.

47. Zhang Y, McCoy RG, Mason JE, Smith SA, Shah ND, Denton BT. Second-line agents for glycemic control for type 2 diabetes: are newer agents better? *Diabetes Care.* 2014;37(5):1338-1345.

48. Fu AZ, Qiu Y, Davies MJ, Radican L, Engel SS. Treatment intensification in patients with type 2 diabetes who failed metformin monotherapy. *Diabetes Obes Metab.* 2011;13(8):765-769.

49. Oderda GM, Brixner D, Lieberman M. PMC1 comparison of EMR data to US national data. *Value Health.* 2007;10(6):A450-A451. ■

www.ajmc.com Full text and PDF

eAppendix. Class Allocation of Second-Line Diabetes Therapies

- Sulfonylureas and meglitinides: glyburide, glipizide, gliclazide, glimepiride, nateglinide, repaglinide
- Thiazolidinediones: rosiglitazone, pioglitazone
- Incretins: saxagliptin, linagliptin, vildagliptin, sitagliptin, exenatide, liraglutide, pramlintide
- Other: miglitol, voglibose, acarbose, colesevelam
- Insulin: aspart, glulisine, lispro, regular, NPH, detemir, glargine, NPH/regular, NPH/lispro, NPH/aspart

Meglitinides were grouped with sulfonylureas due to similar mechanism of action (eg, insulin secretagogue), side effect profile, and relatively small number of patients being treated with them. Sodium-glucose co-transporter 2 (SGLT2) inhibitors were not included in this study, as they were not approved by the FDA until 2013 and were therefore not in use during our study time period.